Aldosterone and arterial hypertension

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Abstract | In the setting of primary aldosteronism, elevated aldosterone levels are associated with increased blood pressure. Aldosterone concentrations within the normal range, however, can also alter blood pressure. Furthermore, the aldosterone-to-renin ratio, an indicator of aldosterone excess, is associated with hypertension, even in patients without excessive absolute aldosterone levels. In this Review we assess the data on the role of aldosterone in the development and maintenance of hypertension. We provide an overview of the complex crosstalk between genetic and environmental factors, and about aldosterone-mediated arterial hypertension and target organ damage. The discussion is organized according to major targets of aldosterone action: the collecting duct in the kidney, the vasculature and the central nervous system. The anti-hypertensive efficacy of mineralocorticoid-receptor blockers, even in patients with aldosterone values in the normal range, supports the evidence that aldosterone plays a part in blood pressure elevation in the absence of primary aldosteronism.


Introduction

The 2002 WHO World Health Report indicates an estimated prevalence for arterial hypertension of up to 1 billion individuals worldwide. Approximately 7.1 million deaths per year can be directly attributed to poor control of blood pressure, which also accounts for 62% of cerebrovascular disease and 49% of ischemic heart disease cases. In around half of patients with arterial hypertension blood pressure cannot be controlled despite concurrent use of at least three antihypertensive drugs, including one diuretic. This so-called resistant hypertension is thought to be remarkably frequent in elderly patients (60% in >75 year-olds) and patients with obesity (30%), chronic kidney disease (63%), diabetes mellitus (75%), or a combination of these, and is an enormous public health problem that makes a major contribution to the global burden of disease.

The development of arterial hypertension is the result of a complex interplay between genetic and environmental factors. The renin–angiotensin–aldosterone system (RAAS) plays a central part in fluid and electrolyte homeostasis and is, therefore, one of the principal regulating systems for blood pressure. In the past, raised blood pressure was linked to dysregulations of the RAAS, in particular those associated with angiotensin II. A growing body of evidence, however, indicates that the mineralocorticoid hormone aldosterone makes a major contribution to the pathogenesis of arterial hypertension. Aldosteronism—overproduction of aldosterone—can be idiopathic, caused by adrenal hyperplasia or by an adrenal adenoma, leading to inappropriately high, at least partly autonomous, aldosterone secretion that is not explained by malfunction of the RAAS and not suppressible by Na+ loading (primary aldosteronism), or by dysfunctions in the RAAS (secondary aldosteronism). In addition, however, several studies have suggested that aldosterone concentrations within the normal range can adversely affect blood pressure.

In this Review we address the proposed mechanisms of aldosterone-mediated blood pressure elevation, including genetic risk factors, discuss the clinical evidence for this involvement, and highlight the role of aldosterone antagonists as potential antihypertensive drugs.

RAAS and regulation of blood pressure

The RAAS molecular cascade is activated by factors that reduce the volume of circulating blood and by decreased renal perfusion pressure or decreased tubular sodium chloride concentration. Activation of the RAAS normalizes circulatory homeostasis (Figure 1). The actions of the RAAS that modulate blood pressure can be grouped into three categories: rapid activation to compensate hypovolemia and hypotension, which occurs through rapid stimulation of adrenal aldosterone synthesis; intermediate-term activation that interferes with salt homeostasis; and long-term activation that contributes to structural alterations of target tissues (such as vascular remodeling).

Continued and inappropriate activation of this system, however, might contribute to the development and progression of arterial hypertension.

The RAAS probably evolved in response to environmental pressures when our early terrestrial ancestors were confronted with low salt availability, and, therefore, a low dietary Na+ intake (<3 g Na+ per day). Under these conditions, activation of the RAAS would favor renal salt conservation and water retention, thus contributing to maintaining sufficient tissue perfusion in a salt-scarce environment.
Key points
- Clinical and experimental evidence shows that aldosterone makes a major contribution to primary aldosteronism and the pathogenesis of arterial hypertension.
- Aldosterone excess contributes to endothelial dysfunction, inflammation and vascular remodeling, which result in the development and maintenance of arterial hypertension, via genomic and nongenomic pathways.
- Aldosterone-mediated effects on epithelial and nonepithelial tissues depend on mineralocorticoid sensitivity, which is modulated by salt and angiotensin II.
- Renal Na\(^+\) and fluid retention, endothelial dysfunction, increased peripheral resistance and central sympathetic drive are major pathogenic pathways of aldosterone-induced arterial hypertension.
- Mineralocorticoid-receptor blockers are useful drugs to treat aldosterone-mediated arterial hypertension, especially when other antihypertensive drugs insufficiently control blood pressure.

Figure 1 | The renin–angiotensin–aldosterone system. Renin is synthesized by the juxtaglomerular cells of the kidney. Renin is the key determinant of the RAAS activity and catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted by the angiotensin-converting enzyme (ACE) to angiotensin II, the primary effector of a variety of RAAS-induced physiological and pathophysiological actions. Angiotensin II, via the type 1 angiotensin II receptor, increases the synthesis of aldosterone by upregulating the CYP11B2 gene, which encodes the enzyme ALDO. ALDO is located in the zona glomerulosa of the adrenal cortex and catalyzes the synthesis of aldosterone. Abbreviations: ADH, antidiuretic hormone; ACTH, adrenocorticotropic hormone; AT1, type 1 angiotensin II receptor; GH, growth hormone; TSH, thyroid-stimulating hormone.

