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CARDIOVASCULAR CONSEQUENCES IN PRIMARY ALDOSTERONISM

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ABSTRACT

Aldosterone, beyond its fundamental role in maintaining water, sodium, and potassium balance, significantly impacts cardiovascular physiology and pathology. Excess aldosterone contributes to endothelial dysfunction, promotes inflammatory cell infiltration, and accelerates the progression of atherosclerosis by increasing plaque instability, arterial stiffness, and calcification. At the cardiac level, it exacerbates inflammation, fibrosis, and myocardial hypertrophy. Clinically, elevated aldosterone levels correlate with a higher risk of cardiovascular events and mortality, particularly in conditions like primary aldosteronism, where its secretion is dysregulated relative to renin levels and sodium intake. Clinical studies indicate that mineralocorticoid receptor antagonists (MRAs) effectively lower cardiovascular mortality in individuals with heart failure with preserved ejection fraction, but the effects on myocardial infarction and atrial fibrillation remain less clear. In cases of primary aldosteronism, treatments like adrenalectomy or MRAs significantly reduce cardiovascular risks, including mortality and atrial fibrillation. This review compiles key preclinical and clinical research on the detrimental cardiovascular effects of aldosterone and the protective role of MRAs in managing cardiovascular disease and primary aldosteronism.

KEYWORDS: Aldosterone, vascular system, left ventricular hypertrophy, heart failure, arrhythmias.

INTRODUCTION

Aldosterone is the main mineralocorticoid hormone secreted by the zona glomerulosa of the adrenal cortex, whose production is controlled by the Renin-Angiotensin System (RAS) and extracellular potassium, and to a lesser extent by Adrenocorticotropic Hormone (ACTH).[1] Aldosterone exerts its effects through two main mechanisms: I) genomic mechanism (slow, long-term effects), and non-genomic mechanism (fast, short-term effects). The first mechanism mediates its effects through the activation of mineralocorticoid receptors, while the second mechanism does so through the activation of a membrane protein binding aldosterone with high affinity for aldosterone, GPR30 (G-protein–coupled receptor 30). These two mechanisms work together to regulate blood pressure, electrolyte balance, and cardiovascular function, but excess aldosterone contributes to conditions like hypertension, heart failure, and fibrosis. Overproduction of aldosterone may result from increased activity of the renin-angiotensin system because of hypovolemia (as occurs in heart failure or ascites), or independent production of aldosterone by renin (as occurs in the broad spectrum of primary aldosteronism, varying from mild forms to overt primary aldosteronism).[2] Beyond its well-known effects on renal tubular epithelium, aldosterone also plays a role in regulating various physiological and pathological processes in extrarenal organs. Over the past two decades, its role in vascular function and disease progression-particularly in conditions like hypertension, atherosclerosis, and heart failure, has become increasingly evident. The excessive activation of mineralocorticoid receptors is particularly associated with increased cardiovascular damage, contributing to a higher risk of cardiovascular events and mortality.[3] Several studies have consistently shown that aldosterone exerts an independent effect on blood pressure regulation, leading to various forms of cardiovascular damage. This includes left ventricular hypertrophy, fibrosis, vascular remodeling, and arterial stiffening, which have been observed in both animal models and human subjects.[4] In a notable 2005 study by Milliez et al., the prevalence of stroke was found to be higher in 124 patients with primary aldosteronism (PA) compared to 456 matched patients with essential hypertension (EH).[5] Similarly, a study by Catena et al. in 2010 compared 54 PA patients to 323 EH patients over a 7-year follow-up period, revealing that PA patients had a greater incidence of stroke than their EH counterparts.

This review provides an overview of the underlying mechanisms by which aldosterone contributes to cardiovascular damage, from both preclinical and clinical perspectives. Additionally, we summarize key findings from major studies that have examined the role of mineralocorticoid receptor antagonists (MRAs) in the treatment and prevention of cardiovascular diseases.

