Aldosterone sensitivity: an opportunity to explore the pathogenesis of hypertension

Zachary Gray[1], Wanzhu Tu[2], Glenn M. Chertow[1,3], Vivek Bhalla[1,3]

[1]Stanford Hypertension Center, Stanford University School of Medicine, Stanford, CA 94305

[2]Department of Biostatistics, Indiana University School of Medicine, Indianapolis Indiana 46202

[3]Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305

Corresponding Author:

Vivek Bhalla, MD, FASN, FAHA (vbhalla@stanford.edu), @Stanford_HTN

Running Title: Differential responses to aldosterone

Word count: 4873

Figures and Tables: 4**; References:** 84

Keywords:

Aldosterone

Renin

Secondary Hypertension

Abbreviations:

MR: mineralocorticoid receptor

ENaC: epithelial sodium channel

This is the author's manuscript of the article published in final edited form as:

Gray, Z., Tu, W., Chertow, G. M., & Bhalla, V. (2021). Aldosterone sensitivity: An opportunity to explore the pathogenesis of hypertension. American Journal of Physiology. Renal Physiology, 320(3), F325–F335. https://doi.org/10.1152/ajprenal.00415.2020

Abstract

Aldosterone sensitivity is defined as an outcome variable for a given circulating level of aldosterone. In basic and translational studies, aldosterone sensitivity has been measured in differential tissue responses, e.g., lower urine sodium and higher urine potassium, as an index of renal response; in clinical studies aldosterone sensitivity has been measured in differential blood pressure responses. The concept of aldosterone sensitivity disrupts the conventional wisdom of the renin-angiotensin-aldosterone system and has the potential to uncover novel mechanisms of hypertension. We review basic and translational science studies that uncovered differential renal responses to aldosterone and connect this earlier work to more recent observational studies and randomized trials that have demonstrated differential blood pressure responses for a given level of aldosterone in healthy and hypertensive persons. Black race and older age are associated with higher aldosterone sensitivity and blood pressure. We also discuss gaps in the field and how future basic and clinical studies might inform mechanisms of differential sensitivity.

Introduction

Aldosterone sensitivity is a term used predominantly in research settings, not having become part of our clinical lexicon. The discussion of variable responses to aldosterone begins with addressing the causes of low-renin hypertension, a common and consequential condition. Twenty to thirty percent of all patients with hypertension have low renin -– the proportion is even higher in Black Americans (18, 48, 49). Furthermore, when associated with primary aldosteronism, low-renin states are associated with cardiovascular events(49). Within low-renin hypertension, there are several different pathophysiologic phenotypes that can be characterized as high, normal, or low aldosterone states. Distinguishing among these forms of hypertension is important as diagnostic tests and treatment strategies may differ.

On one end of the spectrum lie low-renin/high-aldosterone states, composed largely of primary aldosteronism (or Conn's syndrome), characterized by autonomous secretion of aldosterone by one or both adrenal glands, of which there are both sporadic and, more rarely, familial forms. Primary aldosteronism is responsible for hypertension in 5-10% of all diagnosed patients and closer to 20% of those with resistant hypertension(19, 20, 77). Furthermore, patients with primary aldosteronism experience higher rates of mortality, cardiovascular events, and progressive kidney disease, as well as lower health-related quality of life relative to patients with "essential" or otherwise unspecified hypertension(5, 21, 43, 47, 70). Management of primary aldosteronism typically requires unilateral adrenalectomy or medical therapy with mineralocorticoid receptor antagonists or inhibitors of the epithelial sodium channel, ENaC.

On the other end of the spectrum are low-renin/low-aldosterone states, including acquired and genetic conditions, and are referred to as syndromes of apparent mineralocorticoid excess. Acquired forms include Cushing's syndrome and pharmacologic inhibition of 11-beta-

hydroxysteroid dehydrogenase 2, namely glycyrrhizic acid-containing black licorice(30) or, more recently, posaconazole(53). Genetic conditions include loss-of-function of 11-beta-hydroxysteroid dehydrogenase 2(46) and Liddle syndrome (gain-of-function mutation in ENaC)(10, 20, 44, 72).

The majority of patients with low-renin hypertension fall between these two extremes of overt hyperaldosteronism or a syndrome of apparent mineralocorticoid excess. These patients have a low level of renin and low-to-normal aldosterone and do not have a clear etiology for hypertension. Previously, this phenotype may be labeled as subclinical hyperaldosteronism or "essential" hypertension. When this biochemical profile is associated with resistant hypertension, the PATHWAY-2 study demonstrated that this cohort is more sensitive to mineralocorticoid receptor antagonists or ENaC inhibitors than to other antihypertensive agents(81, 82). For patients of this phenotype, we outline the concept of "aldosterone sensitivity", how it may account for elevated blood pressure, and how it may affect outcomes (**Figure 1**).

Aldosterone sensitivity is defined as an outcome variable for a given circulating level of aldosterone(33). In basic and translational studies, aldosterone sensitivity has been defined by end-organ responsiveness (e.g., changes in urine sodium and potassium). For clinical studies, aldosterone sensitivity has been defined by the degree of blood pressure elevation for a given level of aldosterone. Notably, the physiologic mechanisms of aldosterone sensitivity (for example, increased MR vs. ENaC expression) are not yet known. Based on the consequences of low-renin hypertension, as noted above, differences in sensitivity to aldosterone are of clinical significance. There are several small-scale studies in animals and humans that support a compelling theory of sensitivity, and that motivate further work to elucidate mechanisms, which could lead novel diagnostics and treatment strategies.

Basic and Translational studies demonstrating renal sensitivity to aldosterone

Several key studies from the 1970s provided early evidence suggesting that the kidney may have variable responses to aldosterone under a variety of conditions.

In 1976, Kolanowski *et al.* evaluated- in 12 obese women- the influence of fasting on natriuretic response to an aldosterone infusion(42). The authors noted that in the early days of a fast, participants who received an aldosterone infusion showed an attenuated antinatriuretic response (40% lower) compared to the same participants prior to their fast, suggesting some state-dependent influence on end-organ responsiveness and decreased sensitivity to a given level of aldosterone.

Starting in 1977, Adams *et al.* published results from several studies exploring other factors that might influence renal sensitivity to aldosterone in rats(1-3). In the first of these studies, female rats were fed a high vs. low potassium diet, followed by bilateral adrenalectomy(1). The investigators then supplemented the animals with sodium and glucocorticoids, and subsequently injected a series of varying concentrations of aldosterone. They then measured urine levels of sodium and potassium to determine the renal response to aldosterone. The rats were then injected with tritium-labeled aldosterone (^{3}H-aldosterone) and sacrificed to investigate patterns of mineralocorticoid receptor expression in renal tubular epithelial cells. The results of this study demonstrated that in high vs. low potassium-fed rats, there was an increased renal response to a given dose of aldosterone, measured by an increase in the urine potassium: sodium ratio. The authors did not detect a significant difference in mineralocorticoid receptor expression between these groups. A subsequent study within the same paper demonstrated an increase in responsiveness to fixed levels of aldosterone in adrenalectomized rats who were

given increased levels of 5-alpha dihydrocortisol, a cortisol metabolite with minimal mineralocorticoid effect(2). These findings together further support the notion that there are possible physiologic influences on the kidney's ability to respond to a given level of aldosterone, and that adjusting these influences may also adjust the renal sensitivity to aldosterone.

In 1979 Adams *et al.* demonstrated a significant variance in the effect of a given level of aldosterone on end-organ responsiveness. These authors evaluated 13 hypertensive patients to assess whether there were differences in end-organ responsiveness to aldosterone, and whether this could contribute to their development of hypertension(3). This study was conducted in three phases, and at the end of each, they measured plasma levels of aldosterone and renin and urine levels of sodium and potassium to assess renal response to aldosterone (i.e., ratio of urine potassium: sodium after an aldosterone infusion normalized to the ratio pre-infusion). The authors also measured trans-rectal potential difference to assess rectal response to aldosterone (i.e. using a trans-rectal electrode, the maximal potential difference four to six hours after aldosterone infusion). The first phase had all patients on low-sodium diets for four days prior to measuring renal and rectal responses to aldosterone(11, 12, 27). For the next several days, patients were treated with a normal sodium diet at the end of which they received an infusion of aldosterone and a repeat of these measurements. Lastly, they received spironolactone for three more days with a repeat of the same measurements. The results demonstrated a direct correlation between the renal response and rectal response to aldosterone infusion (**Figure 2)**. Notably, patients demonstrated a wide range (6-fold) of these responses, suggesting that a fixed level of aldosterone led to a variable end-organ effect in two aldosterone-sensitive tissues. These data support the notion that patients with hypertension can have an integrated mineralocorticoid effect that is determined by both the plasma hormone concentration, and the kidney's response.

Overall, this series of research studies demonstrated that there are several factors that modulate the kidney's ability to respond to a given level of aldosterone, and that different persons may inherently have different end-organ responses. Of note, other studies have shown variability in upstream factors along the renin-angiotensin-aldosterone axis(4), though these mechanisms would result in differences in aldosterone secretion. These factors include dietary sodium intake, sympathetic stimulation of renin, and angiotensin II-mediated aldosterone secretion. Changes in sodium reabsorption are widely recognized to contribute significantly to blood pressure(23, 46, 58), but the implications of renal sensitivity to aldosterone still require further investigation. Notably, Adam *et al.* demonstrated that responsiveness across organ systems directly correlated(3). Taken together, these data support the notion that there are patients who are particularly sensitive to aldosterone, and that perhaps this has pathophysiologic effects on sodium balance and blood pressure regulation.