Aldosterone

Synthesis

The ALDOS protein (cytochrome P450 11B2, mitochondrial, also known as aldosterone synthase) is the key enzyme involved in aldosterone production and its expression is mainly regulated by angiotensin II, potassium and adrenocorticotropic hormone (ACTH; Figure 2).\(^{10}\) Secretory products derived from visceral adipocytes have also been suggested to upregulate ALDOS expression and stimulate adrenal aldosterone synthesis.\(^{11}\) Furthermore, in hypertensive—but not in normotensive—individuals, increased sympathetic activity and dietary salt intake participate in the regulation of adrenal aldosterone production by modulating the sensitivity of the adrenal gland to angiotensin II.\(^{12}\)

The latter factor might explain why urinary aldosterone levels did not decrease after an oral salt load in hypertensive individuals, whereas they did in normotensive individuals.\(^{13}\) Accordingly, several large observational investigations revealed strong associations between high dietary salt intake and arterial hypertension.\(^{14,15}\) This effect was, however, not observed in all studies, presumably because some of these trials had methodological limitations that might have led to a bias.\(^{16,17}\)

Proposed mechanisms of action in hypertension

High levels of aldosterone lead to increased reabsorption of Na\(^+\) and water from epithelial cells in the distal nephron of the kidney, thus influencing blood pressure levels. Aldosterone binds to the mineralocorticoid receptor, a member of the nuclear receptor family of ligand-dependent transcription factors.\(^{18}\) The activated receptor–hormone complex binds to hormone-response elements and regulates gene transcription, and thereby Na\(^+\) excretion. The mineralocorticoid receptor has also been identified in nonepithelial tissues, such as fibroblasts of the heart and vascular smooth muscle cells (VSMCs), thus modifying the classic view that aldosterone acts exclusively on transport epithelia.\(^{19}\)

In addition to genomic effects, aldosterone induces rapid, nongenomic cellular effects, predominantly in nonepithelial tissues.\(^{20}\) These effects are modulated by intracellular second messenger molecules, such as Ca\(^{2+}\) and cyclic AMP, and/or by phosphorylation of signaling molecules, such as protein kinase C, epidermal growth factor receptor (EGFR) and members of the mitogen-activated protein kinase family.\(^{20}\) The physiological and pathophysiological relevance of these rapid mechanisms remains elusive, but may include regulation of cell volume, oxidation-reduction state and vascular function.\(^{20}\) The interactions between the genomic and nongenomic effects of aldosterone are currently unclear.

The effects of aldosterone are modulated by the RAAS. Evidence supports the existence of a crosstalk between aldosterone and the pathways regulated by angiotensin II and the type 1 angiotensin II receptor;\(^{21}\) and by aldosterone and the mineralocorticoid receptor (in VSMCs and cardiomyocytes).\(^{22}\) This crosstalk is mediated partly by reactive oxygen species (ROS), whose production is increased when aldosterone levels are raised.\(^{21}\) Increased
ROS generation results in the activation of signaling pathways involved in cell growth, contraction, inflammation, collagen deposition, and migration. The pathways regulated by angiotensin II and the type I angiotensin II receptor, and by aldosterone and the mineralocorticoid receptor seem, therefore, to reinforce each other. In rat cardiocytes, raised aldosterone concentrations lead to upregulation of angiotensin-converting enzyme (ACE). Subsequently, elevated angiotensin II levels lead to increased aldosterone synthesis. In humans, aldosterone upregulates the receptors of angiotensin II in VSMCs and potentiates the vasoconstrictor effect of angiotensin II in coronary arteries. The interaction between aldosterone and angiotensin II in VSMCs leads to potentiation of the proliferative action of angiotensin II.

EGFR signaling is thought to play a critical part in the response of VSMCs to hypertension. In renal VSMCs of Dahl salt-sensitive rats EGFR expression was increased compared with that in non-salt-sensitive Sprague-Dawley rats. Genomic and nongenomic aldosterone pathways may potentiate the activity of mitogen-activated protein kinases 1 and 3 in VSMCs and synergistically augment the mitogenic effects of angiotensin II.

In sum, synergistic interactions between aldosterone and angiotensin II in endothelial cells and VSMCs cause direct target-organ damage, but presumably also indirectly promote vascular inflammation, fibrosis, remodeling and, finally, arterial hypertension.

