Pathophysiology and Treatment of Resistant Hypertension: The Role of Aldosterone and Amiloride-Sensitive Sodium Channels

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Summary: Resistant hypertension is a clinically distinct subgroup of hypertension defined by the failure to achieve blood pressure control on optimal dosing of at least 3 antihypertensive medications of different classes, including a diuretic. The pathophysiology of hypertension can be attributed to aldosterone excess in more than 20% of patients with resistant hypertension. Existing dogma attributes the increase in blood pressure seen with increases in aldosterone to its antinatriuretic effects in the distal nephron. However, emerging research, which has identified and has begun to define the function of amiloride-sensitive sodium channels and mineralocorticoid receptors in the systemic vasculature, challenges impaired natriuresis as the sole cause of aldosterone-mediated resistant hypertension. This review integrates these findings to better define the role of the vasculature and aldosterone in the pathophysiology of resistant hypertension. In addition, a brief guide to the treatment of resistant hypertension is presented.
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Maintaining an appropriate arterial pressure is essential for human life. Over hundreds of millions of years, the processes responsible for regulating blood pressure (BP) have evolved to respond to challenges such as change in position, extremes in diet, changes in tissue demands, and acute blood loss. As a result, a complex communication and feedback network has developed to control BP. Since the discovery of renin by Goldblatt et al[1] in an animal model of hypertension, 2 primary regulators of BP, the renin-angiotensin-aldosterone system and the autonomic nervous system, have been identified.[2] Although the interaction of these systems in physiologic models of hypertension is still being debated, research continues to define each system's effects.[3,4] The vasculature, seen as a responder to both systems (ie, vasoconstriction in response to angiotensin II or norepinephrine), may have a direct role in the development of hypertension.[5–10] This article reviews the pathophysiology of hypertension that initially is resistant to medical therapy with a particular focus on aldosterone: its direct effect on the vasculature and the role of aldosterone blockade in the treatment of resistant hypertension.

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DEFINING RESISTANT AND PSEUDORESISTANT HYPERTENSION

Resistant hypertension is defined based on BP response to standard therapy, and identifies a group of high-risk patients who may benefit from specialized care, including evaluation and treatment of secondary causes of hypertension. The definition was established in an American Heart Association scientific statement as "BP that remains above goal despite optimal doses of 3 antihypertensive agents of different classes, one ideally being a diuretic."[11]

Resistant hypertension does not represent a single pathologic entity. Some individuals initially classified as resistant instead may have pseudoresistant hypertension, a distinction arising from limitations in BP measurement and management. Resistant individuals who have increased office BPs as a result of white-coat hypertension, improperly measured BPs, or medication nonadherence are reclassified as having pseudoresistant hypertension.[11,12] This difference is useful not only in identifying pathology, but also in predicting outcomes. Patients with true resistant BP have an increased risk of cardiovascular events including stroke, myocardial infarction, and end-stage renal disease.[13–16]

PATHOPHYSIOLOGY OF RESISTANT HYPERTENSION

Our understanding of the pathology and physiology of hypertension stems from animal models of

hypertension, genetic disorders of hypertension in human beings, kidney transplantation, computer models of BP physiology, and responses to pharmacologic therapy.[17] With few exceptions, all of these areas converge on the kidney as an active participant in the development of hypertension.

Based on computer models, Guyton and Coleman[18] concluded that the kidney's regulation of sodium excretion made up the critical pathway that determines the chronic level of intra-arterial pressure. The high gain (ie, the capacity to return any aberrant pressure back into normal control) of the renal function curve (pressure-natriuresis relationship) are posited in the long run to override any extrarenal mechanisms of BP control.[19] Under this theory, a rightward shifted renal function curve would be observed in all forms of hypertension; rightward shifts have been confirmed both in animal models of hypertension (spontaneously hypertensive rat, Goldblatt hypertension, aldosterone infusion, and angiotensin II infusion) and human hypertension (renovascular hypertension and primary aldosteronism).[18–20]

