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## The Relationship Between Aldosterone and Left Ventricular Hypertrophy in Hypertensive Patients

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The Relationship Between Aldosterone and Left Ventricular Hypertrophy in Hypertensive Patients

**Abstract**

*Background* - Aldosterone is a pertinent hormone in naturally elevating blood pressure within the body by increasing fluid retention in the body via electrolyte reabsorption in the kidneys. Consequently, aldosterone can have an indirect effect on the incidence of LVH considering the hormone can reinforce high blood pressure. However, recent studies have suggested that aldosterone and the renin-angiotensin-aldosterone-system (RAAS) may have a direct role in leading to an increase in left ventricular mass. Patients with hyperaldosteronism, otherwise elevated circulating aldosterone, have shown high frequencies of LVH regardless of the presence of hypertension. Furthermore, cardiomyocytes have been seen to contain mineralocorticoid receptors that bind to aldosterone and can be affected by different RAAS inactivating medications. Overall, current research suggests there may be a regression between LVH and aldosterone.

*Methods and Results* – A retrospective model comparing plasma aldosterone levels and left ventricular hypertrophy measurements in a hypertensive cohort of African Americans from the AddReaCH trial. Follow-up over the course of a year allowed for multivariate analysis to

determine whether elevated levels of plasma aldosterone induced changes in left ventricular mass and diastolic function independent of blood pressure and other variables. Left ventricular hypertrophy was assessed through various left ventricular measurements from contrast-aided MRI examinations. Though average LVMI was greater in patients with greater aldosterone-renin ratios, multivariate analysis suggested that plasma aldosterone-renin ratio does not have a significant, independent relationship to the incidence and severity of LVH. Results call for further research on the topic, as the current study confounds results from prior studies.

## **Introduction**

Cardiovascular disease (CVD) is by far the leading cause of death within the United States. Specifically, congestive heart failure (CHF) continues to complicate the health of Americans annually. The pathophysiology underlying any form of CHF typically involves some cardiac remodeling. One of the most prominent physical changes in the heart involve the enlargement of the left ventricle, otherwise known as left ventricular hypertrophy (LVH). However, while some mechanisms of LVH is well studied, other mechanisms complicate our understanding of the condition. One such complication involves the Renin-Angiotensin-Aldosterone System (RAAS). More specifically, there remains some uncertainty as to whether the different hormones of the RAAS have some sort of direct causational effect on LVH and diastolic function.

## **Purpose**

Urban communities continue to face high incidences of hypertension and hence, are put in great risk of left ventricular hypertrophy. It is critical for the treatment of these patients to understand the various components of LVH causation and development. The renin-angiotensin-

aldosterone system continues to complicate our understanding of cardiac morphology, therefore calling for further research. The purpose of this investigation is to determine whether there are associations with serum aldosterone and left ventricular mass differences. Furthermore, the analysis shall study potential correlations of left ventricular mass with aldosterone and plasma aldosterone-renin ratio.

## **Background**

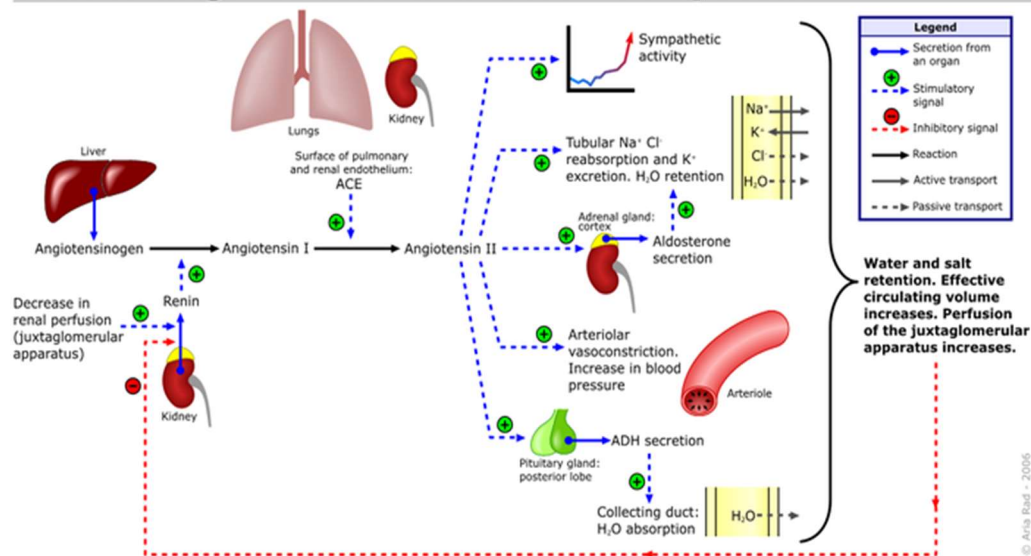
### *The Renin-Angiotensin-Aldosterone System Regulates Blood Pressure*