Paradoxically, salt loading is accompanied by an increase in number and activation of mineralocorticoid receptors in target tissues. Under normal conditions in epithelial tissues, the enzyme 11βHSD2 converts intracellular cortisol and corticosterone to cortisone and 11-dehydrocortisolosterone, which do not activate the mineralocorticoid receptors. Glucocorticoid occupancy of epithelial mineralocorticoid receptors is not blocked, but their ability to act as mineralocorticoid-receptor agonists is decreased, as they bind the receptors in a tonic inhibitory mode. Under conditions of oxidative stress related, for example, to increased salt intake or tissue damage, however, glucocorticoids may become agonists of the mineralocorticoid receptor, which, in concert with the action of aldosterone, leads to increased mineralocorticoid-receptor activation. This condition can lead to worsening of inflammation, fibrosis, endothelial dysfunction and further oxidative stress. In states of low levels of circulating aldosterone, activation of the mineralocorticoid receptor, however, may occur because of increased localized aldosterone synthesis in specific tissues. Increased local aldosterone synthesis may activate the mineralocorticoid receptor independently of the actions of 11βHSD2. Further studies are urgently needed to elucidate the complex modulation of mineralocorticoid receptor function by oxidative stress and dietary salt loads.

Responses in the kidney
In modern societies, where salt consumption is high, the risk of arterial hypertension is notably increased.

![Figure 2](image-url) | Mechanisms of aldosterone-mediated arterial hypertension. Polymorphisms of the CYP11B2 gene, dietary salt intake, the renin–angiotensin–aldosterone system, the hypothalamic–pituitary–adrenal axis, obesity (mineralocorticoid-releasing factors) and the sympathetic nervous system interact in modulating aldosterone synthesis. Nongenomic factors may stimulate aldosterone synthesis directly (full-line box) or indirectly (dotted-line box). A complex interplay between genomic and rapid nongenomic effects mediates mineralocorticoid-induced target-organ and tissue damage within the central nervous system, the kidney and the vasculature, which results in arterial hypertension. Abbreviations: HPA, hypothalamic–pituitary–adrenal axis; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Raised aldosterone levels, however, do not necessarily cause hypertension unless the salt balance has become positive, which is most impressively illustrated by the Yanomama Indians who live on extremely low Na+ intakes (10 mmol per day) and have raised serum aldosterone concentrations (14.7 mmol/l), yet have low blood pressure (mean 102/62 mmHg). Both of these factors seem to be required for the development of hypertension. Upon high levels of Na+ intake, inappropriate downward adjustment in adrenal aldosterone secretion leads to an increase in renal Na+ reabsorption via the epithelial Na+ channel, and thereby water retention, raised plasma volume, cardiac output and concentrations of Ca++ in VSMCs, reflex constriction of peripheral vessels and, ultimately, hypertension.

The concept that the effect of Na+ on blood pressure is mediated by changes in plasma volume, however, is not absolutely correct, as Na+ can also be stored in interaction with negatively charged glycosaminoglycans without altering osmotic balance. Signaling via the...
vascular endothelial growth factor C in mononuclear phagocyte system cells is thought to be a major determinant of blood pressure homeostasis and may be related to the pathogenesis of salt-induced hypertension.  

Responses in the vasculature

Alteration to the geometry of small arteries can lead to raised blood pressure by increases in peripheral resistance. Human endothelial cells and VSMCs express mineralocorticoid receptors and Na⁺-channel genes, thus being sensitive to the actions of aldosterone. Circulating aldosterone exerts different effects on different layers of the blood vessel walls via genomic and nongenomic pathways.  

ROS generation leads to decreased bioavailability of nitric oxide, which is associated with impaired endothelium-dependent relaxation of the arteries and, hence, vasoconstriction. These effects are particularly pronounced in vessels with pre-existing damage.  

Aldosterone-induced activation of mineralocorticoid receptors triggers production of ROS via upregulation of NADPH oxidase. Therefore, under conditions of high oxidative stress stimulation of the mineralocorticoid receptor leads to damage of target tissues by proinflammatory and profibrotic effects.  

Aldosterone also contributes to vasoconstriction and vascular remodeling via nongenomic processes, by activating phospholipase C and intracellular Ca²⁺ pathways in pregglomerular and postglomerular arterioles. In addition, in patients with resistant hypertension aldosterone reduces the bioactivity of nitric oxide in the vasculature, which results in reductions in flow-mediated arterial vasodilatation. Under some conditions aldosterone locally synthesized in blood vessels also contributes to the hypertrophy of VSMCs. Various effects of aldosterone on endothelial cells are modulated by the prevailing Na⁺ concentrations. Increase of Na⁺ concentrations in the presence, but not in the absence, of aldosterone, has been associated with progressive stiffening and reduction of nitric oxide synthesis in monolayer cultures of human endothelial cells. Acute aldosterone exposure has also been shown to result in transient endothelial cell swelling, while long-term aldosterone exposure has led to size growth, and both have led to subsequent endothelial dysfunction and, presumably, increased peripheral resistance. These effects of aldosterone on endothelial cells make physiological sense when plasma volume is low, but may become adverse if endothelial stiffness and endothelial dysfunction become permanent, and if arterial pressure rises as a result of persistently elevated aldosterone levels and high dietary salt intake.  

