Systemic Hormonal Unloading (SHU) in Secondary Hypertension: Addressing the Long-Term Adverse Cardiovascular Outcomes

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ABSTRACT

Excess hormone production from adrenal tumors caused by primary hyperaldosteronism or pheochromocytoma are common etiologies for secondary hypertension. Studies have shown that sustained long-term circulating hormones in excess affect the blood vessels and cardiac structures. Inflammation of cardiomyocytes leads to fibrosis and eventual cardiomyopathy and is clinically presented as arrhythmia, nonfatal myocardial infarction, heart failure, or even death. The tissue changes and/or impaired cardiac function are reversible if early diagnosis and removal of the adrenal tumor by unilateral adrenalectomy is done. However, the condition becomes challenging if the adrenal lesions are bilateral. This article introduces the concept of *systemic hormonal unloading* and will discuss the philosophy of quality of life in managing bilateral adrenal disease.

Key words systemic hormonal unloading, secondary hypertension, primary hyperaldosteronism, pheochromocytoma, bilateral adrenal venous sampling, cardiovascular adverse outcomes, quality of life

INTRODUCTION

Secondary hypertension is a systemic vascular increase in blood pressure (BP) due to excess circulating hormones, particularly from a functioning adrenal adenoma.[1,2] Primary aldosteronism (PA) or Conn's syndrome and pheochromocytoma (PHEO) are known adrenal abnormalities that can secrete excess hormones like aldosterone and catecholamines, respectively, with hypertension as a prominent clinical presentation due to resulting sodium and water retention in PA and systemic vasoconstriction in PHEO.[3] Diagnosis is made through diagnostic measurement of excess circulating hormones and localization of tumors by imaging.[4,5] The successful removal of lesions leads to correcting hypokalemia in PA and normalizing blood pressure for both.[3-5]

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Academic editor: Dr. Warren R. Bacorro

Submitted date: March 3, 2024

Accepted date: March 30, 2024

In recent years, there have been reports on the evolution of clinical presentation of PA and PHEO. More severe and morbid cardiovascular disease (CVD) outcomes have been demonstrated at the outset of consults, like fatal arrhythmia, myocardial infarction, heart failure, and worst of all, death. [6,7] The direct effect of chronic excess circulating aldosterone and catecholamines on cardiomyocytes has been implicated, which results in edema, inflammation, myocyte fibrosis, and eventual cardiomyopathy.[6-14] If diagnosed early, removing the tumor with resolution of excess circulating hormones has been shown to decrease or normalize BP, reverse cardiac dyskinesia, and normalize cardiac function in PHEO.[13-17] Further, BP level and quality of life improvement in cases with bilateral adrenal lesions have been observed after systemic hormonal unloading with unilateral adrenalectomy for PA and PHEO.[15-20]

Systemic hormonal unloading (SHU) is a term our group introduced as a management approach for PA and PHEO where unilateral adrenalectomy for cases with bilateral lesions has improved BP, cardiovascular function, and quality of life.[15-20] Although much has been reported on long-term adverse CVD outcomes caused by excess circulating aldosterone and catecholamines with medical therapy alone that even influenced clinical practice guidelines, specifically in PA,[4] SHU as a specific treatment approach has yet to be elucidated. Therefore, this article aims to discuss and explore strategies for managing patients with primary hyperaldosteronism and PA, particularly those with bilateral adrenal lesions, with an emphasis on alleviating long-term adverse CVD outcomes and thus improving the quality of life.

Clinical Presentations, Diagnosis, and Management of Primary Aldosteronism and Pheochromocytoma

PA is the excess production of the hormone aldosterone from the zona glomerulosa of the adrenal glands, with a prevalence rate ranging from 4.6% to 9.5% among hypertensive individuals. [1,2,21] The highly circulating aldosterone results in hypokalemia, leading to weakness, tingling, muscle spasms, and periods of temporary paralysis. Bilateral adrenal hyperplasia and aldosterone-producing adrenal tumors are the most common causes of PA.[3]