To investigate what kind of role aldosterone has in the pathology of left ventricular hypertrophy, it is necessary to have a closer look at the functionality of RAAS and the mechanisms involved in the causation of LVH.

The renin-angiotensin-aldosterone system is a natural hormonal pathway in the body that regulates ion levels and blood pressure. In response to reduced renal blood flow, the kidneys release renin, which allows for the conversion of inactive angiotensinogen to angiotensin I. Angiotensin converting enzymes (ACE) then act on angiotensin I and convert it to angiotensin II (AngII), which causes vasoconstriction, sympathetic activation, and increase blood flow. Angiotensin II also stimulates the release of aldosterone, a hormone which causes the kidneys to increase reabsorption of sodium and potassium, from the adrenal glands, which ultimately increases water volume and blood pressure. The RAAS is simplified in the diagram below (RAAS Schematic).

### **Schematic 1. Renin-angiotensin-aldosterone system breakdown [1]**

## Renin-angiotensin-aldosterone system



### *The Renin-Angiotensin-Aldosterone System Indirectly Stimulates Heart Enlargement*

RAAS is one of the primary mechanisms in the body that regulates blood pressure. As such, the system, and especially aldosterone, has an indirect effect on cardiovascular health. An irregularly hyperactive RAAS can result in elevated blood pressure, which effectively increases the workload of the heart. Seeing that the heart is composed of myocytes, this increased workload can cause a thickening in the muscle fibers of the left ventricle, similar to muscle growth seen in skeletal muscle after exercise. This enlargement, known as left ventricular hypertrophy, involves fibrosis and stiffening of the heart, therefore inducing complications in ejection fraction and overall functionality.

Interestingly, left ventricular hypertrophy is a useful morphology of the heart to an extent. The enlargement of the heart serves as a method to compensate for the hemodynamics introduced in hypertensive conditions [2]. However, while LVH helps the body to initially adapt to high blood pressure, further stimulation of the heart becomes maladaptive [3]. Continued

growth of the left ventricle puts patients at risk of heart failure, heart attack, stroke, and, ultimately, death.

*Evidence for a Direct Relationship Between Renin-Angiotensin-Aldosterone System Hormones and Left Ventricular Hypertrophy*

The relationship between hypertension and LVH is well pronounced, justifying the indirect effect RAAS has on cardiac morphology. However, recent evidence is now suggesting the RAAS may also introduce direct effects on cardiomyocytes in the development of LVH.

Cardiomyocytes contain AT<sub>1</sub> and AT<sub>2</sub> receptors, which principally attach to Angiotensin II (AngII) and conduct a response within the body [4]. Binding of AngII to AT<sub>1</sub> receptors results in sodium conservation, aldosterone secretion, and vasoconstriction while binding to AT<sub>2</sub> brings about vasodilation and decreased cell growth [4]. The two receptors effectively contrast each other in their effects on cardiac morphology.