Clinical studies on blood pressure sensitivity to aldosterone

While earlier studies demonstrated components of renal sensitivity to aldosterone and how this sensitivity differs across patients, they did not evaluate how this sensitivity might impact blood pressure. More recent clinical studies have sought to assess how renal sensitivity to aldosterone might translate into blood pressure sensitivity as well.

Blood pressure sensitivity to aldosterone is a newer concept, proposed initially by Tu *et al.* based on observations of the differential blood pressure response in Blacks vs. whites to the mineralocorticoid, 9α-fludrocortisone, used to mimic hyperaldosteronism(60, 75). Findings from the experiment were later reinforced by data from observational studies of young Blacks and whites prospectively followed for 20 years from childhood to adulthood. A central observation throughout these studies is that blood pressure increases disproportionately in response to

aldosterone (i.e., an increased aldosterone sensitivity), especially in Blacks, and that aldosterone sensitivity increases with age.

Race/ethnicity differences in blood pressure sensitivity to aldosterone

In Blacks, there is an increased prevalence of hypertension despite lower levels of aldosterone. In 1989, Pratt *et al.* demonstrated in this cohort that Black children had, on average, 40% less aldosterone secreted than white children(60). They also observed that, on average, Black children had higher blood pressures than white children, suggesting a difference in aldosterone's influence on blood pressure.

In 2014, Tu *et al.* published results from this cohort, when study participants reached adulthood, specifically focusing on racial differences between Blacks and whites and the influence of aldosterone on blood pressure as well as responsiveness to 9α-fludrocortisone, an exogenous mineralocorticoid(75). These investigators initially enrolled children ages 5-17 years old in 1986 from Indianapolis schools. These participants underwent testing of plasma renin activity and aldosterone concentrations, as well as blood pressure recordings, which were repeated periodically over the ensuing years. Of note, the authors did not evaluate the effect of dietary sodium on measurements of plasma renin activity and plasma aldosterone concentrations. The same participants were invited back in 2008 to undergo the same testing, at this point excluding participants that were already on antihypertensive treatment. For children of the same age, Blacks had significantly lower levels of aldosterone, plasma renin activity, and a higher aldosterone-to-renin ratio than whites. In adults, a very similar pattern was observed. The authors reported a strong blood pressure association with plasma aldosterone concentration, in Blacks but not in whites, especially when plasma renin activity levels were low. Again, patterns were consistent in children as well as in adults. The observation that aldosterone was able to elicit a stronger blood pressure response when renin was low, points to the influence of

extracellular fluid volume expansion on blood pressure in these participants.

In the same study, Tu *et al.* also enrolled healthy participants to undergo treatment with 9α-fludrocortisone, and measured blood pressure responses with an ambulatory blood pressure monitor(75). After administration of fludrocortisone, Blacks experienced a significant increase in systolic blood pressure of ~5-6mmHg, in weight gain, and in elevation of B-type natriuretic peptide levels, which served as a surrogate for intravascular volume expansion. In contrast, none of these changes were observed in whites. Of note, aldosterone levels decreased in response to fludrocortisone treatment in both groups; however the change was much larger in Blacks. These two studies together suggest that at all ages, Blacks have increased blood pressure sensitivity to mineralocorticoids than whites.

In 2017 Tu *et al.* published another study using data from this cohort investigating the effect of varying aldosterone levels on plasma potassium in Black and white participants(74). The study compared blood pressure, plasma renin activity, plasma aldosterone and serum potassium levels in adults and children of Black or white race. They demonstrated, that on average, Black participants had lower plasma renin activity and lower plasma aldosterone concentrations in comparison to whites, regardless of age. Black children also had higher mean systolic and diastolic blood pressures compared to white children. Despite these factors, mean serum potassium concentrations were nearly identical when comparing Black versus white adults as well as when comparing Black versus white children. They speculated that Blacks required a lower level of aldosterone to maintain serum potassium in a physiologically optimal range, at the expense of elevated blood pressure.

These studies focused on racial differences in blood pressure and physiologic responses to mineralocorticoids. Blacks showed higher aldosterone responsiveness to blood pressure,

potassium handling and extracellular volume expansion. These studies also suggested that these differences were evident in childhood and preserved into adulthood, and provide an opportunity to also explore the role of age on responsiveness to aldosterone.

Age-related differences in blood pressure sensitivity to aldosterone

With increasing age, the incidence of hypertension increases but plasma aldosterone concentrations decrease(36, 45, 50, 78). To assess for age-related changes in blood pressure sensitivity to aldosterone, it is first useful to consider that with age, aldosterone production is increasingly independent of the renin-angiotensin axis. In a series of elegant studies, Nanba and colleagues demonstrated that with low dietary sodium, aldosterone was less effectively stimulated, and with high dietary sodium, aldosterone was less effectively suppressed(50, 51). The aldosterone-to-renin ratio also increased with age. In a parallel cohort, the magnitude of CYP11B2 (aldosterone synthase) expression in adrenal tissue decreased with age, consistent with lower overall aldosterone production; however histologic data showed an increase in the area of presumably autonomous aldosterone-producing cell clusters.

Tu *et al*. demonstrated age-related effects on aldosterone sensitivity and blood pressure in the Indianapolis cohort(76). Estimating the magnitude of the association between plasma concentrations of aldosterone and blood pressure as a function of age, again comparing Blacks and whites (**Figure 3**). In Blacks, the authors demonstrated higher systolic and diastolic blood pressures for the level of plasma aldosterone, an association that strengthened with age. This change was not nearly as robust in whites. Both Blacks and whites demonstrated decreased plasma and urine aldosterone concentrations, plasma renin activity, and an increased aldosterone-to-renin ratio (though this rate of increase was greater in Blacks) among persons older in age. This study demonstrated that aldosterone sensitivity may also increase with age, particularly in Blacks. This cohort was healthy and quite young even in adulthood (<= 37 years),

and younger than the cohorts studied by Nanba *et al*.(50, 51). Taken together, an age-related increase in blood pressure sensitivity to aldosterone may occur prior to the detection of clinical hypertension and may synergize with autonomous aldosterone production to contribute to the development of age-related hypertension.

Clinical studies of the mineralocorticoid receptor as a target for resistant hypertension

Patients with resistant hypertension should be screened for primary aldosteronism according to multiple available hypertension guidelines including the recent American Heart Association/ American College of Cardiology 2017 guidelines and the European Society of Cardiology/European Society of Hypertension 2018 guidelines(20, 80, 83). Interestingly, recent data suggest that screening rates for primary aldosteronism among patients with resistant hypertension are low in clinical practice(40, 62, 69). However, there is still a significant proportion of patients with resistant hypertension who do not carry a diagnosis of primary aldosteronism who may benefit from mineralocorticoid receptor antagonists, many of whom fall into the category of low-renin hypertension(17, 28, 37, 49, 54).

Small studies demonstrating efficacy of mineralocorticoid receptor antagonists in resistant hypertension

Initially small-scale studies were designed to evaluate the utility of mineralocorticoid receptor blockade in management of resistant hypertension.

In 2002 Ouzan *et al.* published a study examining the efficacy of spironolactone in reducing blood pressure in 25 patients with resistant hypertension(57). They classified patients as having resistant hypertension if maximally treated with more than two anti-hypertensive agents with persistently elevated blood pressure, though on average, patients were on three anti-

hypertensives at the time of enrollment. Patients were excluded if they had previously been treated with spironolactone. Patients were then treated with 1mg/kg of spironolactone, which was either added to their regimen or replaced an angiotensin converting enzyme inhibitor. Patients were then monitored with an ambulatory blood pressure device, and once they achieved blood pressure control, they were continued on spironolactone as their providers eliminated other antihypertensives in their regimen. After one month, 23 of 25 patients achieved blood pressures under 140/90 mmHg, and by two months all patients had achieved this blood pressure goal. Average systolic blood pressures dropped from 152 mmHg to 128 mmHg. Furthermore, the average antihypertensive regimen was significantly reduced from 3.2 medications to 2.1 in the three-month period with five patients achieving adequate control on spironolactone monotherapy. While the group did not measure plasma concentrations of aldosterone, the authors demonstrated the efficacy of spironolactone in controlling blood pressures in patients with resistant hypertension and were even able to trim their regimens down once spironolactone was introduced.

Nishizaka *et al.* sought to evaluate spironolactone as an add-on therapy in 76 patients with resistant hypertension in 2003(54). The patients were all held to stricter criteria for resistant hypertension than in the previously described study – they all had to be on at least three anti-hypertensives, one of which was a diuretic. Patients were started on low-dose spironolactone and followed for 6 months. Of the 76 patients, 56 had low-renin hypertension and 34 were found to have primary aldosteronism. Patients experienced a significant decrease in blood pressure with the addition of spironolactone with a mean decrease of 25 mmHg in systolic pressures over a six-month period. Similar effects were seen regardless of whether patients had primary aldosteronism, although those with primary aldosteronism did on average require higher doses of spironolactone to meet efficacy.