Adverse Effects of Aldosterone on Vascular System

Aldosterone has been found to influence vascular function by regulating factors such as contractility, cell growth, and apoptosis. In animal studies, aldosterone's effects on endothelial cell (EC) growth and vasoregulatory activity were observed through the activation of G protein-coupled estrogen receptor (GPER) in rats.[7] Additionally, aldosterone interacts with angiotensin II (Ang-II), promoting apoptosis in rat microvascular endothelial cells by increasing protein tyrosine phosphatase 1B (PTP1B) expression and inhibiting the PI3K/Akt pathway. In vitro research has also shown that aldosterone contributes to the synthesis of collagen and fibrosis in vascular smooth muscle cells (VSMCs) in mice.[8]

Excessive aldosterone is widely recognized for causing increased arterial stiffness due to morphological and functional abnormalities of the vessel walls. Arterial stiffness refers to the decreased ability of arteries to expand, resulting from a combination of active stiffness, which is driven by the contraction of smooth muscle cells, and passive stiffness, which occurs due to changes in the structural components of the vascular wall.[9] This includes changes such as increased carotid intima-media thickness (CIMT) and impaired endothelial function. Animal studies have shown that aldosterone enhances arterial stiffness by influencing both the active component, which is driven by smooth muscle contraction, and the passive component, resulting from changes in the structural properties of the vascular wall.[10] Aldosterone directly increases active stiffness by enhancing vascular myogenic tone and promoting agonist-induced contraction. It also contributes to passive stiffness through significant changes in gene expression within the vascular tissue, as demonstrated in ex vivo studies of mouse aortas.[9,10]

Aldosterone promotes oxidative stress, which leads to endothelial dysfunction, collagen remodeling, and reduced nitric oxide (NO) availability, all of which contribute to vascular stiffness and fibrosis. Endothelial dysfunction is one of the initial stages of vascular atherosclerosis, resulting from the impairment of nitric oxide (NO)-mediated vasodilation.[11] Endothelial progenitor cells in circulation contribute to endothelial function by promoting repair and adjusting the balance of endothelial NO synthase (eNOS) activity.[12] In individuals with primary aldosteronism (PA), the number of these progenitor cells is reduced compared to those with essential hypertension (EH), and their levels are inversely correlated with plasma aldosterone concentrations.[13] Studies have shown that patients with primary aldosteronism (PA) exhibit higher CIMT and arterial stiffness compared to those with essential hypertension (EH), even when blood pressure levels are similar.[14]

Moreover, aldosterone excess has been linked to impaired endothelial progenitor cell (EPC) function, including decreased vascular elasticity, proliferation, differentiation, and migration in PA patients. The loss of EPCs may contribute to increased aortic stiffness and vascular damage. Additionally, endothelial inflammation plays a role in the negative remodeling of cerebral blood vessels, making them less flexible and impairing their ability to dilate during a stroke.[15] Notably, pronounced fibrosis in small resistance arteries has been observed in PA patients when compared to blood pressure matched EH patients.[16]

Adverse Effects of Aldosterone on the Heart

Hypertensive conditions often lead to both structural and functional heart abnormalities.[17] Around 14 to 35% of patients with Primary Aldosteronism (PA) face cardiovascular complications, including myocardial hypertrophy, myocardial fibrosis, coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF).[18,19,20] Furthermore, extensive research across different regions has shown that, among patients with hypertension of similar severity and duration, those with PA tend to experience more cardiovascular complications than those with essential hypertension.[21] Experimental and clinical studies have also demonstrated that cardiomyocytes and cardiac fibroblasts express mineralocorticoid receptors (MR), which have a strong affinity for aldosterone and can be activated by elevated levels of the hormone. The following discussion will focus on how aldosterone contributes to left ventricular hypertrophy (LVH), CAD, HF, and arrhythmias.[6,22]