In the case of LVH, activation of AT<sub>1</sub> receptors by AngII stimulate cardiac remodeling and hypertrophy. Recent studies have investigated the use of angiotensin converting enzyme inhibitors (ACEI) in preventing the increase in left ventricular mass by AngII. Typically, ACEIs are used to treat hypertension and can indirectly prevent LVH in the instance of a decrease in blood pressure. However, without an associated change in blood pressure, ACEIs tend to only halt fibrosis without a decrease in hypertrophy [4]. Part of the issue may arise from the lack of specificity of ACEIs, as blockage of angiotensin conversion inhibits both the hypertrophic effects of AT<sub>1</sub> receptor stimulation and the antigrowth effects of AT<sub>2</sub> receptor stimulation. Therefore, a more novel approach to understanding the direct effects of AngII on LVH would be to investigate the blockage of angiotensin receptors. In multiple studies, angiotensin receptor

blockers (ARBs) that specifically inhibit AT<sub>1</sub> receptors have shown a regression with LVH [3], [5]. Ultimately, AngII seems to play a direct role in the development of LVH. However, what may be of more interest is the impact AngII has on LVH through its ability to stimulate the release of aldosterone.

#### *Unclear Role of Aldosterone in Left Ventricular Hypertrophy*

Aldosterone is known to have a large indirect impact on left ventricular hypertrophy due to its ability to increase blood volume and pressure. However, there is evidence that suggests aldosterone may directly affect fibrosis and cardiac remodeling. Cardiomyocytes have been found to contain mineralocorticoid receptors (MRs), which primarily react with aldosterone [6]. An interesting angle to approach aldosterone's effect on LVH is to look at animal and human models with hyperaldosteronism.

Hyperaldosteronism is a condition in which patients have abnormally high levels of free aldosterone. Some studies have shown that patients with early hyperaldosteronism tend to have a higher incidence and severity of LVH compared to patients with hypertension [7]. In fact, subjects have shown severe forms of LVH due to aldosteronism independent of any effect from blood pressure [8]. This suggests aldosterone may exert some change on cardiomyocyte activity outside of its typical effect on blood pressure. More specifically, studies have shown that MR expression in the heart typically results in some form of cardiotoxic effect [6].

Another approach to accurately determining aldosterone's impact on the development of left ventricular hypertrophy would be to study the effect of mineralocorticoid receptor antagonists (MRAs) on left ventricle mass and function. Spironolactone is a common MRA that is largely used to treat heart failure with preserved ejection fraction [9]. The RALES trial proved

on a large scale the positive effects of spironolactone in treating heart failure and exemplified the cardiac benefit from blocking aldosterone [6]. In the context of LVH, spironolactone has shown to significantly decrease left ventricular mass, though the drug did not exert any effects on actual diastolic function [9].

Eplerenone is a selective aldosterone blocker that has shown to have beneficial cardiac effects similar to spironolactone. The EPHESUS trial suggested eplerenone significantly helped with post MI reparative healing and effectively reduced collagen-volume in the myocardium [10]. With blood pressure staying constant, aldosterone was shown once more to have some sort of morphological effect on the heart.

The mechanisms through which the heart is altered from MR activation involves changes in the extracellular matrix (ECM). Aldosterone has been linked to T-channel activity and increases the relative concentration of collagen within the ECM, therefore increasing mass and stiffening the muscles of the heart [8], [11].

Despite the clinical trials discussed that predict a regression between aldosterone and left ventricular mass, other studies have suggested complicated results. A study investigating the effect of aldosterone associated with salt intake on LVH showed that baseline aldosterone is not independently related to LV mass while post-saline dose aldosterone is independently related to LV mass [12], [13]. Such a result may suggest that salt is required to activate MR expression in cardiomyocytes via oxidative stress of intracellular redox states [12].



## *Mechanisms Outside of the Renin-Angiotensin-Aldosterone System that Affect Left Ventricular Hypertrophy*

In order to compare plasma aldosterone levels to left ventricular hypertrophy, it is necessary to consider and compensate for other factors that may result in heart enlargement. Patients with chronic kidney disease (CKD) have been shown to have incidences and severities of LVH even greater than those in hypertensive patients [14]. A proposed mechanism of LVH related to CKD involves fibroblast growth factor-23 (FGF23). FGF23 is an endocrine hormone that regulates phosphorus homeostasis [14]. As such, FGF23 expression increases as the kidney's ability for phosphorus excretion decreases in CKD patients. Interestingly, FGF23 can alter gene expression in cardiomyocytes and cardiac fibroblasts as well, particularly leading to ECM deposition, hypertrophy, and apoptosis of myocytes [14]. FGF23 has also been seen to be associated with elevated levels of cardiac troponins, suggesting a relationship between FGF23 and cardiac distress [15].