Aldosterone may also be involved in structural remodeling of blood vessels via genomic and nongenomic pathways. For example, in cultured cells in vitro, rodent models and translational human studies mineralocorticoid-receptor activation results in increased expression of plasminogen activator inhibitor 1 (also known as PAI-1), which contributes to vascular remodeling and renal injury as a result of tissue fibrosis. Experimental studies in rats have also shown that long-term exposure to high aldosterone levels with simultaneous salt loading triggers proinflammatory pathways and causes vascular fibrosis. Furthermore, in normotensive and hypertensive African Americans, high plasma aldosterone levels correlated with poor vascular compliance and high pulse pressure, which are markers of vascular stiffness. Moreover, activation of the mineralocorticoid receptor by aldosterone promotes osteoblastic differentiation and mineralization of VSMCs, which results in vascular calcification.

Responses in the CNS

The identification of mineralocorticoid receptors in certain areas of the brain and the experimental indication that aldosterone might be produced locally in specific parts of the central nervous system (CNS) strengthened the idea that central mechanisms might be involved in aldosterone-induced hypertension.  

In Dahl salt-sensitive rats chronic intracerebroventricular infusion of aldosterone was associated with increased rates of sympathoexcitatory responses, concentrations of ouabain-like compounds in the hypothalamus and resting mean arterial pressure, and with impaired baroreflex function. This intensification in sympathetic drive may be due in part to increased numbers of excitatory postsynaptic potentials in sympathetic preganglionic neurons in the spinal cord. Furthermore, central infusion of Na⁺-rich artificial cerebrospinal fluid in rats increased aldosterone concentrations in the hypothalamus and was associated with raised blood pressure. Moreover, concomitant microinjection of ALDOS inhibitors and mineralocorticoid-receptor blockers into hypothalamic areas prevented sympathetic hyperactivity and hypertension after central infusion of Na⁺-rich fluid. Conversely, in an experimental rat model systemic Na⁺ depletion increased expression of ALDOS in the adrenal glands and some areas of the CNS (cerebellum and hippocampus). Other areas within the brain, such as the amygdala and subfornical organ, may be crucial for aldosterone-mediated rises in blood pressure. For example, activation of the mineralocorticoid receptor in the circumventricular organ, an action which is presumably mainly mediated by aldosterone, was associated with increased central sympathetic drive, increased release of vasopressin, and decreased baroreceptor sensitivity in rats. Conversely, the intracerebroventricular infusion of an ALDOS inhibitor was associated with decreased blood pressure, which could be amplified by centrally administered mineralocorticoid receptor antagonists. Furthermore, mineralocorticoid-receptor activation by aldosterone was linked to increased salt appetite, which in turn promoted the development of hypertension.

Genetic risk factors

Several polymorphisms of CYP11B2, which encodes ALDOS, have been found more frequently in patients with hypertension than in normotensive controls, although this observation has not been consistent in all studies. For example, some studies found
the –344C>T polymorphism (located in the promoter region of CYP11B2) is associated with elevated aldosterone levels and aldosterone-to-renin ratio values and is more frequent in hypertensive than in normotensive individuals.70–72 Finally, a meta-analysis demonstrated that homozygous individuals for the –344T allele have a 17% greater risk of developing essential hypertension than homozygous carriers of the –344C allele.73

In a study of mice, genetic modulation of the 3′ untranslated region of CYP11B2 led to upregulation of ALDOS transcription and to a moderate increase in ALDOS activity.74 These animals exhibited increased salt sensitivity and raised blood pressure. Another study has shown that young, normotensive men with a family history of arterial hypertension had inadequately suppressed aldosterone levels after salt loading and hyperresponsiveness of adrenal aldosterone secretion after infusion of angiotensin II, compared with normotensive men who had no history of arterial hypertension.75 These findings strongly support the relation between genetically programmed ALDOS activity and salt-dependent hypertension.

Only modest heritability of plasma aldosterone levels was found in a large community-based population76 and in a study of 43 hypertensive sibling pairs.77 A study in monozygotic and dizygotic twins showed no notable genetic influence on plasma aldosterone levels, but documented heritability for the more solid parameter of urinary excretion of aldosterone, which is less influenced by short-term environmental factors than plasma aldosterone levels.78 Some studies, however, are limited by the fact that only one baseline measurement of plasma aldosterone levels was performed.

A relative aldosterone excess may also reflect genetically programmed upregulation of aldosterone synthesis and secretion independently from existing polymorphisms in CYP11B2. One study that demonstrated heritable susceptibility to an altered aldosterone-to-renin ratio and its linkage to chromosomes 11p and 5p supports this notion.79 In addition, congenital disturbances of the hypothalamic–pituitary–adrenal (HPA) axis are also associated with altered adrenal aldosterone synthesis (Figure 2). In a cross-sectional study in adults (205 men and 106 women), plasma aldosterone levels were measured after dexamethasone suppression of aldosterone synthesis followed by stimulation of aldosterone synthesis by administration of ACTH.66 Raised aldosterone concentrations were positively associated with higher blood pressure and negatively associated with cortisol levels and birth weight. These findings suggest that control of glucocorticoid and mineralocorticoid synthesis may be at least in part regulated by the HPA axis in early life. Accordingly, urinary aldosterone and cortisol concentrations are positively correlated in patients with resistant hypertension.80 By contrast, loss-of-function mutations in the ACTH receptor are associated with salt-losing forms of adrenal hypoplasia in children, which may reflect disturbances of the RAAS.81