- **Left Ventricular Hypertrophy**

In various clinical studies, it has been observed that cardiac remodeling processes, including left ventricular hypertrophy (LVH) and myocardial fibrosis, are more pronounced in patients with primary aldosteronism (PA) than in those with essential hypertension (EH). Left ventricular hypertrophy is the most prominent finding in patients with primary aldosteronism (PA), independent of blood pressure levels. It occurs up to twice as frequently in this patient group, as assessed by electrocardiogram (ECG) or echocardiography.[5,23] Under the influence of different stimuli, including aldosterone, changes occur in cardiomyocytes and non-myocyte resident cells, which can lead to alterations in heart size, mass, geometry, and cardiac function, culminating in LV remodeling. The consequences of LV remodeling may include systolic or diastolic dysfunction of the left ventricle, progressing to heart failure, atrial fibrillation, and various life-threatening arrhythmias.[24] Animal studies have demonstrated that chronic elevations in aldosterone, coupled with high salt intake,

lead to a greater extent of left ventricular hypertrophy (LVH) and cardiac fibrosis.[25] One key finding by Catena et al. was that urinary sodium excretion is linked to the degree of LV reverse remodeling following both medical and surgical treatments in PA patients.[26] These studies underscore the significant role of dietary salt intake in LV remodeling processes, even after successful treatment of PA.

The findings that confirm the hypertrophic effects of aldosterone on the myocardium are numerous, including those of Brilla et al.,[27] who showed that aldosterone, through the increase of mRNA levels for α- and β-myosin heavy chains, can directly stimulate hypertrophy of cardiomyocytes in rats. This occurs either through the activation of mineralocorticoid receptors (MR), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, and protein kinase C-α.[27] In the study conducted by Gros et al.,[28] it was shown that aldosterone mediates the phosphorylation of the myosin light chain in a dose-dependent manner, which was inhibited by an MR antagonist and phosphatidylinositol 3-kinase (PI3K) inhibition. Another finding is the increased level of the cytokine cardiotrophin-1 (CT-1) in the cardiomyocytes of rats with aldosterone infusion and high salt intake, which influences the increase in the expression of myosin light chain and skeletal α-actin, thereby improving the phosphorylation of the myosin light chain.[29] Aldosterone has been found to induce left ventricular hypertrophy (LVH) in wild-type mice, whereas mice lacking cardiotrophin-1 (CT-1) exhibit resistance to LVH and fibrosis induced by aldosterone.[29] In several clinical studies, it has been reported that in patients with PA, both the wall thickness and dimensions of the LV are increased, with greater average thickness of the interventricular septum and posterior wall compared to patients with EH.[30,31] Other studies have shown that patients with PA had reduced diastolic function and increased LV wall thickness, independent of blood pressure values.[32] In the study conducted by Chen et al., it was demonstrated that patients with PA not only have LV abnormalities but also right ventricular dysfunction.[33]

- **Coronary Artery Disease**

Coronary artery disease (CAD) in patients with hyperaldosteronism is not only result of aldosterone's damaging effect on blood vessels but also the role it plays in cardiovascular risk factors through various biochemical mechanisms. Elevated production of cardiac aldosterone has been linked to a higher risk of myocardial infarction (MI), and in turn, MI can increase aldosterone synthase mRNA (the final enzyme in aldosterone synthesis) and aldosterone levels in rats. Aldosterone has also been shown to induce a vascular inflammatory phenotype in the rat heart, significantly raising cyclooxygenase 2 (COX-2) levels in ventricular cardiomyocytes following MI. Furthermore, increased aldosterone levels have been shown to activate mineralocorticoid receptors (MR) in the brain, promoting apoptosis in both myocytes and nonmyocytes in the peri-infarct and infarct regions post-MI, thus contributing to the inflammatory response.[34] A large meta-analysis found that patients with PA have a 1.77-fold higher risk of coronary artery disease compared to those with EH.[3] The prevalence of coronary artery disease in patients with PA, including MI and angina, varies according to study characteristics and diagnostic criteria. Different epidemiological studies have concluded that patients with PA have a higher prevalence of CAD compared to patients with EH.[6,20] Milliez et al., found that non-fatal myocardial infarction was diagnosed in 4.0% of 124 patients with PA and 0.6% of 456 patients with EH.[5] Furthermore, a multicenter study conducted in Japan, which included 2,582 patients with PA, reported that the prevalence of coronary artery disease (which included MI and angina) was 9.4%.[35] It has been observed that patients with PA and hypokalemia have a higher prevalence of ischemic heart disease compared to PA variants without hypokalemia.[18] Individuals with PA, particularly those with unilateral subtype or a plasma aldosterone concentration of ≥125 pg/ml, face an increased risk of cardiovascular disease.[35]