Perhaps the strongest support for the Guytonian theory of the pathophysiology of hypertension is its survival through more than 40 years of experimentation and discovery in the field of hypertension. Kidney transplantation in human beings along with studies of cross-transplantation in animal models provides compelling evidence in support of the underlying theory. In the study by Curtis et al,[21] 6 individuals with hypertension resulting in nephrosclerosis and kidney failure underwent bilateral nephrectomy and kidney transplantation from normotensive unrelated donors. After 4.5 years of follow-up evaluation, all 6 participants were normotensive and had evidence of reversal of hypertensive damage to the heart and retinal vessels.[21] Although the effects of bilateral renal denervation cannot be isolated from the return of a normal renal function curve, this study definitely identifies the kidney as a central mediator of human hypertension, and is consistent with kidney transplantation in animal models, in which BP nearly always follows the kidney.[22–24]

The mouse angiotensin type 1A (AT_{1A})-receptor knockout model is worth discussing in detail because it relates to our understanding of the pathophysiology of hypertension. In a cross-renal transplant model of AT_{1A}-receptor–deficient mice and their wild-type littermates, identical levels of BP reduction were seen in the mice with whole-body AT_{1A}-receptor deficiency plus intact kidney AT_{1A} receptors and mice with intact extrarenal AT_{1A} receptors plus deficient kidney AT_{1A} receptors.[21,22] The reduction in BP seen with a lack of whole-body AT_{1A} receptors was shown to be independent of aldosterone or sympathetic nervous system effects, suggesting that AT_1-receptor actions in systemic tissues such as the vascular and/or the central nervous systems make additional contributions to BP regulation.[21,22] Regulation of BP by the renin-angiotensin system is mediated both within and outside the kidney.

These same cross-renal transplant models were investigated in the setting of hypertension. Throughout 4 weeks of continuous infusion of angiotensin II, hypertension was sustained only in mice with intact kidney AT_{1A} receptors.[24] Therefore, angiotensin II causes hypertension primarily through AT_1 receptors in the kidney, which is consistent with Guyton's hypothesis.[18,19] The persistently low BP seen in mice without extrarenal AT_{1A} receptors can be explained by a leftward shift of the renal function curve, providing evidence for an extrarenal mechanism of adjusting the pressure natriuresis set point.

The pathophysiology of resistant hypertension also involves a rightward shift of the renal function curve. However, it offers specific phenotypes for which a cause of hypertension can be identified (Table 1). Resistance to standard pharmacologic therapies (ie, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, thiazide diuretics, β-blockers, α-blockers, central acting agents, and peripheral vasodilators) characterizes secondary forms of hypertension.[11] The majority of secondary causes of hypertension can be grouped by plasma renin activity level, with low-renin causes involving the distal nephron's handling of sodium either through dysfunction of the mineralocorticoid receptor (MR) or direct tubular pathology (ie, epithelial sodium channel [ENaC] or sodium chloride co-transporter) (Table 1). Rare (eg, glucocorticoid-remediable aldosteronism) and very rare (eg, Liddle's syndrome and familial hyperkalemic hypertension) secondary causes of hypertension have been well described.[17,25] Primary aldosteronism is a common secondary cause of hypertension with a prevalence among individuals with resistant hypertension ranging from 20% to 23%.[26,27]

ALDOSTERONE AND THE MINERALOCORTICOID RECEPTOR

Aldosterone is a mineralocorticoid produced in the zona glomerulosa of the adrenal cortex in response to angiotensin II, increased serum potassium, and corticotropin. Classically, it regulates total body sodium and potassium balance through genomic effects that follow binding and activating MR in the distal collecting duct of the kidney.[28–30] More recently, extrarenal effects of aldosterone have been described in vascular endothelial and smooth muscle cells.[5–10] The effects of aldosterone on vascular cells include inflammation, fibrosis, hypertrophic remodeling, endothelial stiffening, and oxidative stress, which are exacerbated in experimental animals on a high-salt diet.[10,31]

Similar to the AT_1 receptor, the extrarenal effects of aldosterone also may contribute to the control of systemic BP. Aldosterone excess is undoubtedly a