The blood pressure response to dietary salt intake differs between individuals and may be partially due to genetic predisposition.82 Several mutations in the family of Na+ channel genes are associated with increased prevalence of arterial hypertension, but not with raised plasma aldosterone levels.83 An association between these mutations and salt-sensitive hypertension has been purported, but no causal link has yet been demonstrated.84 A study has also postulated an association between hypertension and genetic variance of SGK1, the gene that encodes the serine/threonine-protein kinase Sgk1 (also known as serum/glucocorticoid-regulated kinase 1), which prolongs the half-life of Na+ channels.85

**Clinical evidence**

**Primary aldosteronism**

A link between hypertension and adrenal tumors was suggested by Lityński in 1953,86 and causal evidence was provided in 1954 by Conn and Louis, who documented cure of arterial hypertension after surgical removal of an adrenal tumor that had led to excessive production of aldosterone.87 In 1956 Genest et al.88 suggested that primary hypertension is a state of mild, chronic aldosteronism. A link between adrenocortical abnormalities, such as adenomas, hyperplasia, and hypertension has also been documented in an autopsy series.89 Even in the absence of the classic criteria of primary aldosteronism, inappropriately elevated aldosterone concentrations have been implicated in the pathogenesis and progression of primary hypertension. Inappropriately increased absolute aldosterone levels (Table 1) and an elevated aldosterone-to-renin ratio (Table 2) both seem to be important features of aldosterone-mediated hypertension.

The rate of autonomous aldosterone secretion or the elevation of the aldosterone-to-renin ratio increase with increasing severity of arterial hypertension.90 This pattern is seen in approximately 5–10% of patients with essential hypertension, and is higher in people with drug-resistant hypertension (17–23%) than in other hypertensive patients.91,92 This observation has led to the claim of an unrecognized epidemic of primary aldosteronism,93,94 although this claim has been disputed: some studies suggest that the increased prevalence is the result of more-intense screening and improvements in sensitivity of laboratory procedures.95

**Aldosterone and other forms of hypertension**

Raised blood pressure has been seen in patients with elevated aldosterone levels in the presence or absence of primary aldosteronism compared with that in patients with normal or reduced aldosterone levels.96 Results from the Framingham Heart Disease Epidemiology Study6 have shown that the risks of a rise in blood pressure and developing hypertension increased per quartile of nonpathophysiological plasma aldosterone level; during follow-up of around 4 years, 34% of patients were reclassified at least one blood pressure category higher, and the incidence of hypertension had increased by 15%. A French case-control study also found that in middle-aged nonhypertensive individuals, high plasma aldosterone levels and low renin levels were predictive for rises in systolic blood pressure and the development of hypertension.97 In a large cohort of individuals, those with the highest
aldosterone-to-renin ratio values had an elevated risk of progressive increases in blood pressure and incident hypertension during a 3-year follow-up (odds ratios per SD increment 1.23 [95% CI 1.11–1.37] and 1.16 [95% CI 1.00–1.33], respectively).79 Furthermore, the aldosterone-to-renin ratio correlated strongly with mean arterial pressure and vascular stiffness in a community-based population, although evaluation of vascular stiffness via tonometry and biomarker measurement was not performed at the same time as aldosterone and renin levels were measured.89 Our research group confirmed a strong association between the aldosterone-to-renin ratio and peripheral as well as central aortic blood pressure in a cross-sectional analysis, whereas only modest associations between blood pressure and absolute plasma aldosterone levels were found.99

Different conditions of inappropriately activated aldosterone production and/or relative excess of aldosterone for any given level of renin might represent a hormonal continuum in arterial hypertension. Idiopathic