- **Heart Failure**

Aldosterone plays a key role in the remodeling processes of the left ventricle, both in the presence and absence of ischemic events, increasing the risk of systolic and diastolic dysfunction, heart failure, and higher cardiovascular mortality. In myocardial infarction, the loss of cardiomyocytes exceeds the heart's regenerative capacity, leading to the replacement of normally functioning myocardial cells with fibrotic tissue, which causes post-infarction ventricular remodeling. Meanwhile, in the absence of ischemic heart disease, ventricular remodeling occurs due to hemodynamic overload and neurohormonal mechanisms, resulting in left ventricular hypertrophy and cardiac fibrosis.[24]

In vitro studies have shown that aldosterone, in addition to stimulating collagen synthesis by fibroblasts,[25] helps in cardiomyocyte hypertrophy,[27] cardiac myofibroblast proliferation,[36] and increased release of matrix metalloproteinases by cardiomyocytes through the MAPK (mitogen-activated protein kinases) cascade.[36,37]

In studies with mice, it was found that aldosterone infusion is associated with perivascular and interstitial fibrosis. Aldosterone induces cardiac fibrosis through perivascular and interstitial fibrosis and by directly altering the deposition of the extracellular matrix.[24]

A study published in The American Journal of Hypertension in 2009 reported that a French cohort of 460 patients with PA had a greater frequency of heart failure (7.4% vs. 3.6%) compared to controls.[38] Additionally, a study published in the Journal of the American Heart Association in August 2023 investigated the cardiovascular impacts in patients with PA. The findings revealed that these patients face a higher risk of

developing coronary artery disease and heart failure compared to individuals with essential hypertension.[39] A recent study published in Hypertension in 2023 explored the mortality rates of patients with PA in comparison to the general population. The study revealed that PA was associated with a higher risk of all-cause mortality, cardiovascular disease, and stroke. Specifically, 14.3% of patients with PA died during a median follow-up of 8.1 years, compared to 11.3% of the control group. These findings suggest that PA is connected to an increased risk of cardiovascular events, including heart failure.[40]

- **Arrhythmias**

Atrial fibrillation (AF) is a common arrhythmia that can occur in patients with primary aldosteronism (PA). Aldosterone creates a favorable environment for atrial fibrillation through its direct effects on cardiomyocytes by increasing cytosolic calcium load,[41] via the activation of L-type and T-type calcium channels. The L-type channel, through the activation of the ryanodine receptor, increases Ca2+ in the cytosolic space, with its activity being further enhanced by MR receptor activation.[42] Rapid depolarizations increase intracellular calcium, MR expression, and aldosterone sensitivity in atrial cardiomyocytes, creating a positive feedback loop that fuels a vicious cycle, ultimately contributing to the development of AF.[43]

The indirect mechanisms through which aldosterone favors the development of atrial fibrillation include a variety of cardiovascular changes, such as left atrial enlargement, increased blood pressure, and electrolyte imbalances (like hypokalemia). These factors create an environment that promotes atrial remodeling and increased susceptibility to arrhythmias like AF.[44] Several studies have found that patients with PA are at a higher risk for developing AF compared to those with essential hypertension. One of the mechanisms behind this is aldosterone’s effect on the heart's electrical system, which can lead to changes in atrial tissue and promote the development of AF.[45]

Patients with PA were reported to have a 12-fold increased risk of AF compared to patients with essential hypertension.[5] In a prospective study of hypertensive patients with AF, it was found that 42% had PA[46], indicating that AF is a common clinical manifestation of PA.