In 2005, Saha *et al.* explored the effects of ENaC inhibition on management of hypertension in Black patients with hypertension not controlled by calcium channel blockers and more proximally-acting diuretics(63). They conducted a study of factorial design and randomized Black patients who were already taking a calcium channel blocker plus either a loop or thiazide/thiazide-type diuretic into groups taking either a direct ENaC inhibitor (amiloride), an indirect inhibitor by antagonism of the mineralocorticoid receptor (spironolactone), a combination of the two or placebo. Patients were excluded if they had elevated baseline creatinine or if they had a plasma renin activity >0.56 ng/L in order to focus on patients whose hypertension was more volume-dependent. Patients underwent therapy for nine weeks, and 98 patients were included in the analysis. The study found that amiloride reduced systolic and diastolic pressures by 9.8 ±1.6 and 3.4±1.0 mmHg, respectively – for spironolactone, blood pressures were decreased by 4.6 and 1.8mmHg, respectively. The combination had an additive effect without observed interaction. This study further demonstrated that in the Black population, patients with lower plasma renin activity experienced augmented blood pressure control by inhibitors of the ENaC pathway.

These studies demonstrated the effects of mineralocorticoid receptor antagonists for management of patients with resistant hypertension. Furthermore, Nishizaka *et al.* studied a population with a high proportion of low-renin hypertension without primary aldosteronism who also benefited from the medication. Similar effects have been demonstrated with eplerenone in patients with resistant hypertension(20, 79).

PATHWAY-2 Trial

Until 2015 there had been no large-scale randomized trials to explore mineralocorticoid receptor antagonism as a treatment for resistant hypertension. A meta-analysis by Dahal *et al.* in 2015 had concluded, largely from observational data, that aldosterone antagonism was an effective

therapy in treatment of resistant hypertension(24). However, in 2015 the PATHWAY-2 group published a large clinical trial to demonstrate this effect.

The intention of PATHWAY-2 was to compare spironolactone to other add-on therapies for patients with resistant hypertension(81). The investigators enrolled patients between 18 and 79 years old who remained hypertensive after maximal doses on three medications (ACE inhibitor, calcium channel blocker, and a diuretic). Patients with a diagnosis of primary aldosteronism were excluded. PATHWAY-2 trial patients were initially treated with a month of placebo, and then randomized into 12-week cycles through four groups of treatment – placebo, spironolactone, doxazosin, or bisoprolol as add-ons to their existing therapy. Patients were then invited to a 12-week open-label cycle with amiloride. Primary outcomes were the difference between blood pressures in spironolactone vs. placebo groups, as well as difference between home blood pressures in spironolactone vs. other medication treatment groups. The authors also measured plasma renin activity and aldosterone in patients prior to randomization to examine whether these measurements would correlate with responses to spironolactone.

The findings of this trial demonstrated that spironolactone produced the strongest reduction in systolic and diastolic blood pressures compared to placebo, bisoprolol, and doxazosin. Furthermore, the blood pressure response with spironolactone was inversely correlated with plasma renin concentration; the largest change in blood pressure was found in patients with low-renin states. However, regardless of plasma renin concentration, the majority of patients had a larger reduction in blood pressure with spironolactone. Almost 60% of enrolled patients achieved adequate blood pressure control, defined as home systolic blood pressure < 135 mmHg with the addition of spironolactone during the three months in which they took this medication.

Substudies were conducted on the PATHWAY-2 population to elucidate mechanistic explanations for the effect of spironolactone on resistant hypertension(82). In the spironolactone group, investigators showed that the higher the baseline aldosterone: renin ratio, the greater the reduction in blood pressure was observed. They also were able to predict based on the plasma renin concentration alone, though to a lesser degree; plasma aldosterone provided less discriminatory power. Neither plasma renin concentration nor aldosterone predicted the response to other antihypertensive agents. Also, using thoracic electrical bioimpedance cardiography, patients who were treated with spironolactone had the largest reduction in thoracic fluid volumes rather than through systemic vasodilation, implicating natriuresis as a mechanism of the superior benefit observed with spironolactone. Furthermore, patients demonstrated an equivalent blood pressure response with spironolactone compared to amiloride, implicating ENaC as the main target of spironolactone (**Figure 4**). Changes in ENaC activity may alter renal and therefore, blood pressure sensitivity to aldosterone; however, ENaC is expressed in other tissues(58). Therefore, although these data are congruent with those of Adam *et al.*(3), parallel assessment of renal and blood pressure sensitivity within the same cohort is needed.

The PATHWAY-2 trial demonstrated several findings. First, there is a significant improvement in blood pressure control when patients with resistant hypertension add mineralocorticoid receptor antagonists to their regimen(81). Second, this benefit can be predicted by the level of plasma renin concentration and even more so by the aldosterone-to-renin ratio. Taken together with findings by Brown *et al*.(17), these studies show that within the subset of patients with resistant hypertension, primary and subclinical hyperaldosteronism may be underrecognized. A possible mechanism for this form of hypertension may be two-fold: (1) independent low-level aldosterone secretion as shown by Nanba *et al.*(50, 51) and (2) an accentuated response (or sensitivity) to aldosterone. One might consider this duality a “syndrome of inappropriate aldosterone action”

wherein normal or near normal plasma concentrations of aldosterone are higher than what would be required to maintain plasma volume, blood pressure, and cardiac output.

Implications for future basic and clinical research

The basic and clinical research studies described herein demonstrate a wide range of responses to aldosterone or to blockade of its action via mineralocorticoid receptor antagonists or ENaC inhibitors. Multiple investigators spanning decades of research have shown that regulation of ENaC activity plays a pivotal role in aldosterone-mediated sodium reabsorption and hypertension(14, 71). Other pathways downstream of aldosterone contribute to blood pressure regulation, including the indirect, via potassium, and direct regulation of sodium-chloride co-transport in the distal convoluted tubule and more recently, pendrin in the intercalated cells(9, 59, 61). Extrarenal actions of aldosterone and ENaC are also operative in blood pressure regulation and contributed to end-organ effects on the cardiovascular system(55, 58).

Thus far, in clinical practice, with the rare exceptions of the syndrome of apparent mineralocorticoid excess, direct inhibition of ENaC is rarely used. However, the largest subset of low-renin hypertension may be appropriate candidates for blockade of aldosterone action whether by mineralocorticoid receptor antagonists or ENaC inhibition. Genetic forms of the Liddle phenotype are likely more common than appreciated and warrant ENaC inhibition(6, 41, 73).

Blood pressure sensitivity to aldosterone may exist across a broad spectrum that differs across race/ethnic groups and perhaps, within persons. Tu *et al.* have compared a small cohort of Blacks vs. whites, but where other race/ethnic groups fall along this spectrum is unknown.

Oliver, *et al.* reported that Yanomami people have very high levels of plasma aldosterone (and plasma renin activity) but virtually no hypertension(56) - within the context of our current discussion, this would suggest low aldosterone sensitivity among the Yanomami population. This phenomenon may be the result of their 'no-salt, high-potassium' diet, but nonetheless, represents a contrast to Blacks, and requires further study to better understand potential mechanisms.

From the perspective of basic and translational research, we speculate that differences in renal sensitivity to aldosterone may be due to increases in mineralocorticoid receptor expression, either within a cell or along the nephron, or a higher tonic level of activity or an amplified response to a fixed dose of aldosterone. Topics for future basic research must bridge the gap between our knowledge of aldosterone signaling in the distal nephron, mechanisms of differential renal sensitivity to aldosterone, and cohorts with differential blood pressure sensitivity to aldosterone (e.g., Black vs. white, and older vs. younger patients). ENaC subunits exhibiting Liddle's syndrome mutations demonstrate what would be maximal aldosterone sensitivity on one end of a continuum (**Figure 1**). While the few kindreds of Liddle's syndrome patients have not been assayed, preclinical models of Liddle's syndrome mutations demonstrate higher responses to aldosterone than wild-type ENaC *in vitro*(7, 52) and *in vivo*(13, 25).

Potential areas of exploration include but are not limited to: 1) mineralocorticoid receptor activity; 2) downstream mediators of aldosterone action, SGK1-Nedd4-2-ENaC; 3) abundance of MR and ENaC-expressing cells; and (4) other aldosterone-mediated transporters of sodium and chloride. MR expression can be regulated by ubiquitination(31). Regulation of MR is primarily via ligand binding (primarily aldosterone or cortisol), but rare mutations in MR may alter ligand affinity and lead to aberrant MR activation(35). Also, rare mutations and more common polymorphisms in 11β-HSD2, the rate-limiting enzyme that provides specificity for aldosterone

(vs. cortisol) to bind MR, can lead to variable severity of hypertension(32). More subtle regulation of 11β-HSD2 abundance or activity may also influence MR activation(16, 32). Increased MR responsiveness may occur through binding of a small GTPase, Rac-1. This enhancer of MR activation has been implicated in salt-sensitive hypertension(66), proteinuric kidney disease(67), and heart failure(8). Dephosphorylation of MR in intercalated cells, mediated by angiotensin II or hypokalemia can increase pendrin abundance and contribute to hypertension(9, 59, 65, 68). MR can have genomic and nongenomic effects. One of the most well-characterized genomic effects is rapid up-regulation of SGK1(22, 31). SGK1 is a MR-dependent mediator of ENaC-mediated sodium transport by phosphorylation and inhibition of Nedd4-2, a potent inhibitor of ENaC, implicated in the pathogenesis of Liddle's syndrome(15, 26). SGK1 activation or Nedd4-2 deletion may also increase hypertension via increased ENaC activity in principal cells(38, 39, 64). We also speculate that differences in the number of MR and ENaC-expressing cells in the collecting duct, as observed with stimuli of tubular remodeling, may be another factor in aldosterone sensitivity(29, 84). Aldosterone may also stimulate hypertension independent of ENaC, e.g., via sodium-chloride co-transporters and pendrin(9, 59, 61).

