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Research Article

Aldosterone as a mediator of microvascular and macrovascular damage in a population of normotensive to early-stage hypertensive individuals

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Abstract

We investigated whether aldosterone concurrently mediates microvascular and macrovascular impairment, in a population of treatment-naïve young- to middle-aged individuals free from cardiovascular comorbidities. Newly diagnosed, never-treated essential hypertensive patients and normotensive individuals participated in the study. Pulse wave velocity (PWV) and augmentation index were estimated with applanation tonometry. Microalbuminuria was determined from 24-hour urine collections. Laboratory tests included measurement of plasma renin activity, serum aldosterone, and high-sensitivity C-reactive protein. In 221 individuals aged 42.0 ± 12.3 years, classification in the highest aldosterone tertile was associated with the highest levels of blood pressure (BP), PWV, and high-sensitivity C-reactive protein ($P < .05$ for all). These individuals also exhibited twice the prevalence of microalbuminuria, compared to the first tertile ($P = .081$). Multivariate analysis showed that the positive association between PWV and increasing aldosterone tertiles remained significant after adjustment for BP and other parameters ($P = .035$). Likewise, aldosterone independently predicted microalbuminuria ($P = .026$) in the logistic regression analysis. In treatment-naïve individuals whose BP ranges from normal to early-stage hypertension, significant interactions exist between aldosterone and indices of microvascular and macrovascular damage. These findings suggest that aldosterone concurrently modulates microvascular and macrovascular function from the very early stages of essential hypertension and is dynamically implicated in the pathogenesis of hypertensive vascular disease. J Am Soc Hypertens 2017;■(■):1–8.

Keywords: Arterial stiffness; hypertension; microalbuminuria.

Introduction

Aldosterone is a key steroid hormone with mineralocorticoid activity released in response to angiotensin II, whose classical role is to regulate body fluid balance, potentiating sodium reabsorption and potassium excretion at the distal convoluted tubule and the collecting duct of the kidney. Other than that, aldosterone exerts pleiotropic effects on the cardiovascular system, mainly at the level of the heart and the vasculature, either indirectly through extracellular volume overload or directly through genomic and nongenomic effects via its binding to mineralocorticoid and other receptors present in cells throughout the vasculature (myocardial cells, endothelial, mesangial, and smooth muscle cells).[1,2] The pleiotropic prooxidant, proinflammatory, and profibrotic effects of aldosterone that trigger endothelial dysfunction, oxidative stress, inflammatory processes, fibrosis, and hypertrophic vascular remodeling have been described in various experimental models of hypertension.[3]

On a clinical basis, the role of aldosterone in cardiovascular remodeling is emphasized in patients with primary aldosteronism, which is the clinical expression of aldosterone overproduction. Compared to patients with essential hypertension, patients with primary aldosteronism experience

Conflict of interest: None.

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more cardiovascular events.[4] Furthermore, a recent meta-analysis of case–control studies confirmed that primary aldosteronism is associated with a higher degree of subclinical vascular damage, evidenced by accelerated atherosclerosis, impaired endothelial function, and increased arterial stiffness.[5] On the contrary, it remains under investigation whether relative aldosterone overexpression, even within the normal range, contributes to subclinical vascular damage from the very early stages of essential hypertension.

Macrovascular changes, mainly large artery stiffening, play a central role in the pathophysiology of hypertension. Increased arterial stiffness, due to functional and structural changes of the arterial wall, involves mainly dearrangement and loss of elastin fibers and replacement by collagen.[6] The microvasculature is typically affected in the course of hypertension as well. At the renal microvascular level, microalbuminuria is a marker of early intrarenal vascular dysfunction and corresponds to a state of generalized microvascular impairment in hypertensive patients.[7] A continuous relationship of increased urinary albumin loss with cardiovascular risk exists, even below the threshold values usually considered for microalbuminuria.[8] Both arterial stiffness[9] and microalbuminuria[10] are potent predictors of future cardiovascular events in hypertensive patients and the general population, while their presence in normotensive individuals denotes increased likelihood of incident hypertension in initially normotensive individuals.[11,12] However, only a small number of studies have attempted to investigate whether and to which extent these conditions are associated with aldosterone levels, especially in the initial stages of essential hypertension or even in normotensive individuals.

Hence, the aim of the present study was to investigate whether aldosterone levels are concurrently associated with impaired microvascular and macrovascular function, evidenced by increased urinary albumin loss and arterial stiffness, respectively, in a population of young- to middle-aged individuals free from cardiovascular comorbidities, whose blood pressure (BP) ranged from normal to early-stage essential hypertension.

Methods

The study population consisted of individuals who attended our Outpatient Clinic either because of reported increased BP or for their regular check-up appointments, who wished to have their BP measured and receive counseling. Individuals were asked to participate provided they did not receive any antihypertensives or other types of medication currently, and they had never been previously treated with antihypertensive agents. Patients with secondary causes of hypertension and other comorbidities, including acute illness, endocrine diseases, diabetes, renal disease, arrhythmias, cardiac and peripheral vascular diseases, were excluded from the study. Absence of such comorbidities was verified through history, medical examination, and laboratory tests. The study was conducted in accordance with the principles of the Helsinki declaration and was approved by the Institutional Ethics Committee. All patients were Caucasian adults and gave their written informed consent prior to enrollment.

Office BP was measured in the sitting position in both arms using a validated oscillometric device (Microlife Exact BP, Microlife AG, Widnau, Switzerland) and was determined as the mean of the second and third value of three consecutive measurements with a 2-minute interval in the arm with the higher BP. Essential hypertension was defined as systolic and/or diastolic BP (SBP/DBP) higher than 140/90 mm Hg according to the guidelines.[13]

Assessment of Arterial Stiffness and Wave Reflections

The technique of applanation tonometry with the Sphygmocor device (AtCor Medical, Sydney, Australia) was applied for the assessment of carotid-femoral pulse wave velocity (PWV), as a robust marker of arterial stiffness, and augmentation index (AIx), as a measure of wave reflections. In particular, a micromanometer-tipped probe (Millar instruments) was used to detect the radial pulse waveform. The artery was compressed between the underlying structures and the probe, and the intraarterial pressure was transmitted through the arterial wall to the sensor of the probe. The radial pressure waveform was used to estimate the aortic pressure waveform, and AIx was calculated as the increased systolic pressure (due to the reflected wave) divided by pulse pressure. Because AIx is influenced by heart rate, we used AIx adjusted to a standard rate of 75 bpm for our analysis.[14] Only high-quality recordings, defined as an in-device quality operator index of >90% and acceptable curves on visual inspection, were included in the analysis.

The aortic carotid-femoral PWV was measured according to a standard protocol, during which sequential recordings of the pulse wave were obtained in the carotid and femoral artery. An electrocardiogram was simultaneously recorded to synchronize the carotid and femoral pulse wave times and calculate wave transit time. The distance traveled by the pulse wave was calculated from the difference between the distances from sternal notch to the recording sites (sternal notch to carotid site and sternal notch to femoral site). PWV was calculated as the distance traveled by the pulse wave divided by time (PWV = $\Delta d/\Delta t$), with higher levels indicating greater arterial stiffness.[15] Procedures were performed after a 15-minute resting period in the supine position in a quiet room. Participants were advised to abstain from caffeine, smoking, alcohol, and intense physical activity for at least 12 hours before assessment of arterial properties.