In patients with unilateral PA, adrenalectomy lowers the risk of developing AF to levels comparable to those observed in EH.[47] However, individuals with PA who are treated with MRA continue to exhibit a higher risk of AF. When MRA therapy is adjusted to elevate renin levels, the risk of AF aligns more closely with that of patients with EH, emphasizing the need for careful management of MRA therapy.[48]

CONCLUSIONS

Excess aldosterone, particularly in conditions like primary aldosteronism (PA), plays a central role in the development and progression of various cardiovascular diseases, such as hypertension, coronary artery disease, heart failure, and atrial fibrillation. In clinical practice, elevated aldosterone levels are strongly associated with an increased risk of cardiovascular events, especially in PA patients. Interventions like adrenalectomy and mineralocorticoid receptor antagonists (MRAs) have demonstrated efficacy in reducing cardiovascular risks, including mortality and the development of atrial fibrillation. Given the increasing recognition of aldosterone's significant impact on cardiovascular health, early detection and targeted treatment of primary aldosteronism are crucial to mitigating the burden of cardiovascular diseases, particularly in high-risk populations.

Future research should focus on the long-term effects of MRA therapy on cardiovascular morbidity and mortality in PA patients, as well as elucidating the mechanisms by which aldosterone contributes to arrhythmogenesis in atrial fibrillation. A more profound understanding of aldosterone’s cardiovascular effects will pave the way for the development of more effective prevention and management strategies, ultimately improving the quality of life for patients affected by these conditions.

Conflict of interest: None declared.

REFERENCES

1. Gros R, Ding Q, Sklar LA, Prossnitz EE, Arterburn JB, Chorazyczewski J, Feldman RD. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. Hypertension, 2011; 57: 442–451. doi: 10.1161/HYPERTENSIONAHA.110.161653.
2. Buffolo F, Monticone S, Pecori A, Pieroni J, Losano I, Cavaglià G, Tetti M, Veglio F, Mulatero P. The spectrum of low-renin hypertension. Best Pract Res Clin Endocrinol Metab, 2020; 34: 101399. doi: 10.1016/j.beem.2020.101399.
3. Monticone S, D’Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol, 2018; 6: 41–50. doi: 10.1016/S2213-8587(17)30319-4.
4. Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. Ann N Y Acad Sci., 2002; 970: 89–100.
5. Milliez P, Girerd X, Plouin PF, et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol, 2005; 45: 1243–8.
6. Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary

aldosteronism after treatment. Arch Intern Med., 2008; 168: 80–5.
7. Gros R, Ding Q, Liu B, Chorazyczewski J, Feldman RD. Aldosterone mediates its rapid effects in vascular endothelial cells through GPER activation. Am J Physiol Cell Physiol., 2013; 304: C532–40. doi: 10.1152/ajpcell.00203.2012.
8. Briet M, Schiffrin EL. Vascular actions of aldosterone. J Vasc Res., 2013; 50: 89–99. doi: 10.1159/000345243.
9. Ross D. Feldman, Rohan Sanjanwala, Raj Padwal, Alexander A. Leung, Revising the Roles of Aldosterone in Vascular Physiology and Pathophysiology: From Electocortin to Baxdrostat, Canadian Journal of Cardiology, 2023; 39(12), ISSN 0828-282X, https://doi.org/10.1016/j.cjca.2023.08.035.
10. Newfell BG, Iyer LK, Mohammad NN, McGraw AP, Ehsan A, Rosano G, Huang PL, Mendelsohn ME, Jaffe IZ. Aldosterone regulates vascular gene transcription via oxidative stress-dependent and -independent pathways. Arterioscler Thromb Vasc Biol., 2011; 31: 1871–1880. doi: 10.1161/ATVBAHA.111.229070.
11. Ungvari Z, Tarantini S, Kiss T, Wren JD, Giles CB, Griffin CT, Murfee WL, Pacher P, Csiszar A. Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. Nat Rev Cardiol, 2018; 15: 555–565. doi: 10.1038/s41569-018-0030-z.
12. Hill JM, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, Finkel T. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med., 2003; 348: 593–600. doi: 10.1056/ NEJMoa022287.
13. Wu VC, Lo SC, Chen YL, Huang PH, Tsai CT, Liang CJ, Kuo CC, Kuo YS, Lee BC, Wu EL, et al; TAIPAI Study Group. Endothelial progenitor cells in primary aldosteronism: a biomarker of severity for aldosterone vasculopathy and prognosis. J Clin Endocrinol Metab, 2011; 96: 3175–3183. doi: 10.1210/jc.2011-1135.
14. Holaj R, Zelinka T, Wichterle D, Petrák O, Strauch B, Widimský J. Jr. Increased intima-media thickness of the common carotid artery in primary aldosteronism in comparison with essential hypertension. J Hypertens, 2007; 25: 1451–7. doi: 10.1097/HJH.0b013e3281268532.
15. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol, 2003; 2: 43–53. doi: 10.1016/S1474-4422(03)00266-7.
16. Rizzoni D, Paiardi S, Rodella L, Porteri E, De Ciuceis C, Rezzani R, et al. Changes in extracellular matrix in subcutaneous small resistance arteries of patients with primary aldosteronism. J Clin Endocrinol Metab, 2006; 91: 2638–42. doi: 10.1210/jc.2006-0101.
17. Petramala L, Concistrè A, Olmati F, Saracino V, Chimenti C, Frustaci A, Russo MA, Letizia C. Cardiomyopathies and Adrenal Diseases. International Journal of Molecular Sciences, 2020; 21(14): 5047. https://doi.org/10.3390/ijms21145047.