<table>
<thead>
<tr>
<th>Study (study design)</th>
<th>Number of probands</th>
<th>Ethnicity</th>
<th>Blood pressure status</th>
<th>Key finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingelsson et al.7 (prospective)</td>
<td>2,292</td>
<td>Not given</td>
<td>Nonhypertensive and hypertensive</td>
<td>Serum aldosterone levels were positively associated with change in systolic blood pressure after mean follow-up of 2.9 years ($P=0.023$)</td>
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<td>Meneton et al.27 (case-control)</td>
<td>1,984</td>
<td>White</td>
<td>Nonhypertensive</td>
<td>Raised plasma aldosterone levels were positively associated with the increase in systolic pressure ($P=0.01$) and the risk of hypertension after 5 years of follow-up ($P=0.04$)</td>
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<td>Vasan et al.6 (prospective)</td>
<td>1,688</td>
<td>Not given</td>
<td>Nonhypertensive</td>
<td>A 16% increase ($P=0.002$) in the risk of elevation in blood pressure and a 17% increase ($P=0.03$) in the risk of hypertension were observed per quartile increment of serum aldosterone levels after 4 years of follow-up</td>
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<td>Kotchen et al.53 (case-control)</td>
<td>3,018</td>
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<td>Nonhypertensive and hypertensive</td>
<td>Blood pressure and pulse pressure were correlated with aldosterone levels in hypertensive and normotensive individuals ($P&lt;0.01$)</td>
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<td>Kidambi et al.144 (case-control)</td>
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<td>Black</td>
<td>Nonhypertensive and hypertensive</td>
<td>Ambulatory blood pressure levels were positively correlated with plasma aldosterone levels ($P&lt;0.0001$)</td>
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<td>Gaddam et al.80 (case-control)</td>
<td>279</td>
<td>White and Black</td>
<td>Resistant hypertensive</td>
<td>Plasma aldosterone values were higher in patients with resistant hypertension than in normotensive and hypertensive controls ($P&lt;0.001$)</td>
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<tr>
<td>Tomaschitz et al.99 (cross-sectional)</td>
<td>3,056</td>
<td>White</td>
<td>Nonhypertensive and hypertensive</td>
<td>A modest association between aldosterone and blood pressure levels was observed ($P&lt;0.05$)</td>
</tr>
<tr>
<td>Schunkert et al.145 (cross-sectional)</td>
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<td>White</td>
<td>Nonhypertensive and hypertensive</td>
<td>Aldosterone levels were significantly related to blood pressure levels ($P=0.02$)</td>
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<td>Walker et al.113 (cross-sectional)</td>
<td>574</td>
<td>White and Black</td>
<td>Nonhypertensive and hypertensive</td>
<td>Aldosterone and diastolic blood pressure levels had a significant negative correlation ($P&lt;0.00001$)</td>
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<tr>
<td>Grim et al.114 (cross-sectional)</td>
<td>513</td>
<td>White and Black</td>
<td>Nonhypertensive and hypertensive</td>
<td>Both average systolic and diastolic blood pressure levels were correlated with supine and standing plasma aldosterone levels ($P&lt;0.006$); correlations of blood pressure and aldosterone levels were more consistent and more striking in black than in white individuals ($P&lt;0.004$)</td>
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<td>Bochud et al.108 (cross-sectional)</td>
<td>356</td>
<td>Black</td>
<td>Nonhypertensive and hypertensive</td>
<td>Plasma aldosterone and blood pressure levels were positively associated ($P=0.05$)</td>
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<td>Reynolds et al.96 (cross-sectional)</td>
<td>311</td>
<td>Not given</td>
<td>Hypertensive</td>
<td>Elevated aldosterone levels after doxymethasone suppression and ACTH stimulation were associated with elevated blood pressure levels ($P&lt;0.001$)</td>
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<td>El-Gharbawy et al.146 (cross-sectional)</td>
<td>182</td>
<td>White and Black</td>
<td>Hypertensive</td>
<td>In black individuals, supine plasma aldosterone levels were positively correlated with night-time systolic and diastolic blood pressure levels ($P&lt;0.01$ and $P&lt;0.001$); in white individuals with obesity, supine plasma aldosterone levels correlated with night-time diastolic and systolic blood pressure levels ($P&lt;0.02$ and $P&lt;0.01$)</td>
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<td>Ljungman et al.147 (cross-sectional)</td>
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<td>Not given</td>
<td>Nonhypertensive and hypertensive</td>
<td>Plasma aldosterone and blood pressure levels were positively associated in individuals who were not on antihypertensive treatment ($P=0.02$)</td>
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<td>Tolagen et al.111 (cross-sectional)</td>
<td>120</td>
<td>Not given</td>
<td>Normotensive</td>
<td>No correlation was observed between aldosterone and blood pressure levels in normotensive individuals</td>
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<tr>
<td>Lamarre-Cliche et al.148 (cross-sectional/prospective)</td>
<td>57</td>
<td>Not given</td>
<td>Hypertensive</td>
<td>No association between aldosterone levels and blood pressure was found at baseline</td>
</tr>
</tbody>
</table>
aldosteronism, which reflects absolute aldosterone excess, would be in one end of this continuum, preceded by essential hypertension, normal-renin hypertension and, finally, low-renin essential hypertension (LREH). The findings that primary aldosteronism is highly prevalent in patients with LREH and that these patients are characterized by a strong blood pressure response to mineralocorticoid receptor blockade supports this concept. Furthermore, similar polymorphisms of CYP11B2 (the ALDOS gene) are found in patients with primary hyperaldosteronism and LREH. Moreover, two-thirds of patients with LREH are resistant to antihypertensive treatment probably because of Na⁺ retention by the kidney owing to an increased activity of Na⁺ channels in epithelial cells.

Of note, raised aldosterone levels are related to resistant hypertension. Lower plasma renin activity, higher aldosterone-to-renin ratio values and higher 24h urinary aldosterone levels were found in patients with resistant hypertension than in patients with normotension or patients with hypertension controlled with fewer than three antihypertensive medications. In a study of ambulatory blood pressure in patients with resistant hypertension despite antihypertensive treatment, 24h, night-time and daytime mean systolic blood pressure values were significantly higher in patients with elevated plasma aldosterone levels than in those with normal plasma renin activity and aldosterone in 24h urine samples.

Aldosterone excess is also strongly associated with insulin resistance and obesity. Therefore, aldosterone may contribute to the development of drug-resistant hypertension via direct hemodynamic effects, such as endothelial dysfunction, but also indirectly, for instance by impairing insulin metabolic signaling.