From the perspective of clinical research, it will be important to elucidate whether aldosterone sensitivity differs in healthy persons alone as demonstrated by Pratt and colleagues, or across a population of patients with hypertension as suggested by Adam *et al*.(3, 75, 76).
Novel measures to assess for changes in aldosterone sensitivity in large cohorts will also advance the field. Assessment of a renal, or rectal response to a controlled aldosterone infusion is not pragmatic in clinical medicine. Response to mineralocorticoid receptor antagonists may be useful but may not address effects of aldosterone sensitivity on medium-term (e.g., left ventricular hypertrophy) or long-term cardiovascular events (e.g., myocardial infarction, atrial fibrillation, heart failure, stroke, or kidney disease). Perhaps a metric based on both

epidemiologic and clinical data that incorporates blood pressure with plasma renin activity, aldosterone, and potassium would be a valuable surrogate. The implications of demonstrating and accounting for changes in blood pressure sensitivity to aldosterone would fundamentally alter how we currently interpret plasma aldosterone for the diagnosis of Conn's syndrome or syndromes of apparent mineralocorticoid excess(34).

Other endocrine systems harbor differential sensitivity to hormones (e.g., insulin resistance and growth hormone resistance), so it is not surprising that sensitivity to aldosterone exists. However, despite our knowledge of the renin-angiotensin-aldosterone system, there is still much to learn about downstream aldosterone action and its clinical utility in addressing cardiovascular health.

Acknowledgements:

The authors have no relevant conflicts to declare. The authors would like to thank Drs. Howard Pratt and Alan Pao for valuable discussions and Dr. Pablo Garcia for preparation of the visual abstract.

References:

1. **Adam WR, and Funder JW**. Increased renal sensitivity to aldosterone in the rat: induction by a high potassium diet. *Clin Exp Pharmacol Physiol* 4: 283-293, 1977.

2. **Adam WR, Funder JW, Mercer J, and Ulick S**. Amplification of the action of aldosterone by 5 alpha-dihydrocortisol. *Endocrinology* 103: 465-471, 1978.

3. **Adam WR, and Mendelsohn FA**. Measurement of the end-organ responses to aldosterone in man: diversity of response and its possible biological significance. *Aust N Z J Med* 9: 278-283, 1979.

4. **Adler GK, Moore TJ, Hollenberg NK, and Williams GH**. Changes in adrenal responsiveness and potassium balance with shifts in sodium intake. *Endocr Res* 13: 419-445, 1987.

5. **Ahmed AH, Gordon RD, Sukor N, Pimenta E, and Stowasser M**. Quality of life in patients with bilateral primary aldosteronism before and during treatment with spironolactone and/or amiloride, including a comparison with our previously published results in those with unilateral disease treated surgically. *J Clin Endocrinol Metab* 96: 2904-2911, 2011.

6. **Akintunde A, Nondi J, Gogo K, Jones ESW, Rayner BL, Hackam DG, and Spence JD**. Physiological Phenotyping for Personalized Therapy of Uncontrolled Hypertension in Africa. *Am J Hypertens* 30: 923-930, 2017.

7. **Auberson M, Hoffmann-Pochon N, Vandewalle A, Kellenberger S, and Schild L**. Epithelial Na+ channel mutants causing Liddle's syndrome retain ability to respond to aldosterone and vasopressin. *Am J Physiol Renal Physiol* 285: F459-471, 2003.

8. **Ayuzawa N, Nagase M, Ueda K, Nishimoto M, Kawarazaki W, Marumo T, Aiba A, Sakurai T, Shindo T, and Fujita T**. Rac1-Mediated Activation of Mineralocorticoid Receptor in Pressure Overload-Induced Cardiac Injury. *Hypertension* 67: 99-106, 2016.

9. **Ayuzawa N, Nishimoto M, Ueda K, Hirohama D, Kawarazaki W, Shimosawa T, Marumo T, and Fujita T**. Two Mineralocorticoid Receptor-Mediated Mechanisms of Pendrin Activation in Distal Nephrons. *J Am Soc Nephrol* 31: 748-764, 2020.

10. **Baudrand R, and Vaidya A**. The Low-Renin Hypertension Phenotype: Genetics and the Role of the Mineralocorticoid Receptor. *Int J Mol Sci* 19: 2018.

11. **Beevers DG**. Mineralocorticoids and rectal potential difference. *Lancet* 2: 682-683, 1973.

12. **Beevers DG, Morton JJ, Tree M, and Young J**. Rectal potential difference in the diagnosis of aldosterone excess. *Gut* 16: 36-41, 1975.

13. **Bertog M, Cuffe JE, Pradervand S, Hummler E, Hartner A, Porst M, Hilgers KF, Rossier BC, and Korbmacher C**. Aldosterone responsiveness of the epithelial sodium channel (ENaC) in colon is increased in a mouse model for Liddle's syndrome. *J Physiol* 586: 459-475, 2008.

14. **Bhalla V, and Hallows KR**. Mechanisms of ENaC regulation and clinical implications. *J Am Soc Nephrol* 19: 1845-1854, 2008.

15. **Bhalla V, Soundararajan R, Pao AC, Li H, and Pearce D**. Disinhibitory pathways for control of sodium transport: regulation of ENaC by SGK1 and GILZ. *Am J Physiol Renal Physiol* 291: F714-721, 2006.

16. **Bocchi B, Kenouch S, Lamarre-Cliche M, Muffat-Joly M, Capron MH, Fiet J, Morineau G, Azizi M, Bonvalet JP, and Farman N**. Impaired 11-beta hydroxysteroid dehydrogenase type 2 activity in sweat gland ducts in human essential hypertension. *Hypertension* 43: 803-808, 2004.

17. **Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, and Vaidya A**. The Unrecognized Prevalence of Primary Aldosteronism. *Ann Intern Med* 2020.

18. **Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, and Buhler FR**. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 286: 441-449, 1972.

19. **Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, and Weissmann P**. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* 40: 892-896, 2002.

20. **Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB, American Heart Association Professional/Public E, Publications Committee of the Council on H, Council on C, Stroke N, Council on Clinical C, Council on G, Precision M, Council on Peripheral Vascular D, Council on Quality of C, Outcomes R, and Stroke C**. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension* 72: e53-e90, 2018.

21. **Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, and Sechi LA**. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med* 168: 80-85, 2008.

22. **Chen SY, Wang J, Liu W, and Pearce D**. Aldosterone responsiveness of A6 cells is restored by cloned rat mineralocorticoid receptor. *Am J Physiol* 274: C39-46, 1998.

23. **Coffman TM**. The inextricable role of the kidney in hypertension. *J Clin Invest* 124: 2341-2347, 2014.

24. **Dahal K, Kunwar S, Rijal J, Alqatahni F, Panta R, Ishak N, and Russell RP**. The Effects of Aldosterone Antagonists in Patients With Resistant Hypertension: A Meta-Analysis of Randomized and Nonrandomized Studies. *Am J Hypertens* 28: 1376-1385, 2015.

25. **Dahlmann A, Pradervand S, Hummler E, Rossier BC, Frindt G, and Palmer LG**. Mineralocorticoid regulation of epithelial Na+ channels is maintained in a mouse model of Liddle's syndrome. *Am J Physiol Renal Physiol* 285: F310-318, 2003.

26. **Debonneville C, Flores SY, Kamynina E, Plant PJ, Tauxe C, Thomas MA, Munster C, Chraibi A, Pratt JH, Horisberger JD, Pearce D, Loffing J, and Staub O**. Phosphorylation of Nedd4-2 by Sgk1 regulates epithelial Na(+) channel cell surface expression. *EMBO J* 20: 7052-7059, 2001.

27. **Edmonds CJ, and Richards P**. Measurement of rectal electrical potential difference as an instant screening-test for hyperaldosteronism. *Lancet* 2: 624-627, 1970.

28. **Eide IK, Torjesen PA, Drolsum A, Babovic A, and Lilledahl NP**. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. *J Hypertens* 22: 2217-2226, 2004.

29. **Ellison DH, Velazquez H, and Wright FS**. Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Invest* 83: 113-126, 1989.

30. **Farese RV, Jr., Biglieri EG, Shackleton CH, Irony I, and Gomez-Fontes R**. Licorice-induced hypermineralocorticoidism. *N Engl J Med* 325: 1223-1227, 1991.

31. **Faresse N, Ruffieux-Daidie D, Salamin M, Gomez-Sanchez CE, and Staub O**. Mineralocorticoid receptor degradation is promoted by Hsp90 inhibition and the ubiquitin-protein ligase CHIP. *Am J Physiol Renal Physiol* 299: F1462-1472, 2010.

32. **Ferrari P, Lovati E, and Frey FJ**. The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension. *J Hypertens* 18: 241-248, 2000.

33. **Funder JW**. Sensitivity to aldosterone: plasma levels are not the full story. *Hypertension* 63: 1168-1170, 2014.

34. **Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, and Young WF, Jr.** The Management of Primary Aldosteronism: Case Detection, Diagnosis,

and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 101: 1889-1916, 2016.

35. **Geller DS, Farhi A, Pinkerton N, Fradley M, Moritz M, Spitzer A, Meinke G, Tsai FT, Sigler PB, and Lifton RP**. Activating mineralocorticoid receptor mutation in hypertension exacerbated by pregnancy. *Science* 289: 119-123, 2000.