18. Born-Frontsberg E, Reincke M, Rump LC, Hahner S, Diederich S, Lorenz R, et al. Cardiovascular and cerebrovascular comorbidities of hypokalemic and normokalemic primary aldosteronism: results of the German Conn's Registry. J Clin Endocrinol Metab, 2009; 94: 1125– 30. doi: 10.1210/jc.2008-2116 82.
19. Marney AM, Brown NJ. Aldosterone and end-organ damage. Clinical science (London, England: 1979), 2007; 113: 267–78. doi: 10.1042/CS20070123 83.
20. Savard S, Amar L, Plouin PF, and Steichen O. Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. Hypertension (Dallas, Tex.: 1979), 2013; 62: 331–6. doi: 10.1161/HYPERTENSIONAHA.113.01060.
21. Turchi F, Ronconi V, di Tizio V, Ceccoli L, Boscaro M, Giacchetti G. Primary aldosteronism and essential hypertension: assessment of cardiovascular risk at diagnosis and after treatment. Nutr Metab Cardiovasc Dis., 2014; 24: 476–82. doi: 10.1016/j.numecd.2013.09.009.
22. Ohno Y, Sone M, Inagaki N, Kawashima A, Takeda Y, Yoneda T, et al. Nadir aldosterone levels after confirmatory tests correlated with left ventricular hypertrophy in primary aldosteronism. Hypertension (Dallas, Tex.: 1979). 2020; 75: 1475–82. doi: 10.1161/HYPERTENSIONAHA.119. 14601.
23. Wu Q, Hong M, Xu J, Tang X, Zhu L, Gao P, et al. Diurnal blood pressure pattern and cardiac damage in hypertensive patients with primary aldosteronism. Endocrine, 2021; 72: 835–43. doi: 10.1007/s12020-021-02606-3.
24. Tsai CH, Pan CT, Chang YY, Chen ZW, Wu VC, Hung CS, Lin YH. Left ventricular remodeling and dysfunction in primary aldosteronism. J Hum Hypertens, Feb. 2021; 35(2): 131-147. doi: 10.1038/s41371-020-00426-y. Epub 2020 Oct 16. PMID: 33067554; PMCID: PMC7895762.
25. Brilla CG, Weber KT. Mineralocorticoid excess, dietary sodium, and myocardial fibrosis. J Lab Clin Med., 1992; 120: 893–901.
26. Catena C, Colussi G, Novello M, Verheyen ND, Bertin N, Pilz S, et al. Dietary salt intake is a determinant of cardiac changes after treatment of primary aldosteronism: a prospective study. Hypertension, 2016; 68: 204–12. doi: 10.1161/HYPERTENSIONAHA.116.0761.
27. Okoshi MP, Yan X, Okoshi K, Nakayama M, Schuldt AJ, O'Connell TD, et al. Aldosterone directly stimulates cardiac myocyte hypertrophy. J Card Fail., 2004; 10: 511–8. doi: 10.1016/j.cardfail.2004.03.002.
28. Gros R, Ding Q, Armstrong S, O'Neil C, Pickering JG, Feldman RD. Rapid effects of aldosterone on clonal human vascular smooth muscle cells. Am J