Chronic kidney disease has been shown to have a significant relationship with cardiovascular health and therefore has to be accounted for in any study of LVH.

## *Accurate Measurement of Left Ventricular Mass and Diastolic Function*

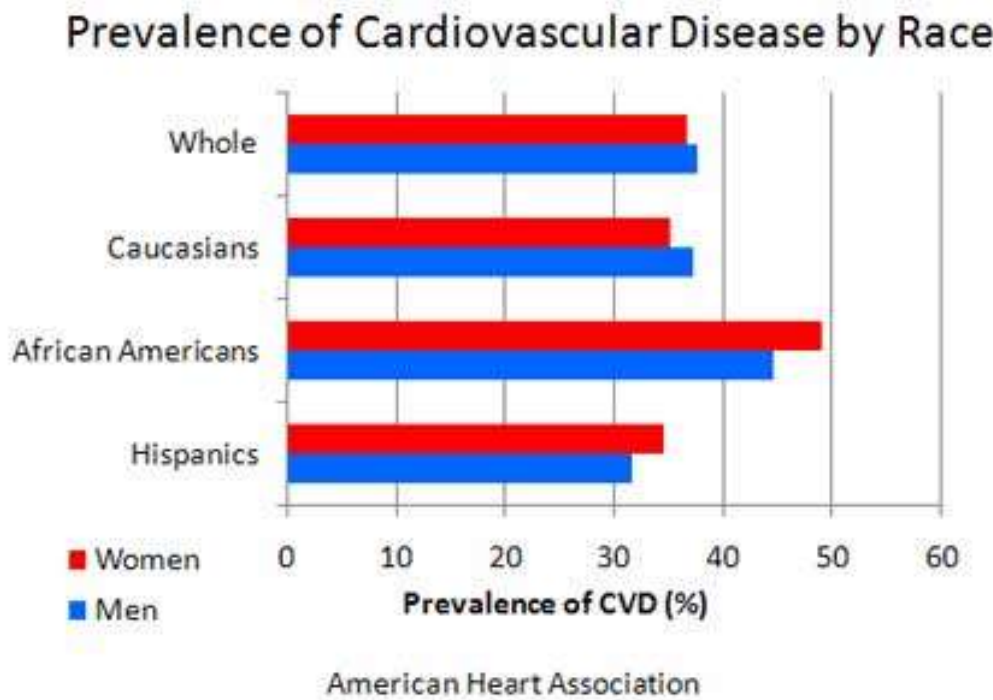
One of the challenges in studying left ventricular mass and heart function lies in accurately measuring different pertinent variables. Current recommendations in measuring LVH suggest the use of echocardiography in quantifying the following variables: morphologic change, mitral inflow, pulmonary venous flow, flow propagation velocity, diastolic velocity, left ventricular untwisting, and left ventricular filling pressures [16]. Prior studies involving the study of aldosterone and left ventricular hypertrophy have taken the recommended approach and

utilized echocardiography to quantify the incidence and severity of LVH. However, it is arguable that magnetic resonance imaging (MRI) may be able to provide a more accurate representation of LVH and diastolic function in most patients. Few studies on aldosterone-LVH regression have been conducted with an MRI as the primary instrument for left ventricular mass and diastolic function measure. Utilization of MRI may therefore provide more accurate, interesting, and potentially different results

### *Racial Disparities Underlying Hypertension and Left Ventricular Hypertrophy*

Race has been proven to be a significant determinant of hypertension incidence in any population. Typically, African Americans have a higher risk of having high blood pressure and, therefore, early onset heart disease, as seen by the bar graph below [17].