Pheochromocytoma (PHEO), on the other hand, is a rare adrenomedullary tumor with an incidence of 0.1% to 0.6%.[1,2,22] Mortality is high and about 0.05% to 0.1% of PHEO cases are undiagnosed in autopsy studies.[22–24] These tumors can synthesize, metabolize, store, and secrete catecholamines and their metabolites.[25] PHEOs originate from adrenomedullary chromaffin cells that commonly produce epinephrine, norepinephrine, and dopamine. Chromaffin cells evolve into 80% to 85% PHEOS and 15% to 20% as paragangliomas. [6] A high index of clinical suspicion remains the pivotal point to initiate biochemical studies, particularly in those patients with a specific pattern of spells, BP elevation (paroxysmal or alternating with hypotension), drug-resistant hypertension, sudden palpitations (in some patients accompanied by pallor), unexplained sweating, especially during the night or in cold weather, unexplained hyperglycemia, and a hereditary predisposition for PHEO.[3,5,6,15,25] Bilateral PHEO is commonly seen among those with syndromic abnormalities. [26] Because PA and PHEO are caused by excess secretion of hormones from functional adrenal tumors that can produce an elevation of BP, the entity is also called adrenal hypertension.[3]

Localization of adrenal tumors follows only after a positive biochemical and hormonal work-up.[4,5] The current imaging modalities include anatomical (CT and MRI) and functional (molecular) imaging procedures using various radiopharmaceutical tracers, depending on the clinical situation.[4-6,25] Resolution of hypokalemia in PA with either normalization of BP or decrease in the number of antihypertensive medications in both PA and PHEO after unilateral adrenalectomy signals therapeutic success.[3-5,15-19] For equivocal imaging results, bilateral adrenal venous sampling (BAVS) is the "gold standard" to distinguish unilateral from bilateral lesions in PA.[4] Although BAVS has been performed to diagnose and localize PHEO, it is not part of a clinical practice guideline.[15-17]

Long-Term Adverse Cardiovascular Outcomes of Chronically Systemic Increase in Circulating Aldosterone and Catecholamines

Delay in the diagnosis and treatment of PA and PHEO has been shown to result in long-term

untoward cardiovascular (CV) complications, namely myocardial infarction, stroke, fatal arrhythmias, chronic kidney disease, and death.[6-14] In 2005, Milliez and colleagues reported that patients presenting with PA experienced more cardiovascular events like nonfatal myocardial infarction and atrial fibrillation than those with essential hypertension. [8] With a bigger controlled population of subjects, Savard and his group reported that PA patients had a significantly higher prevalence of coronary artery disease (adjusted odds ratio, 1.9), nonfatal myocardial infarction (adjusted odds ratio, 2.6), heart failure (adjusted odds ratio, 2.9), and atrial fibrillation (adjusted odds ratio, 5.0). The prevalence of electrocardiographic and echocardiographic left ventricular hypertrophy was about twice as high in patients with PA, even after adjustment for hypertension duration.[10]

Sztechman, et al. have elaborated on the pathogenesis of the long-term adverse effect of increased circulating aldosterone.[12] Physiologically (Figure 1), through aldosterone binding with mineralocorticoid receptors (MRs), the reaction causes activation of several intracellular pathways and MR-dependent rapid genomic and non-genomic effects. Angiotensin II (Ang II), a cleavage product from angiotensinogen produced by the actions of renin and angiotensin-converting enzyme (ACE), binds to AT1Rs and AT2Rs (angiotensin 1 and 2 receptors) and leads to activation of AT1Rs in the adrenal cortex, which in turn stimulates synthesis and release of aldosterone. Aldosterone upregulates the