Physiol Cell Physiol., 2007; 292: C788–94. doi: 10.1152/ajpcell.00407.2006.
29. Lopez-Andres N, Martin-Fernandez B, Rossignol P, Zannad F, Lahera V, Fortuno MA, et al. A role for cardiotrophin-1 in myocardial remodeling induced by aldosterone. Am J Physiol Heart Circ Physiol, 2011; 301: H2372–82. doi: 10.1152/ajpheart.00283.2011.
30. Milan A, Magnino C, Fabbri A, Chiarlo M, Bruno G, Losano I, et al. Left heart morphology and function in primary aldosteronism. High Blood Press Cardiovasc Prev., 2012; 19: 11–7. doi: 10.2165/11593690-000000000-00000.
31. Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension (Dallas, Tex., 1979; (2013) 62: 62–9. doi: 10.1161/HYPERTENSIONAHA.113.01316.
32. Chang YY, Liao CW, Tsai CH, Chen CW, Pan CT, Chen ZW, et al. Left Ventricular Dysfunction in Patients With Primary Aldosteronism: A Propensity Score-Matching Follow-Up Study With Tissue Doppler Imaging. J Am Heart Assoc, 2019; 8: e013263. doi: 10.1161/JAHA.119.013263.
33. Chen YL, Xu TY, Xu JZ, Zhu LM, Li Y, Wang JG. A speckle tracking echocardiographic study on right ventricular function in primary aldosteronism. J Hypertens, 2020; 38: 2261–9. doi: 10.1097/HJH.0000000000002527.
34. Jia D, Chen S, Bai P, Luo C, Liu J, Sun A, Ge J. Cardiac Resident Macrophage-Derived Legumain Improves Cardiac Repair by Promoting Clearance and Degradation of Apoptotic Cardiomyocytes After Myocardial Infarction. Circulation, May 17, 2022; 145(20): 1542-1556. doi: 10.1161/CIRCULATIONAHA.121.057549. Epub 2022 Apr 18. PMID: 35430895.
35. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, Takeda Y, et al. Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: a multicenter study in Japan. Hypertension., 2018; 71: 530–7. 10.1161/HYPERTENSIONAHA.117.10263.
36. Stockand JD, Meszaros JG. Aldosterone stimulates proliferation of cardiac fibroblasts by activating Ki-RasA and MAPK1/2 signaling. Am J Physiol Heart Circ Physiol, 2003; 284: H176–H184. doi: 10.1152/ ajpheart.00421.2002.
37. Rude MK, Duhaney TA, Kuster GM, Judge S, Heo J, Colucci WS, Siwik DA, Sam F. Aldosterone stimulates matrix metalloproteinases and reactive oxygen species in adult rat ventricular cardiomyocytes. Hypertension, 2005; 46: 555–561. doi: 10.1161/01.HYP.0000176236.55322.18.
38. Leonardo A. Sechi, GianLuca Colussi, Alessandro Di Fabio, Cristiana Catena, Cardiovascular and Renal Damage in Primary Aldosteronism: Outcomes After Treatment, *American Journal of Hypertension*, December 2010; 23(12): 1253–1260, https://doi.org/10.1038/ajh.2010.169.
39. Patil S, Rojulpote C, Amanullah A. Primary Aldosteronism and Ischemic Heart Disease. Front Cardiovasc Med., May 23, 2022; 9: 882330. doi: 10.3389/fcvm.2022.882330. PMID: 35677685; PMCID: PMC9168042.
40. Gkaniatsa E, Zverkova Sandström T, Rosengren A, Trimpou P, Olsson DS, Lind M, Muth A, Johannsson G, Ragnarsson O. Mortality in Patients With Primary Aldosteronism: A Swedish Nationwide Study. Hypertension, Dec. 2023; 80(12): 2601-2610. doi: 10.1161/HYPERTENSIONAHA.123.21895. Epub 2023 Oct 19. PMID: 37855142.
41. Denham NC, Pearman CM, Caldwell JL, Madders GWP, Eisner DA, Trafford AW, Dibb KM. Calcium in the pathophysiology of atrial fibrillation and heart failure. Front Physiol, 2018; 9: 1380. doi: 10.3389/fphys.2018.01380.
42. Marks AR. Clinical implications of cardiac ryanodine receptor/calcium release channel mutations linked to sudden cardiac death. Circulation, 2002; 106: 8–10. doi: 10.1161/01.cir.0000021746.82888.83.
43. Tsai CT, Chiang FT, Tseng CD, Hwang JJ, Kuo KT, Wu CK, Yu CC, Wang YC, Lai LP, Lin JL. Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. J Am Coll Cardiol, 2010; 55: 758–770. doi: 10.1016/j.jacc.2009.09.045.
44. Reil JC, Hohl M, Selejan S, et al. Aldosterone promotes atrial fibrillation. Eur Heart J., 2012; 33(16): 2098-2108. doi:10.1093/eurheartj/ehr266.
45. Seccia TM, Caroccia B, Adler GK, Maiolino G, Cesari M, Rossi GP. Arterial Hypertension, Atrial Fibrillation, and Hyperaldosteronism: The Triple Trouble. Hypertension, Apr. 2017; 69(4): 545-550. doi: 10.1161/HYPERTENSIONAHA.116.08956.
46. Seccia T.M, C. Letizia, M.L.Muiesan, et al., Atrial fibrillation as presenting sign of primary aldosteronism: results of the prospective appraisal on the prevalence of primary aldosteronism in hypertensive (PAPPHY) study, J. Hypertens, 2020; 38: 332–339.
47. Rossi GP, Maiolino G, Flego A, Belfiore A, Bernini G, Fabris B, Ferri C, Giacchetti G, Letizia C, Maccario M, et al; PAPY Study Investigators. Adrenalectomy lowers incident atrial fibrillation in primary aldosteronism patients at long term. Hypertension, 2018; 71: 585–591. doi: 10.1161/ HYPERTENSIONAHA.117.10596
48. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Incidence of atrial fibrillation and mineralocorticoid receptor activity in patients with medically and surgically treated primary aldosteronism. JAMA Cardiol, 2018; 3: 768–774. doi: 10.1001/jamacardio.2018.2003