A small number of studies have obtained results that are inconsistent with the above reported evidence. In a study in normotensive individuals no significant correlation was found between plasma aldosterone and blood pressure levels. Other studies have found either no or an inverse correlation between plasma aldosterone levels and blood pressure in hypertensive white patients. These studies, however, have limitations: cross-sectional designs, small sample sizes, nonstandard conditions of aldosterone measurement (that is, no adequate control for posture, dietary salt intake and other confounding factors), single blood pressure measurements, and ongoing antihypertensive drug therapy.

### Ethnicity

Ethnic differences may account for the variety of roles of aldosterone in the development and pathogenesis of arterial hypertension. For example, the correlation of aldosterone, and particularly of the aldosterone-to-renin ratio, with blood pressure is reported to be stronger in black than in white individuals. Furthermore, in a cross-sectional analysis in hypertensive and normotensive African Americans higher aldosterone levels and lower plasma renin activity were found in hypertensive individuals, in whom systolic and diastolic pressures positively correlated with plasma aldosterone levels. Whether black individuals have different Na⁺-channel activity, or whether a higher frequency of relative aldosterone excess and/or salt-sensitive hypertension can be found in black populations remains to be elucidated.

### Table 2 | Studies reporting associations between aldosterone-to-renin ratio and arterial hypertension

<table>
<thead>
<tr>
<th>Study (study design)</th>
<th>Number of probands</th>
<th>Ethnicity</th>
<th>Blood pressure status</th>
<th>Key finding</th>
</tr>
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<tbody>
<tr>
<td>Newton-Cheh et al.⁷⁰ (prospective)</td>
<td>3,326</td>
<td>Not given</td>
<td>Nonhypertensive and hypertensive</td>
<td>Higher baseline ARR was associated with increased risk of blood pressure recategorization (P&lt;0.0001) and incident hypertension in nonhypertensives after 3 years of follow-up (P=0.05)</td>
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<tr>
<td>Gaddam et al.⁹⁵ (case-control)</td>
<td>279</td>
<td>White and Black</td>
<td>Resistant hypertensive</td>
<td>ARR levels were higher in patients with resistant hypertension than in normotensive and hypertensive controls (P&lt;0.0001)</td>
</tr>
<tr>
<td>Tomaschitz et al.⁹⁹ (cross-sectional)</td>
<td>3,056</td>
<td>White</td>
<td>Nonhypertensive and hypertensive</td>
<td>ARR was the second strongest independent predictor of mean systolic blood pressure and the strongest of mean diastolic blood pressure (P&lt;0.0001)</td>
</tr>
<tr>
<td>Lieb et al.⁹⁸ (cross-sectional)</td>
<td>2,000</td>
<td>Not given</td>
<td>Nonhypertensive and hypertensive</td>
<td>ARR was positively associated with mean arterial pressure levels (P&lt;0.0001)</td>
</tr>
<tr>
<td>Grim et al.¹¹⁴ (cross-sectional)</td>
<td>513</td>
<td>White and Black</td>
<td>Nonhypertensive and hypertensive</td>
<td>Among black individuals average daytime and night-time systolic and diastolic blood pressure levels were correlated with the ARR (P&lt;0.0005); in white individuals blood pressure levels did not correlate with the ARR</td>
</tr>
<tr>
<td>Lamarre-Cliche et al.¹¹⁵ (cross-sectional/prospective)</td>
<td>57</td>
<td>Not given</td>
<td>Hypertensive</td>
<td>No association between the ARR and blood pressure levels at baseline was found</td>
</tr>
<tr>
<td>Mahmud et al.¹¹⁶ (cross-sectional)</td>
<td>24</td>
<td>Not given</td>
<td>Hypertensive</td>
<td>ARR was positively correlated with aortic systolic blood pressure levels, but was not correlated with brachial blood pressure levels (P&lt;0.01)</td>
</tr>
</tbody>
</table>

Abbreviation: ARR, aldosterone-to-renin ratio.
Inhibition of aldosterone action
Mineralocorticoid-receptor blockade
Mineralocorticoid receptors have been viewed as useful targets for hypertensive therapy because of the crosstalk with angiotensin II and thereby their role in the control of aldosterone levels. In a transgenic mouse model, where the human mineralocorticoid receptor was overexpressed in cardiomyocytes, the adverse effects of angiotensin II infusion on cardiac remodeling were treated effectively by pharmacological mineralocorticoid-receptor antagonism. This finding indicates that the effects of the mineralocorticoid receptors are additive to those of angiotensin II.115 In rats mineralocorticoid-receptor blockade attenuates expression of vascular angiotensin II receptors independently of blood pressure and causes at least partial improvement of angiotensin-II-induced vascular pathology,116 while mineralocorticoid-receptor antagonism and ALDOS inhibition decrease hypertrophy and interstitial fibrosis of the kidney and heart caused by angiotensin II and high salt load.117

Mineralocorticoid-receptor blockers, administered as monotherapy or add-on therapy, are efficacious in the treatment of arterial hypertension, which provides strong evidence for the role of mineralocorticoid-receptor activation by aldosterone in the pathogenesis of this disease.118