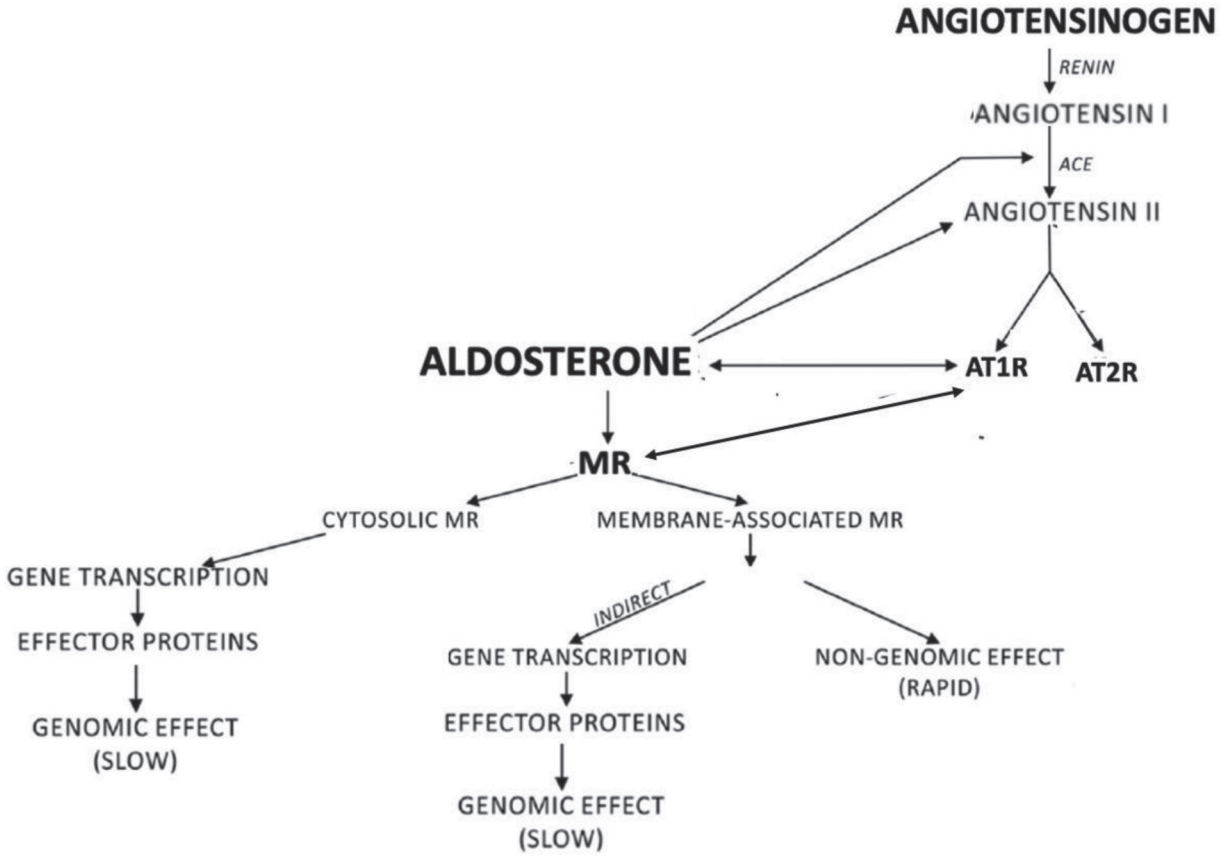

Figure 1. Physiologic aldosterone interaction with renin-angiotensin system and consequence in binding with mineralocorticoid receptor (MR). Angiotensin II (Ang II) is cleaved from angiotensinogen and angiotensin I by actions of renin and angiotensin-converting enzyme (ACE), respectively. Ang II binds to AT1Rs and AT2Rs. Activation of AT1Rs in the adrenal cortex stimulates synthesis and release of aldosterone. Aldosterone upregulates expression of AT1Rs, AT2Rs and ACE, and enhances binding of Ang II to AT1Rs increasing thereby activity of the renin-angiotensin system. The cross-talk between aldosterone and Ang II reciprocally potentiates effects of both hormones on remodeling of the cardiovascular system. Aldosterone binds either to cytosolic or to cell membrane-associated MRs. The activation of cytosolic MRs leads to gene transcription and synthesis of proteins and enzymes. Binding of aldosterone to MRs associated with the cell membrane causes activation of several intracellular pathways and MR-dependent rapid non-genomic effects as well as delayed changes in the gene expression. Partially adapted from Sztechman D, Czarzasta K, Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Zera T. J Physiol Pharmacol. 2018;69. DOI: 10.26402/jpp.2018.6.01.