36. **Gurven M, Blackwell AD, Rodriguez DE, Stieglitz J, and Kaplan H**. Does blood pressure inevitably rise with age?: longitudinal evidence among forager-horticulturalists. *Hypertension* 60: 25-33, 2012.

37. **Hood SJ, Taylor KP, Ashby MJ, and Brown MJ**. The spironolactone, amiloride, losartan, and thiazide (SALT) double-blind crossover trial in patients with low-renin hypertension and elevated aldosterone-renin ratio. *Circulation* 116: 268-275, 2007.

38. **Huang DY, Boini KM, Friedrich B, Metzger M, Just L, Osswald H, Wulff P, Kuhl D, Vallon V, and Lang F**. Blunted hypertensive effect of combined fructose and high-salt diet in gene-targeted mice lacking functional serum- and glucocorticoid-inducible kinase SGK1. *Am J Physiol Regul Integr Comp Physiol* 290: R935-944, 2006.

39. **Huang DY, Boini KM, Osswald H, Friedrich B, Artunc F, Ullrich S, Rajamanickam J, Palmada M, Wulff P, Kuhl D, Vallon V, and Lang F**. Resistance of mice lacking the serum- and glucocorticoid-inducible kinase SGK1 against salt-sensitive hypertension induced by a high-fat diet. *Am J Physiol Renal Physiol* 291: F1264-1273, 2006.

40. **Jaffe G, Gray Z, Krishnan G, Stedman M, Zheng Y, Han J, Chertow GM, Leppert JT, and Bhalla V**. Screening Rates for Primary Aldosteronism in Resistant Hypertension: A Cohort Study. *Hypertension* 75: 650-659, 2020.

41. **Jones ES, Spence JD, McIntyre AD, Nondi J, Gogo K, Akintunde A, Hackam DG, and Rayner BL**. High Frequency of Variants of Candidate Genes in Black Africans with Low Renin-Resistant Hypertension. *Am J Hypertens* 30: 478-483, 2017.

42. **Kolanowski J, Desmecht P, and Crabbe J**. Sodium balance and renal tubular sensitivity to aldosterone during total fast and carbohydrate refeeding in the obese. *Eur J Clin Invest* 6: 75-83, 1976.

43. **Kunzel HE, Apostolopoulou K, Pallauf A, Gerum S, Merkle K, Schulz S, Fischer E, Brand V, Bidlingmaier M, Endres S, Beuschlein F, and Reincke M**. Quality of life in patients with primary aldosteronism: gender differences in untreated and long-term treated patients and associations with treatment and aldosterone. *J Psychiatr Res* 46: 1650-1654, 2012.

44. **Laffer CL, Elijovich F, Eckert GJ, Tu W, Pratt JH, and Brown NJ**. Genetic variation in CYP4A11 and blood pressure response to mineralocorticoid receptor antagonism or ENaC inhibition: an exploratory pilot study in African Americans. *J Am Soc Hypertens* 8: 475-480, 2014.

45. **Landahl S, Bengtsson C, Sigurdsson JA, Svanborg A, and Svardsudd K**. Age-related changes in blood pressure. *Hypertension* 8: 1044-1049, 1986.

46. **Lifton RP, Gharavi AG, and Geller DS**. Molecular mechanisms of human hypertension. *Cell* 104: 545-556, 2001.

47. **Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, and Mourad JJ**. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 45: 1243-1248, 2005.

48. **Monticone S, Losano I, Tetti M, Buffolo F, Veglio F, and Mulatero P**. Diagnostic approach to low-renin hypertension. *Clin Endocrinol (Oxf)* 89: 385-396, 2018.

49. **Mulatero P, Verhovez A, Morello F, and Veglio F**. Diagnosis and treatment of low-renin hypertension. *Clin Endocrinol (Oxf)* 67: 324-334, 2007.

50. **Nanba K, Vaidya A, and Rainey WE**. Aging and Adrenal Aldosterone Production. *Hypertension* 71: 218-223, 2018.

51. **Nanba K, Vaidya A, Williams GH, Zheng I, Else T, and Rainey WE**. Age-Related Autonomous Aldosteronism. *Circulation* 136: 347-355, 2017.

52. **Nesterov V, Krueger B, Bertog M, Dahlmann A, Palmisano R, and Korbmacher C**. In Liddle Syndrome, Epithelial Sodium Channel Is Hyperactive Mainly in the Early Part of the Aldosterone-Sensitive Distal Nephron. *Hypertension* 67: 1256-1262, 2016.

53. **Nguyen MH, Davis MR, Wittenberg R, McHardy I, Baddley JW, Young BY, Odermatt A, and Thompson GR**. Posaconazole Serum Drug Levels Associated With Pseudohyperaldosteronism. *Clin Infect Dis* 70: 2593-2598, 2020.

54. **Nishizaka MK, Zaman MA, and Calhoun DA**. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 16: 925-930, 2003.

55. **Ohno Y, Sone M, Inagaki N, Kawashima A, Takeda Y, Yoneda T, Kurihara I, Itoh H, Tsuiki M, Ichijo T, Katabami T, Wada N, Sakamoto R, Ogawa Y, Yoshimoto T, Yamada T, Kawashima J, Matsuda Y, Kobayashi H, Kamemura K, Yamamoto K, Otsuki M, Okamura S, Izawa S, Okamoto R, Tamura K, Tanabe A, Naruse M, and Group JJS**. Nadir Aldosterone Levels After Confirmatory Tests Are Correlated With Left Ventricular Hypertrophy in Primary Aldosteronism. *Hypertension* 75: 1475-1482, 2020.

56. **Oliver WJ, Cohen EL, and Neel JV**. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. *Circulation* 52: 146-151, 1975.

57. **Ouzan J, Perault C, Lincoff AM, Carre E, and Mertes M**. The role of spironolactone in the treatment of patients with refractory hypertension. *Am J Hypertens* 15: 333-339, 2002.

58. **Pao AC**. Update on the Guytonian view of hypertension. *Curr Opin Nephrol Hypertens* 23: 391-398, 2014.

59. **Pham TD, Verlander JW, Wang Y, Romero CA, Yue Q, Chen C, Thumova M, Eaton DC, Lazo-Fernandez Y, and Wall SM**. Aldosterone Regulates Pendrin and Epithelial Sodium Channel Activity through Intercalated Cell Mineralocorticoid Receptor-Dependent and -Independent Mechanisms over a Wide Range in Serum Potassium. *J Am Soc Nephrol* 31: 483-499, 2020.

60. **Pratt JH, Jones JJ, Miller JZ, Wagner MA, and Fineberg NS**. Racial differences in aldosterone excretion and plasma aldosterone concentrations in children. *N Engl J Med* 321: 1152-1157, 1989.

61. **Roy A, Al-Qusairi L, Donnelly BF, Ronzaud C, Marciszyn AL, Gong F, Chang YP, Butterworth MB, Pastor-Soler NM, Hallows KR, Staub O, and Subramanya AR**. Alternatively spliced proline-rich cassettes link WNK1 to aldosterone action. *J Clin Invest* 125: 3433-3448, 2015.

62. **Ruhle BC, White MG, Alsafran S, Kaplan EL, Angelos P, and Grogan RH**. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. *Surgery* 165: 221-227, 2019.

63. **Saha C, Eckert GJ, Ambrosius WT, Chun TY, Wagner MA, Zhao Q, and Pratt JH**. Improvement in blood pressure with inhibition of the epithelial sodium channel in blacks with hypertension. *Hypertension* 46: 481-487, 2005.

64. **Shi PP, Cao XR, Sweezer EM, Kinney TS, Williams NR, Husted RF, Nair R, Weiss RM, Williamson RA, Sigmund CD, Snyder PM, Staub O, Stokes JB, and Yang B**. Salt-sensitive hypertension and cardiac hypertrophy in mice deficient in the ubiquitin ligase Nedd4-2. *Am J Physiol Renal Physiol* 295: F462-470, 2008.

65. **Shibata S, Ishizawa K, Wang Q, Xu N, Fujita T, Uchida S, and Lifton RP**. ULK1 Phosphorylates and Regulates Mineralocorticoid Receptor. *Cell Rep* 24: 569-576, 2018.

66. **Shibata S, Mu S, Kawarazaki H, Muraoka K, Ishizawa K, Yoshida S, Kawarazaki W, Takeuchi M, Ayuzawa N, Miyoshi J, Takai Y, Ishikawa A, Shimosawa T, Ando K, Nagase M, and Fujita T**. Rac1 GTPase in rodent kidneys is essential for salt-sensitive hypertension via a mineralocorticoid receptor-dependent pathway. *J Clin Invest* 121: 3233-3243, 2011.

67. **Shibata S, Nagase M, Yoshida S, Kawarazaki W, Kurihara H, Tanaka H, Miyoshi J, Takai Y, and Fujita T**. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. *Nat Med* 14: 1370-1376, 2008.

68. **Shibata S, Rinehart J, Zhang J, Moeckel G, Castaneda-Bueno M, Stiegler AL, Boggon TJ, Gamba G, and Lifton RP**. Mineralocorticoid receptor phosphorylation regulates ligand binding and renal response to volume depletion and hyperkalemia. *Cell Metab* 18: 660-671, 2013.

