

# Aldosterone: The Giraffe in the Room

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The idiom “elephant in the room” refers to an obvious challenge or controversy that people avoid discussing, due to discomfort or disquietude. A similar situation prevails in modern day blood pressure management.

The giraffe enjoys special status, not only in existential evolution, but in sociocultural symbolism as well. Its unique biology sets it apart from other land mammals. A large-sized heart (weighing up to 11 kg, as opposed to the human’s 250 g), generates a systolic blood pressure (BP) of up to 300 mmHg, setting them apart from all other mammalian species which survive and thrive on a systolic BP of 120 mmHg. Jugular veins with elastic walls and specialized valves ensure BP maintenance in varied postures<sup>1</sup>. We explore, in this editorial, the giraffe in the room.

Fifty years have passed since the first national report on hypertension (HT) management<sup>2</sup>. Though the situation has improved markedly, as compared to the ante-World War II period, when high BP was considered a beneficial, compensatory mechanism, BP control still remains a challenge. Awareness about BP, and its control, are far from optimal.

One reason is the difficulty in identifying the etiology of HT. While most cases of high BP are considered ‘primary’ or essential in nature, an increasing number of patients are now identified as being secondary to a specific cause<sup>3</sup>. More often than not, these conditions are endocrine in nature. Advances in evaluation and interpretation of endocrine analytes have facilitated identification of endocrine HT.

The renin-angiotensin-aldosterone system (RAAS) is a homeostatic reno-adrenal axis, which regulates BP through salt and water retention<sup>4</sup>. Evolved as an adaptive mechanism, to allow survival on land, RAAS hyperactivation may lead to vasopressor dysregulation. This is termed as primary hyperaldosteronism (PA). It is not a black-or-white diagnosis. Rather, PA represents a wide spectrum of disease, associated with an equally wide range of adrenal biochemistry, imaging and histopathology<sup>5,6</sup>. Though we are able to recognize these patterns in an increasing proportion of patients with high BP, a globally accepted definition of PA still eludes us. This, we feel, is the giraffe in the room.

Indian researchers have highlighted the importance of screening for hyperaldosteronism in patients with uncontrolled HT and high-risk vascular phenotypes, e.g., persons with hypokalemia, sleep apnea, atrial fibrillation, and a strong family history of HT. Modern guidelines in fact, suggest that every person with HT be screened at least once in a lifetime for PA<sup>7-9</sup>. The techniques and tools for doing so, however, are poorly defined. One reason for this has been the complexity and cost of screening for aldosterone and renin. Another explanation, however, may have been the lack of effective and efficient treatment modalities for dysregulated aldosterone physiology.

Captopril, which was developed from the venom of Brazilian pit viper (*Bothrops jararaca*), was granted patent in 1977, and approved for medical use only in 1980. The development of other angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has allowed achievement of BP targets in many. Aldosterone breakthrough, however, prevents all persons from attaining normal aldosterone levels. Mineralocorticoid receptor antagonists do provide added efficacy, but are unable to prevent the nongenomic effects of aldosterone on vascular health. Renin antagonists, such as aliskiren, have been discontinued because of unacceptable adverse effects.

The expected approval of aldosterone synthase inhibitors, such as baxdrostat<sup>9</sup>, however, now allows us to tackle the giraffe in the room. The Bax24 and BaxHTN trials have demonstrated the efficacy, safety, and tolerability of baxdrostat in the management of high BP<sup>10,11</sup>.

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While the terms resistant and refractory HT have been in use, uncontrolled or difficult-to-control BP expands the spectrum of use of this, and other drugs.

Along with progress in pharmaceuticals, advances in academics are essential. Enhanced emphasis on the expansive epidemiology, etiology, and evaluation of HT, with focus on aldosterone physiology, is essential. This can improve outcomes, not only in terms of systolic and diastolic BP numbers, but also cardiovascular, renal, and metabolic health.

The majestic giraffe is a farsighted creature. Taking inspiration from it, we can use modern medication to catch aldosterone, metaphorically, by the neck. This will help us achieve better BP control, in a physio-friendly, person-friendly manner.

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