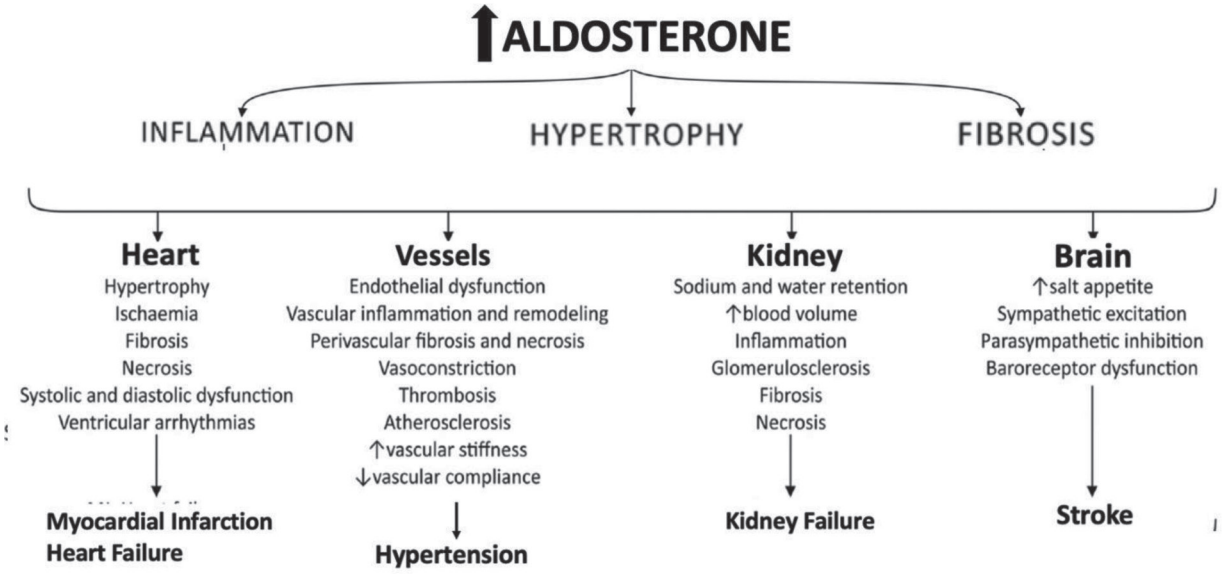

Figure 2. Increased aldosterone in pathological remodeling of the cardiovascular system. Activation of varied mediators and mechanisms leads to functional and morphological changes in the heart, vessels, kidneys and the brain that eventually result in atherosclerosis, myocardial infarction, heart failure, hypertension, renal insufficiency and stroke. The aldosterone-induced processes associated with the development of hypertension, in turn augments pathological changes in the cardiovascular system. Partially adapted from Sztechman D, Czarzasta K, Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Zera T. J Physiol Pharmacol. 2018;69. DOI: 10.26402/jpp.2018.6.01.

expression of AT1Rs, AT2Rs, and ACE and enhances the binding of Ang II to AT1Rs, thereby increasing the renin-angiotensin system's activity. Some non-genomic effects of aldosterone are independent of MRs and overlap with AT1R signaling pathways. The cross-talk between aldosterone and Ang II reciprocally potentiates the effects of both hormones on the remodeling of the cardiovascular system.[12] Pathologically (Figure 2), aldosterone promotes the development of inflammation, hypertrophy, and fibrosis of cardiovascular structures. Activation of varied mediators and mechanisms leads to functional and morphological changes in the heart, vessels, kidneys, and brain that eventually result in atherosclerosis, myocardial infarction, heart failure, renal insufficiency, and stroke. Aldosterone-induced processes are associated with the development of hypertension, which in turn augments pathological changes in the cardiovascular system.[12]

A similar finding of adverse cardiovascular events has been reported by Stolk, et al. in patients with PHEO.[27] Although blood pressure was significantly lower among PHEO patients compared with subjects with essential hypertension (153/91+35/15 mmHg vs. 170/103+18/8 mmHg, respectively, $p<0.02$), a significantly higher rate of patients with PHEO suffered a cardiovascular event as compared to hypertensive patients ((13.8% vs. 1.1%, respectively, $p<0.001$), the difference in event rates could not be attributed to differences in other cardiovascular risk factors.[27] Our group has elucidated the evolution of PHEOs clinical presentation with a summary in Figure 3.