69. **Sivarajah M, Beninato T, and Fahey TJ, 3rd**. Adherence to consensus guidelines for screening of primary aldosteronism in an urban healthcare system. *Surgery* 167: 211-215, 2020.

70. **Sonino N, Tomba E, Genesia ML, Bertello C, Mulatero P, Veglio F, Fava GA, and Fallo F**. Psychological assessment of primary aldosteronism: a controlled study. *J Clin Endocrinol Metab* 96: E878-883, 2011.

71. **Soundararajan R, Pearce D, Hughey RP, and Kleyman TR**. Role of epithelial sodium channels and their regulators in hypertension. *J Biol Chem* 285: 30363-30369, 2010.

72. **Spence JD, and Rayner BL**. Hypertension in Blacks: Individualized Therapy Based on Renin/Aldosterone Phenotyping. *Hypertension* 72: 263-269, 2018.

73. **Tapolyai M, Uysal A, Dossabhoy NR, Zsom L, Szarvas T, Lengvarszky Z, and Fulop T**. High prevalence of liddle syndrome phenotype among hypertensive US Veterans in Northwest Louisiana. *J Clin Hypertens (Greenwich)* 12: 856-860, 2010.

74. **Tu W, Eckert GJ, Decker BS, and Howard Pratt J**. Varying Influences of Aldosterone on the Plasma Potassium Concentration in Blacks and Whites. *Am J Hypertens* 30: 490-494, 2017.

75. **Tu W, Eckert GJ, Hannon TS, Liu H, Pratt LM, Wagner MA, Dimeglio LA, Jung J, and Pratt JH**. Racial differences in sensitivity of blood pressure to aldosterone. *Hypertension* 63: 1212-1218, 2014.

76. **Tu W, Li R, Bhalla V, Eckert GJ, and Pratt JH**. Age-Related Blood Pressure Sensitivity to Aldosterone in Blacks and Whites. *Hypertension* 72: 247-252, 2018.

77. **Vaidya A, Mulatero P, Baudrand R, and Adler GK**. The Expanding Spectrum of Primary Aldosteronism: Implications for Diagnosis, Pathogenesis, and Treatment. *Endocr Rev* 39: 1057-1088, 2018.

78. **Weidmann P, De Myttenaere-Bursztein S, Maxwell MH, and de Lima J**. Effect on aging on plasma renin and aldosterone in normal man. *Kidney Int* 8: 325-333, 1975.

79. **Weinberger MH, White WB, Ruilope LM, MacDonald TM, Davidson RC, Roniker B, Patrick JL, and Krause SL**. Effects of eplerenone versus losartan in patients with low-renin hypertension. *Am Heart J* 150: 426-433, 2005.

80. **Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD, and Wright JT, Jr.** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2017.

81. **Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ, and British Hypertension Society's PSG**. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 386: 2059-2068, 2015.

82. **Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, Ford I, Cruickshank JK, Caulfield MJ, Padmanabhan S, Mackenzie IS, Salsbury J, Brown MJ, British Hypertension Society programme of P, and Treatment of Hypertension With Algorithm based Therapy Study G**. Endocrine and haemodynamic changes in resistant

hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 6: 464-475, 2018.

83. **Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement D, Coca A, De Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen S, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder R, Shlyakhto E, Tsioufis K, Aboyans V, Desormais I, and List of authors/Task Force m**. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 36: 2284-2309, 2018.

84. **Wu H, Chen L, Zhou Q, Zhang X, Berger S, Bi J, Lewis DE, Xia Y, and Zhang W**. Aqp2-expressing cells give rise to renal intercalated cells. *J Am Soc Nephrol* 24: 243-252, 2013.

Figure legends:

Figure 1:

Spectrum of low-renin hypertension. Low-renin hypertension is comprised of 20-25% of all patients with hypertension. Among these patients, approximately 40% have Conn's syndrome or primary aldosteronism have the highest circulating aldosterone with normal to low sensitivity (*white bar*). Approximately 2% have a syndrome of apparent mineralocorticoid excess, arguably have the lowest aldosterone levels with the highest effective level of aldosterone (*blue bar*). The majority of patients fall between these extremes and have (1) subclinical hyperaldosteronism for which a proportion may have heightened aldosterone sensitivity or (2) essential hypertension (*red bar*). APA, aldosterone-producing adenoma; BAH-bilateral adrenal hyperplasia; AME, apparent mineralocorticoid excess.

Figure 2:

(**A**) The relationship between the responses of the kidney and rectum to an aldosterone infusion. Black squares represent individual values in the patients and (X), repeat studies in four of the patients after being on spironolactone 100 mg three times a day for four days. The correlation between the two responses was highly significant ($P < 0.001$). (**B**) The relationship between 24-hour urine $[K^+]/[Na^+]$ (as a measure of the integrated aldosterone effect) and the predicted aldosterone activity (obtained by multiplying the log of the 24-hour urinary aldosterone excretion by the rectal response, r1). The relationship was highly significant ($P < 0.02$). Adapted from Adam, *et al.*, 1979(3).

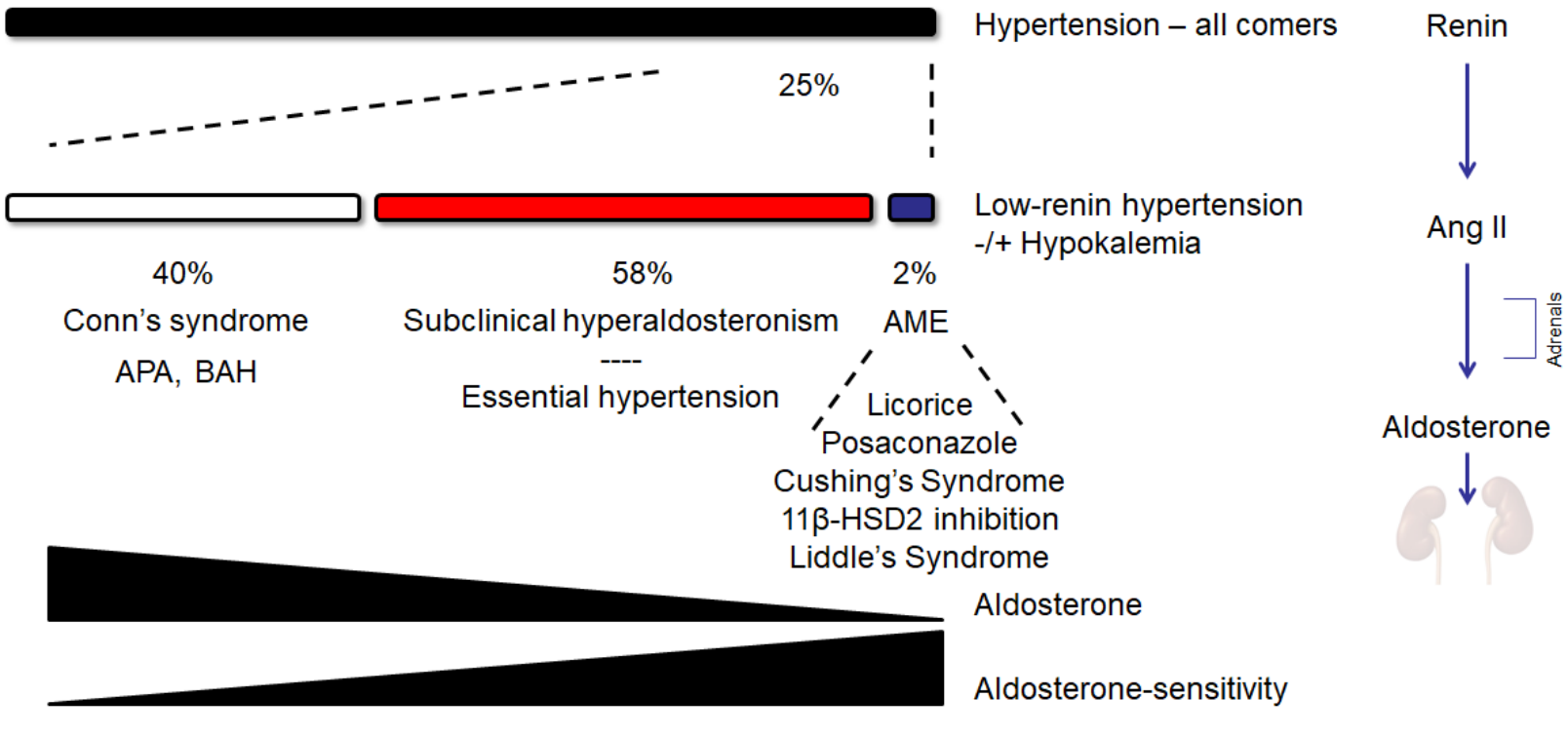
Figure 3:

Age-specific estimates of the aldosterone-systolic blood pressure (SBP) association in Blacks and whites. **A** and **B**, Magnitudes of the estimated aldosterone-SBP association significantly increased with age in Blacks ($P<0.01$) but not in whites. The 2 estimated regression coefficient