**Bar Graph 1. Racial Distribution of Cardiovascular Disease [18].**



African Americans exemplify similar risk in developing left ventricular hypertrophy and diastolic dysfunction based on modifiable sociodemographic variables [19]. For these reasons, African Americans provide a cohort of individuals that can be used to investigate LVH in patients with essential hypertension.

## **Hypothesis**

It is hard to ignore the evidence connecting aldosterone to the development of left ventricular hypertrophy. Current understanding of the mechanisms involving RAAS and the heart suggest there would be a positive relationship between serum aldosterone levels and left ventricular mass. We hypothesize such a trend will be significant amongst multiple variables measuring left ventricular remodeling.

## **Methods**

### *Study Design*

The current study took a prospective approach with a priori anticipation for controlling for aldosterone-renin ratio and aldosterone in assessing the relationship between plasma aldosterone levels and left ventricular hypertrophy. All patient data was pooled from the AdDReaCH trial (NCT01260476), a prospective, longitudinal, randomized, controlled, IRB reviewed study. Data points related to blood pressure, left ventricular hypertrophy, plasma aldosterone, and other useful values were collected by standard protocol of the AdDReaCH trial and were utilized retrospectively.

### *Study Population*

The AddReaCH study selectively enrolled asymptomatic, hypertensive, African American patients from an urban, academic medical center. The study assessed the efficacy of Vitamin D supplementation, in conjunction with antihypertensive therapy, in reducing the severity of left ventricular hypertrophy. Recruited had blood pressures that measured greater than 160/90 and were vitamin D deficient. Any patients with a hypertensive emergency or had any clinical history of extraneous cardiovascular, renal, hepatic, or neurological conditions were excluded.

### *Study Protocol*

Subjects who were enrolled into the AddReaCH study were screened within the emergency department (ED). Patients then proceeded for follow-up as outpatients for cardiac MRI examinations and blood pressure intervention in order to assess the effects of Vitamin D therapy on left ventricular hypertrophy and blood pressure. Cardiac magnetic resonance (CMR) imaging took place a week prior to randomization for screening purposes as well as 16 and 52 weeks after randomization for follow-up. Blood pressure was measured in the ED, two weeks prior to randomization, as well as at all follow-up CMR visits. Plasma aldosterone and renin was measured at screening and 52 week CMR appointments. Patients received antihypertensive medications over the course of the year along with either placebo or vitamin D supplement.

Blood pressure readings throughout the study were collected from automated brachial cuffs and typically recorded as an average of two readings done immediately after one another. Left ventricular hypertrophy and diastolic function variables were measured through the performance of gadolinium contrast-guided MRI. Such variables included left ventricular mass (LVM), left ventricular mass indexed (LVMI) to body surface area (BSA), septal wall thickness, anterior wall thickness, and left ventricular stroke volume (LVSV).

Original data was retrieved from Oncore (Forte Research Systems, Madison, WI) and was extracted into Microsoft Excel.

### *Data Analysis*

Seeing that renin causes indirect change in aldosterone release, it is necessary to compensate for its impact to better organize patients in the current study with regards to the magnitude of serum aldosterone levels prior to RAS activation. Subject data was organized into four distinct groups defined by varying renin and aldosterone levels.

**Table 1. Criteria for Different Renin-Aldosterone Analysis Groups**

Plasma Renin-Aldosterone Group	Plasma Renin Level (ng/mL/hr)	Plasma Aldosterone Level (ng/dL)
Low Renin Low Aldosterone	< 1	< 15
Low Renin High Aldosterone	< 1	> 15
High Renin Low Aldosterone	> 1	< 15
High Renin High Aldosterone	> 1	> 15

The four groups were assessed for a difference in left ventricular mass at baseline and follow-up using mean and median.

Plasma Aldosterone-renin ratios (ARR) are typically used to diagnose primary aldosteronism and provide another measure of renin-compensated plasma aldosterone in the body. The typical cutoff to distinguish aldosteronism from healthy patients is 30 ng/dL per ng/(mL x h). As such, subjects were divided into two groups; one above and one below the ARR cutoff. Student's t-test and chi-square tests were done to compare LVM measurements in patients with high and low calculated-ARRs. Similar analysis was completed to compare patients with serum aldosterone measurements above and below the healthy upper limit (15 ng/dL).