Hypercatecholaminemia has been associated with takotsubo syndrome, a reversible cardiac condition characterized by acute left ventricular dysfunction.[28-30] The cardiomyocyte inflammation leads to eventual fibrosis and cardiomyopathy.[13,14,28-30] Using cardiac magnetic resonance imaging, Ferreira and her group demonstrated persistence of focal cardiomyocyte fibrosis even with normalization of the left ventricular ejection fraction after removal of the adrenal PHEO. Notably, the systolic and diastolic strain rate remained abnormal even after curable surgery of PHEO compared with healthy controls.[30] Further, the groups of Templin and Sharma have respectively, reported that patients with takotsubo cardiomyopathy have a higher prevalence of neurologic or psychiatric disorders than those with acute coronary syndrome and with a high burden of mortality (19.7% to 27.8%), contributing to significantly high mortality in patients

Parameter	Clinical Features
Age (years)	20's to 40's
Signs and symptoms	Headache, agitations, diaphoresis, nausea, vomiting
	Acute coronary syndrome
	Severe congestive heart failure
	Arrhythmia
Laboratory	Elevated creatine kinase
	Normal to elevated troponin
Imaging	Normal angiogram
	Dyskinesia, hypokinesia, akinesia by 2D Echo
	Diffuse myocardial edema by cardiac MRI
	Postoperative persistence of myocardial fibrosis
Clinical outcome	Resolution of signs and symptoms after adrenalectomy
	Normalized LV function and ejection fraction
	Persistent systolic and diastolic impairment
	Death

Figure 3. Dramatic clinical presentations, laboratory and imaging findings, and clinical outcomes of patients with unsuspecting pheochromocytoma. Adapted from: Mercado-Asis LB, Siao RMS, Amba NFA. J Med UST. 2017;1. DOI 10.35460/2546-1621

afflicted with COVID-19.[28,29] During long-term follow-up, the rate of major adverse cardiac and cerebrovascular events was 9.9% per patient-year, and the rate of death was 5.6% per patient-year. [28]

Systemic Hormonal Unloading (SHU): Quality of life in addressing the challenge of long-term sustained increased circulating aldosterone and catecholamines in bilateral PA and PHEO

It is now apparent that long-term sustained elevation in the levels of aldosterone and catecholamines will lead to irreversible cardiovascular system damage.[9-12,27-30]. Likewise, there is substantial morbidity and mortality in the long-term course. [28] The primary concern lies in cases with bilateral

lesions. Nonetheless, quality of life has been shown to improve after unilateral adrenalectomy in PA, and PHEO patients with bilateral adrenal tumors or hyperplasia.[18,20] Sukor and colleagues have shown improvement in BP in 15% to 20% of their cases. As the aldosterone-renin ratio normalized, the diastolic BP and left ventricular mass index decreased. A similar observation has been reported by our group (Gomez, et al.).[19] The patient, diagnosed with bilateral PA by adrenal venous sampling (AVS), eventually underwent unilateral adrenalectomy after unsuccessful eplerenone therapy with an intolerability issue.[19] Tang and colleagues have recently reported that dose-dependent side effects limit the efficacy of medical therapy in PA.[31]

On the other hand, Zhou, et al. reported that in their patients diagnosed with multiple endocrine neoplasia (MEN) with multiple foci of PHEO, bilateral adrenalectomy or tumor enucleation resulted in patients' improvement of the quality of life.[20] Similarly, our group has demonstrated that in our patients with bilateral PHEO, systemic hormonal unloading by unilateral adrenalectomy significantly decreased the BP of patients with resolution of multisystem adrenergic-associated symptoms such as palpitations, headache, nausea, vomiting, insomnia, and attacks of severe anxiety.[17]

SUMMARY AND INSIGHT

The clinical evolution of PA and PHEO from simple BP elevation to long-term cardiovascular system complications has been demonstrated to result from sustained elevation in the circulating aldosterone and catecholamines, respectively. SHU is a promising approach of management and has been shown to benefit affected individuals with bilateral adrenal lesions through unilateral or bilateral adrenalectomy or tumor enucleation, leading to improvement in the quality of life with significant resolution of associated symptoms.

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