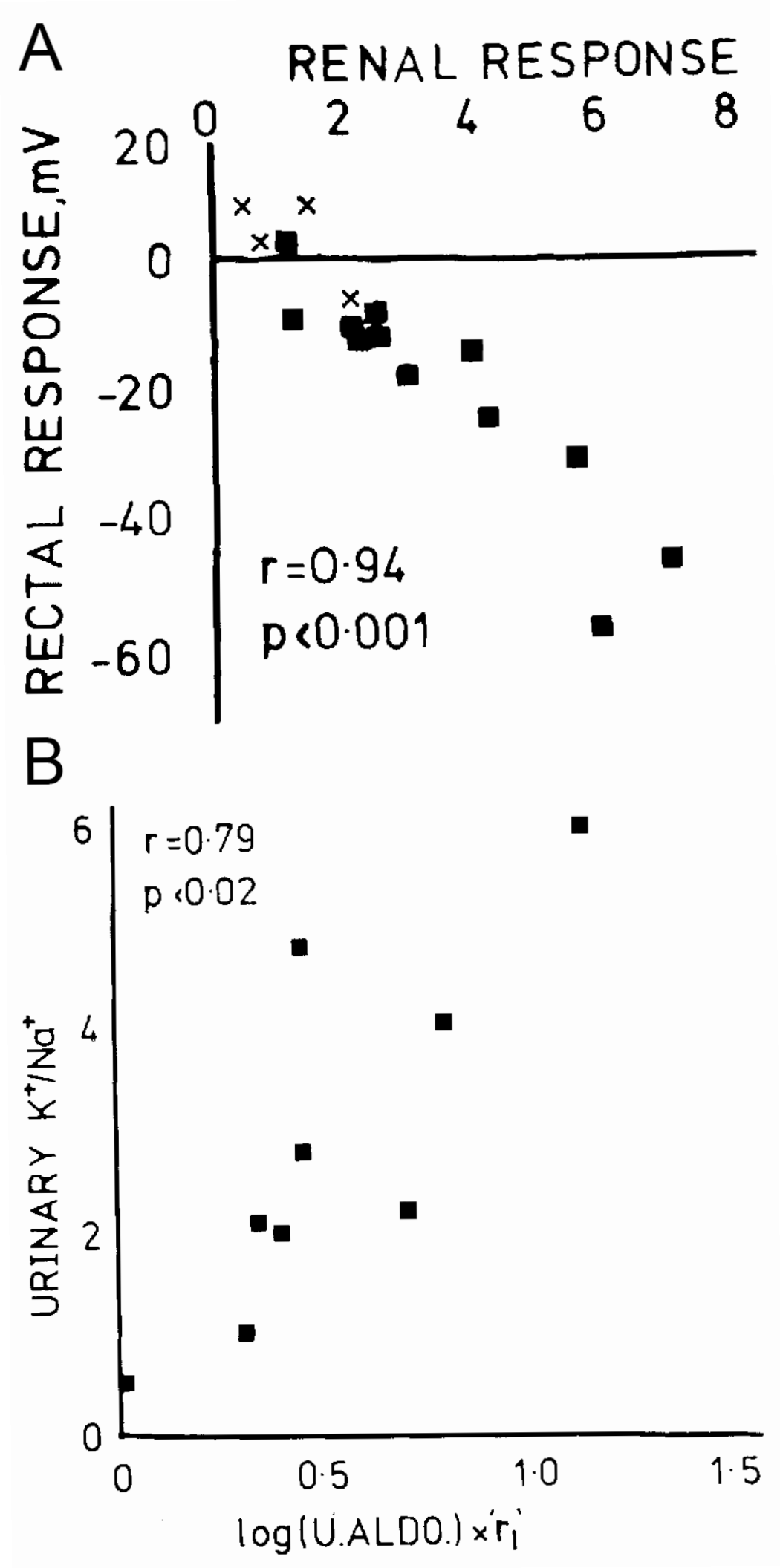
curves were significantly different per bootstrap test (P=0.023). **C** and **D**, Age-specific estimates of the aldosterone-diastolic BP (DBP) in whites and in Blacks. Shaded regions represent 95% pointwise confidence intervals of the mean curves. Adapted from Tu *et al.* 2018(76).

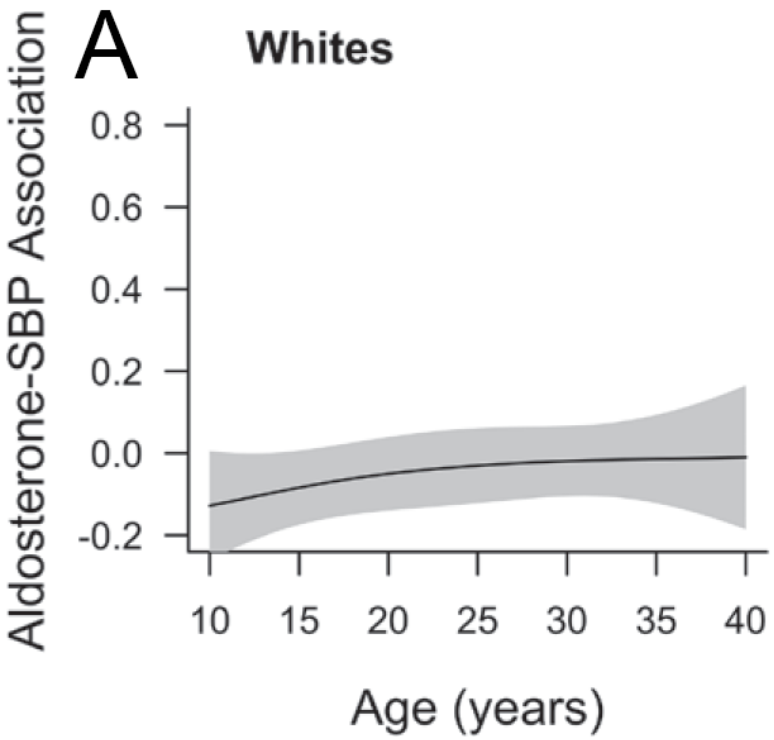
Figure 4:

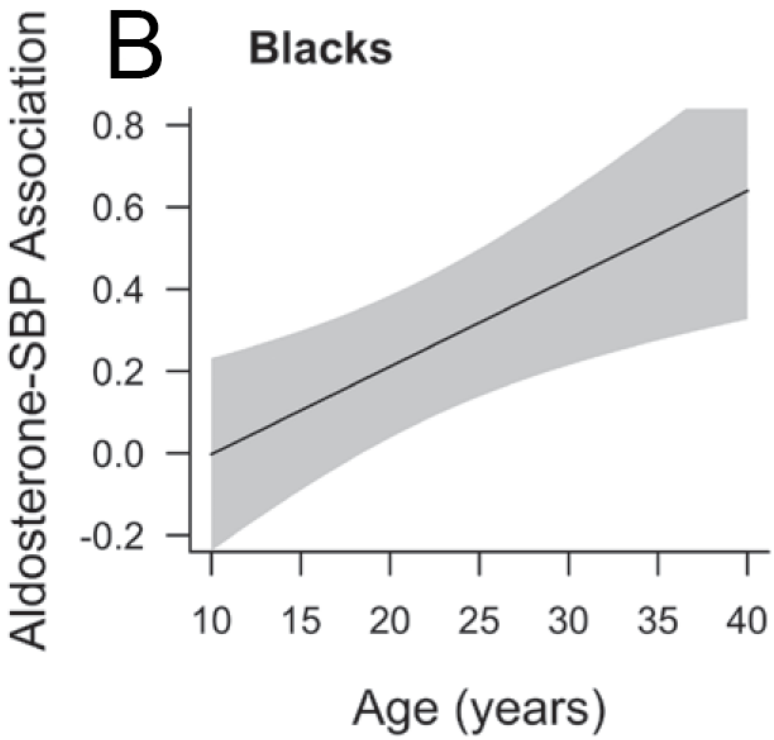
Correlations of plasma aldosterone, renin, and ARR, with blood pressure response to spironolactone averaged (mean) across the 6-week and 12-week visits of each treatment cycle (A) Relation between baseline plasma renin, aldosterone, and the ARR and the home systolic blood pressure response to spironolactone. (B) Best-fit relation between plasma aldosterone and renin concentrations at baseline. Regression equations for change in systolic blood pressure (y): $y=(-25{\cdot}20)+6{\cdot}86 \times (\log_{10}\text{renin})$, $r^2=0{\cdot}116$ (proportion of variance accounted for by the model); $y=8{\cdot}92-9{\cdot}85 \times (\log_{10}\text{aldosterone})$, $r^2=0{\cdot}034$; and $y=(-8{\cdot}87)-6{\cdot}87 \times (\log_{10}\text{ARR})$, $r^2=0{\cdot}138$. Regression equation for aldosterone vs renin: $\text{log10aldosterone}=2{\cdot}60-0{\cdot}279 \times (\log_{10}\text{renin}) + 0{\cdot}081 \times (\log_{10}\text{renin})^2$, $r^2=0{\cdot}043$. ARR=aldosterone-to-renin ratio. Adapted from Williams *et al.* 2018(82).