Multivariate least-squares regression modeling was completed to determine if plasma aldosterone, plasma renin, and plasma aldosterone-renin ratio had an independent correlation with LVM regression whilst controlling for age, sex, blood pressure, creatinine, and sodium at the screening and 52-week CMR. Least-squares regression modeling was also completed to determine if a change in plasma aldosterone and plasma aldosterone-renin ratio from screening to 52-week follow up resulted in a change in LVM.

## **Results**

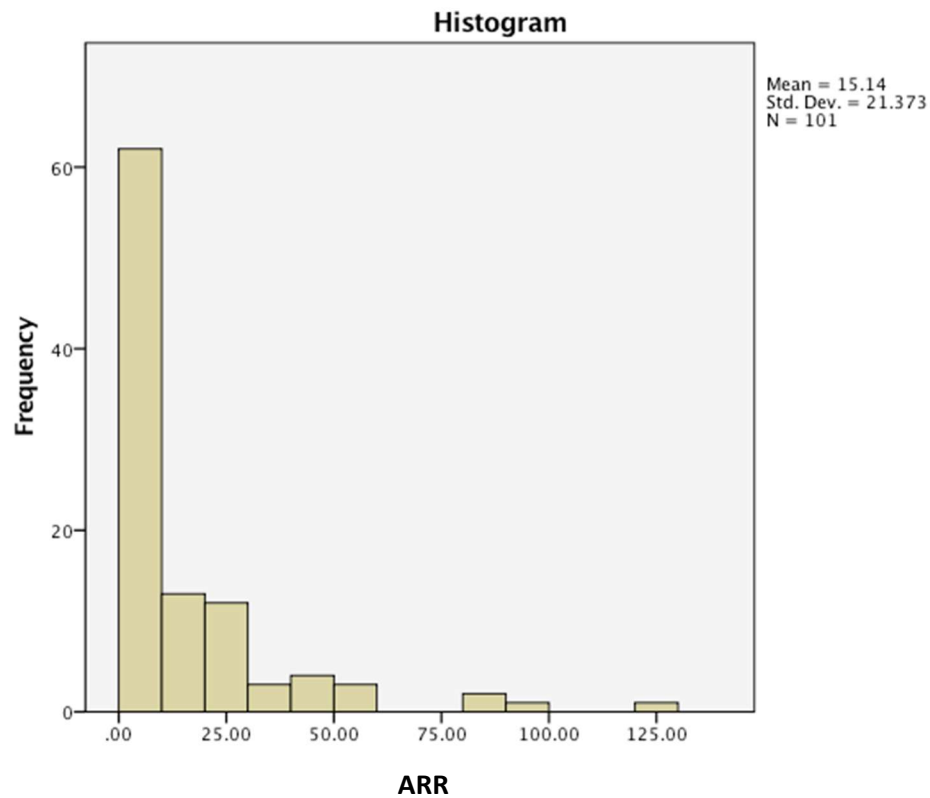
Data was abstracted from 113 subjects, of which 101 subjects had relevant aldosterone and LVMI measurements completed up until the 52 week follow up. All subjects were African American, with 53% of patients being female. It is important to note that all subjects had some form of left ventricular hypertrophy, otherwise they were excluded from the study. As such, the data gives insight not to the presence of hypertrophy in relation to aldosterone, but rather the changes in hypertrophy severity.

**Table 2. Distribution of Renin-Aldosterone Analysis Groups**

Group	N	Mean LVMI	Median LVMI
Low Aldosterone, Low Renin	62	96.8056	96.5
Low Aldosterone, High Renin	41	97.3934	93.17
High Aldosterone, Low Renin	6	108.74	97.66
High Aldosterone, High Renin	4	92.1625	85.82

In the analysis of subjects based on aldosterone-renin ratio threshold, only 14 subjects presented with a ratio greater than 30 ng/dL.