Spironolactone
The first of these drugs to be brought to market, almost 50 years ago, was spironolactone. This drug was shown to effectively lower blood pressure in patients with LREH when used as monotherapy.119 In a head-to-head comparison, spironolactone lowered blood pressure as effectively as thiazide diuretics in patients with low renin levels and high aldosterone-to-renin ratio values.120 Spironolactone is also efficacious in patients with resistant hypertension, irrespective of prevailing aldosterone and renin concentrations.121 Furthermore, several studies have shown that spironolactone, even at very low doses, contributes to the lowering of blood pressure when used as fourth-line, add-on therapy in patients with resistant hypertension.122,123

The mechanism of action underlying the natriuretic effect of spironolactone, however, is not the only process by which this drug leads to a decrease in blood pressure, because spironolactone lowered blood pressure even in anuric patients on maintenance hemodialysis.124

Eplerenone
A second-generation mineralocorticoid-receptor blocker is eplerenone. In randomized, placebo-controlled trials, this drug effectively reduced blood pressure in patients with hypertension, including LREH,125 and even in patients with mild to moderate hypertension.126

Eplerenone was as effective as spironolactone in lowering blood pressure and was more effective than calcium-channel blockers,127 ACE inhibitors128 and angiotensin-II–receptor blockers,129,130 and other drugs frequently used to treat hypertension. Eplerenone is also useful as add-on therapy in patients with hypertension whose blood pressure is inadequately controlled by ACE inhibitors or angiotensin-II–receptor blockers alone.131

This drug has been shown in vitro to prevent cell stiffening and reduction of nitric oxide synthesis in endothelial cells and might, therefore, have a beneficial role in hypertensive patients with vascular remodeling.132

Prediction of outcomes
A prospective study showed that a raised aldosterone-to-renin ratio value at baseline was highly predictive for the efficiency of mineralocorticoid-receptor blockade with spironolactone,133 although another study did not confirm this finding.134 The aldosterone-to-renin ratio predicted the blood pressure response to mineralocorticoid-receptor blockade in previously untreated patients with hypertension, but it did not predict this response in patients already on a multidrug regimen.135 The fact that the lowering of blood pressure per se changes aldosterone and renin levels, even when the antihypertensive drugs used do not directly act on the RAAS, should be taken into account.

Adverse effects
Spironolactone use can be associated with hyperkalemia (defined as serum potassium >5.5 mmol/l) and sex-hormone-related adverse effects, dependent on dose and duration of therapy.136 The major advantage of eplerenone when compared with spironolactone is the lower frequency of gynecomastia associated with the use of the drug.137 Hyperkalemia during eplerenone treatment has been reported to occur in 0.8–4.2% of patients, but no clinical symptoms or complications associated with this physiologic state were observed.138 This result may not, however, reflect the increased risk in general practice for several reasons: serum potassium levels may be more closely monitored in clinical trials; conditions that favor the development of hyperkalemia, such as impaired renal function, might be more frequently overlooked in clinical practice; inappropriately high doses of mineralocorticoid blockers might be more often prescribed in clinical practice; combination with other antihypertensive drugs might increase the risk for hyperkalemia; and the fact that in clinical practice fasting potassium but not clinical practice; combination with other antihypertensive drugs might increase the risk for hyperkalemia; and the fact that in clinical practice fasting potassium but not postprandial serum potassium is usually measured.139 Several novel mineralocorticoid-receptor blockers or inhibitors of aldosterone synthesis are being developed and/or assessed.

Na+–channel blockers
Amiloride, a drug that blocks Na+–channel activity, can be considered as an indirect aldosterone inhibitor. In individuals with resistant hypertension, addition of amiloride to an antihypertensive drug regimen that included a diuretic led to a dose-dependent decrease in blood pressure.101 In African Americans with resistant hypertension, amiloride was associated with a greater blood pressure response than spironolactone alone.140 These drugs, given separately and in combination, effectively lowered blood pressure when administered as add-on therapy.140,141

Effects on the CNS and vasculature
Mineralocorticoid-receptor blockers may also decrease sympathetic drive via blocking aldosterone effects in the...
such ‘relative hyperaldosteronism’ provides a rationale for wider use of mineralocorticoid-receptor blockade, especially when other antihypertensive drugs control blood pressure insufficiently. Further studies are urgently needed to elucidate the role of relative aldosterone excess in increasing blood pressure, to evaluate the role of rapid aldosterone-mediated effects in long-term blood pressure rise and to investigate the interaction of salt and stress with aldosterone-mediated arterial hypertension and target organ damage.

**Review criteria**

A literature review of English-language articles published between 1975 and 2009 was performed in two independent MEDLINE searches. A third opinion was obtained when the results of the two searches differed. Search terms included “aldosterone”, “mineralocorticoid”, “aldosterone-to-renin ratio”, “blood pressure” and “hypertension”. Additional articles were obtained from the reference lists of these articles. Some particularly important studies for the field of aldosterone-associated hypertension published before 1975 were also included. Studies of patients with confirmed primary aldosteronism exclusively were not considered. Studies were selected according to quality and level of evidence. Some articles were not included owing to space restrictions.

Acknowledgments
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