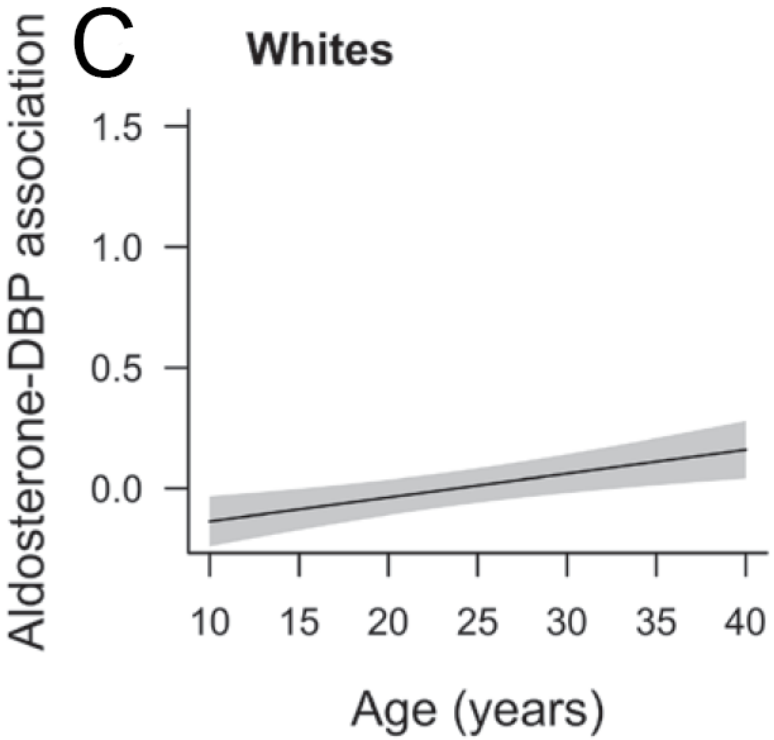

Hypertension – all comers
25%
Low-renin hypertension
-/+ Hypokalemia
40%
Conn's syndrome
APA, BAH
58%
Subclinical hyperaldosteronism

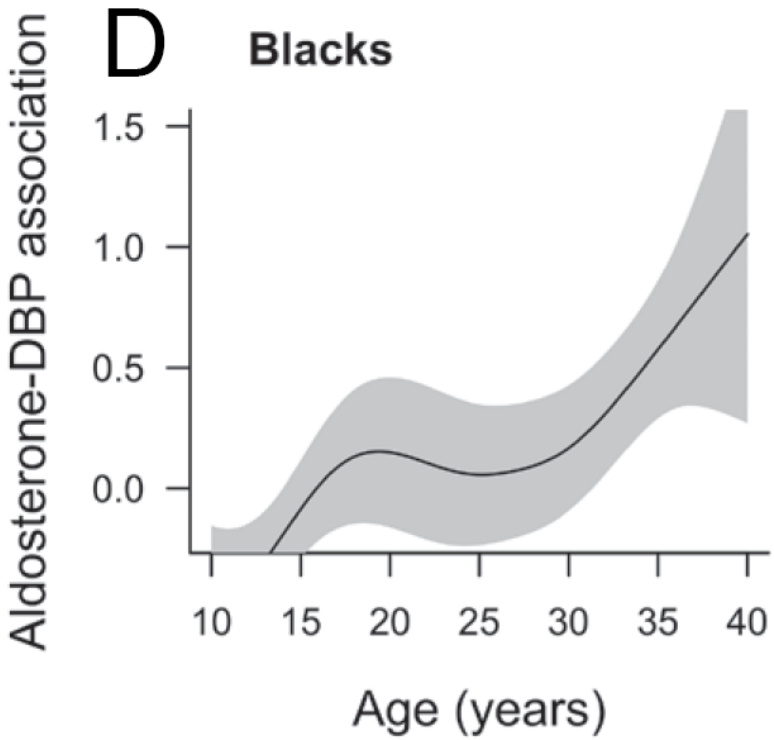
Essential hypertension
2%
AME
Licorice
Posaconazole
Cushing's Syndrome
11β-HSD2 inhibition
Liddle's Syndrome
Aldosterone
Aldosterone-sensitivity
Renin
Ang II
Adrenals
Aldosterone

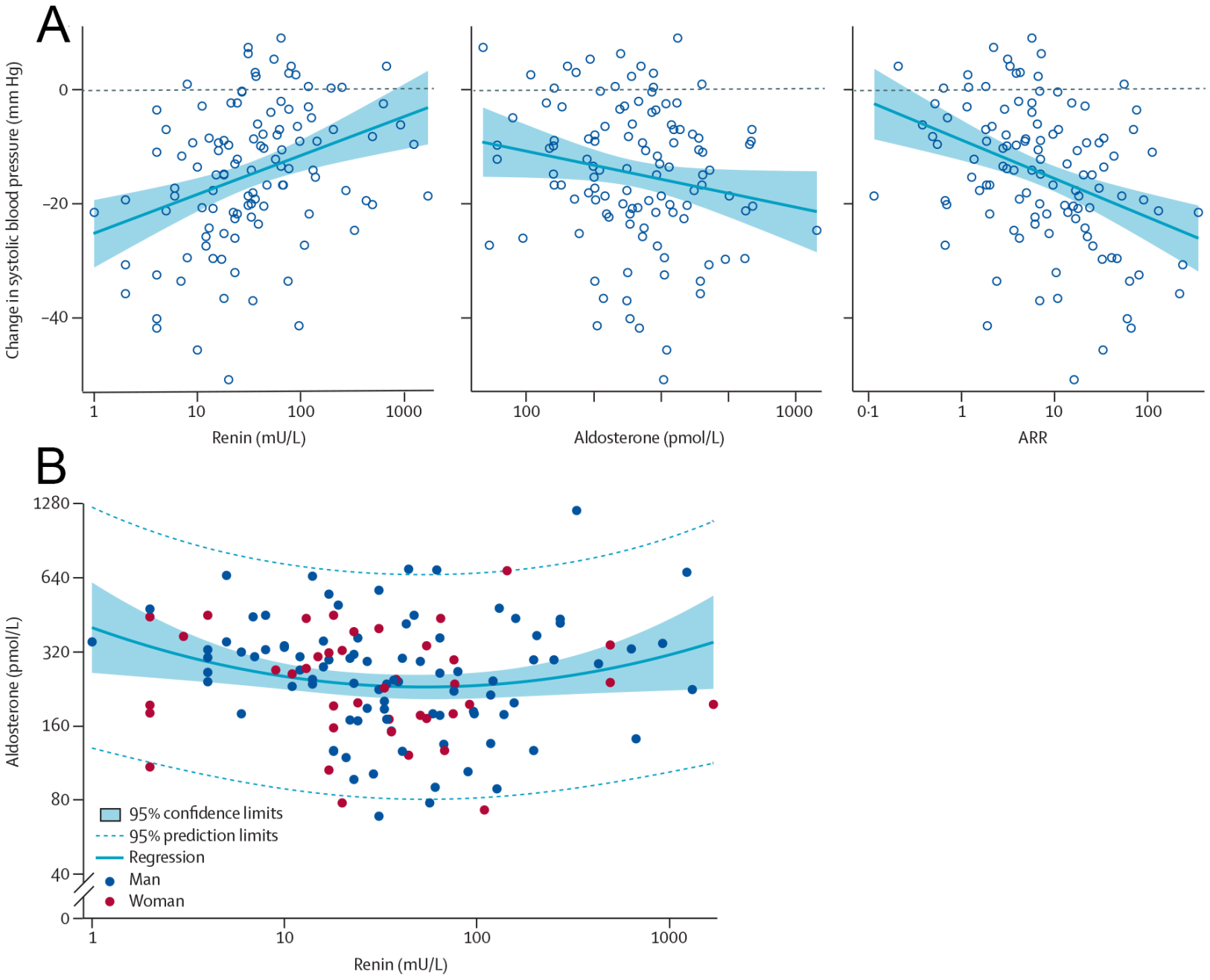

A
RENAL RESPONSE
0
2
4
6
8
20
0
-20
-40
-60
RECTAL RESPONSE, mV
r = 0·94
p < 0·001
B
6
4
2
0
r = 0·79
p < 0·02
URINARY K+/Na+
0
0·5
1·0
1·5
log (U.ALDO.) × r


A
Whites
Aldosterone-SBP Association
0.8
0.6
0.4
0.2
0.0
-0.2
10
15
20
25
30
35
40
Age (years)


B
Blacks
Aldosterone-SBP Association
0.8
0.6
0.4
0.2
0.0
-0.2
10
15
20
25
30
35
40
Age (years)


C
Whites
Aldosterone-DBP association
1.5
1.0
0.5
0.0
10
15
20
25
30
35
40
Age (years)


D
Blacks
Aldosterone-DBP association
1.5
1.0
0.5
0.0
10
15
20
25
30
35
40
Age (years)


A
Change in systolic blood pressure (mm Hg)
0
−20
−40
1
10
100
1000
Renin (mU/L)
100
1000
Aldosterone (pmol/L)
0·1
1
10
100
ARR
B
Aldosterone (pmol/L)
1280
640
320
160
80
40
0
95% confidence limits
95% prediction limits
Regression
Man
Woman
1
10
100
1000
Renin (mU/L)

Aldosterone sensitivity: an opportunity to explore the pathogenesis of hypertension

Review

Basic and Translational studies

Several factors modulate the kidney's ability to respond to a given level of aldosterone

Different persons have different responses

-Aldosterone action is an integration of aldosterone secretion and tissue response

-Recent discoveries including regulation of MR may underlie aldosterone sensitivity

Clinical studies

BP increases disproportionately in response to aldosterone, mainly in blacks and sensitivity increases with age

A significant proportion of patients with low-renin resistant hypertension and normal aldosterone, benefit from mineralocorticoid receptors antagonists or ENaC inhibitors

CONCLUSION Variable responses to aldosterone have been demonstrated in patients. Black race and older age are associated with higher aldosterone sensitivity and blood pressure. Mechanistic studies of end-organ response to aldosterone and clinical biomarkers for aldosterone response are needed to inform the pathogenesis of low-renin hypertension.

doi here