**Histogram 1. Distribution of Patients with Regards to Aldosterone-Renin Ratio**



Patients below and above the threshold were compared for a significant difference in LVMI. Not assuming equal variances, a t-test for equality of means suggested no significant difference in LVMI ( $t = 1.458$ ). T-test comparing patients above and below the aldosterone threshold of 15 ng/dL provided a similar, insignificant difference between groups ( $t = -0.641$ ).

On multiple regression modeling, aldosterone-renin ratio was statistically insignificant predictor of LVMI while controlling for age, sex, and systolic blood pressure. The least squared regression for ARR resulted in an  $R^2 = 0.213$ , suggesting a far from linear relationship to LVMI. Analysis of individual coefficients suggested only the female gender and systolic blood pressure are significant predictors in the development of LVH.

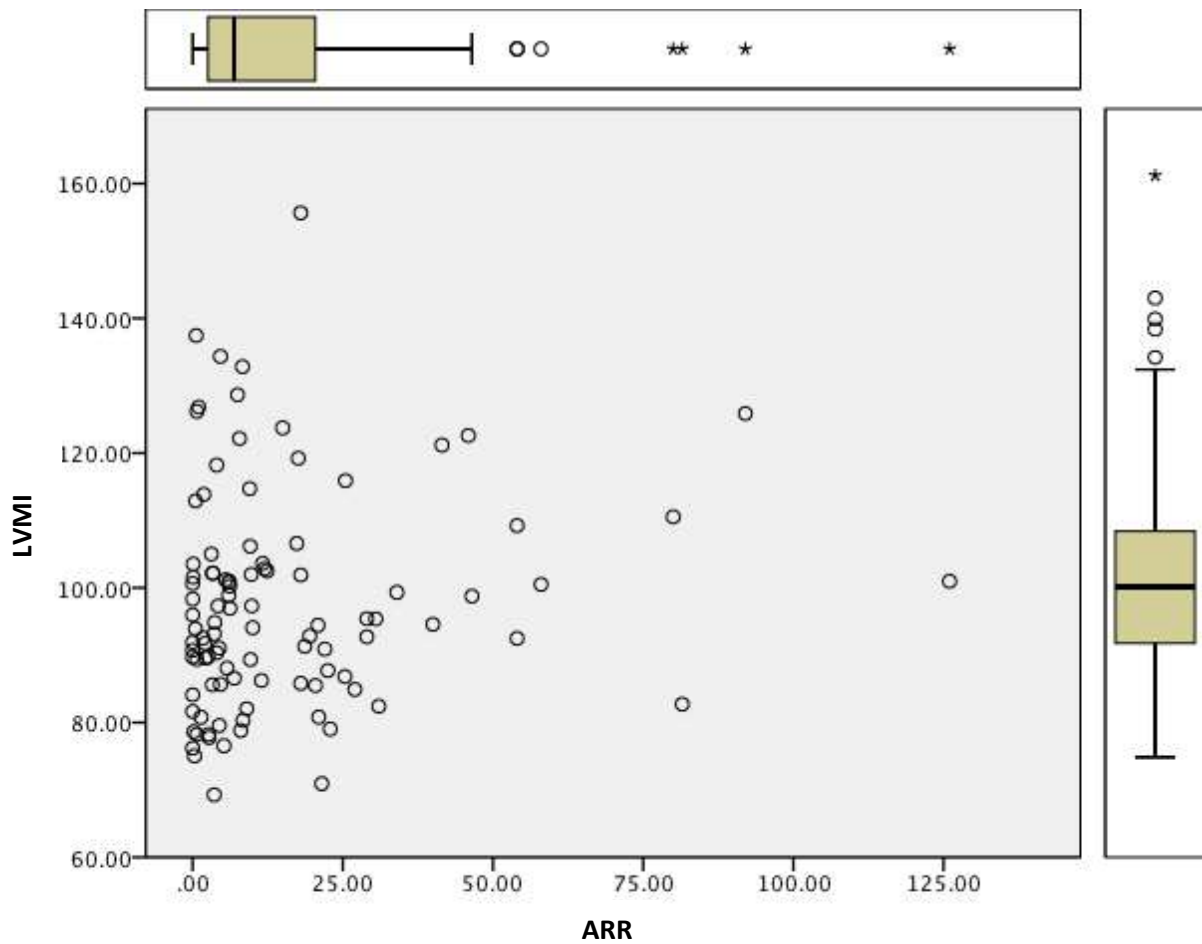
**Table 3. Multivariate Regression Significance Results**

<b>Coefficients<sup>a</sup></b>						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	71.887	14.383		4.998	.000
	ARR	.044	.071	.058	.615	.540
	Age	.122	.162	.068	.755	.452
	Female	-12.631	2.873	-.392	-4.396	.000
	SBP	.151	.058	.243	2.598	.011

a. Dependent Variable: LVMI

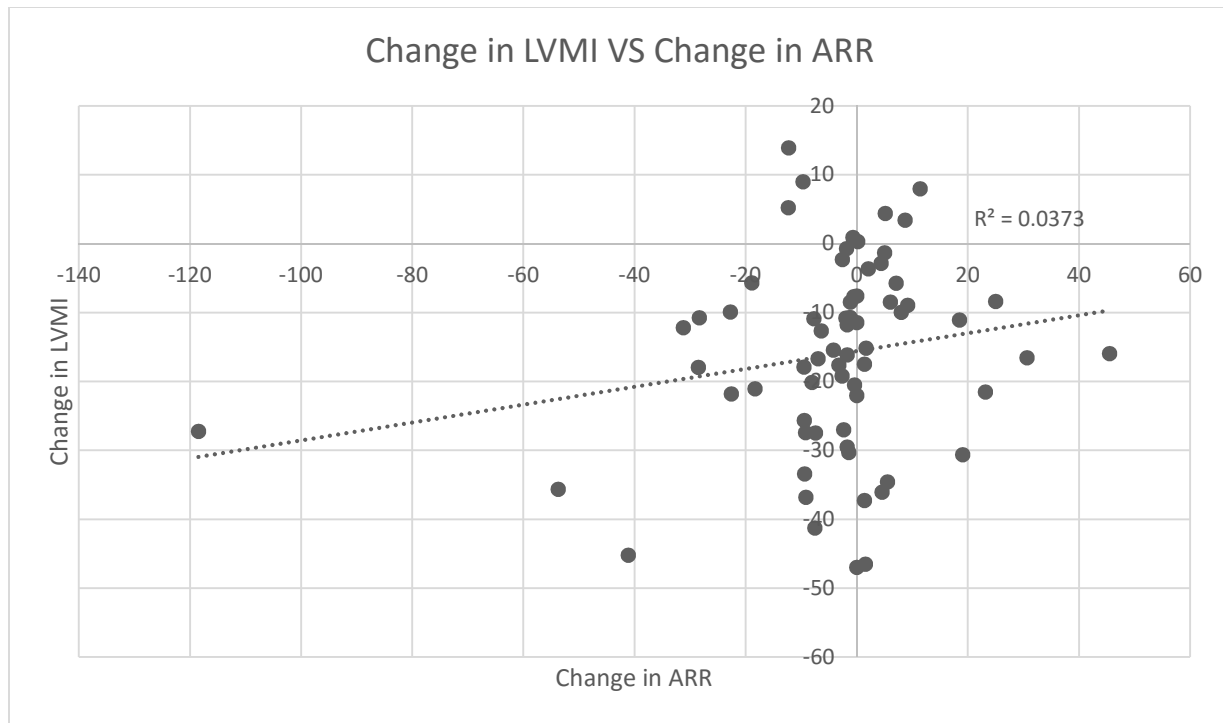


**Graph 1. Multivariate Regression Model of LVMI VS ARR**



The final analysis involved an independent regression of change in LVMI versus change in aldosterone-renin ratio. Change in aldosterone-renin ratio was a poor indicator of change in LVMI ( $p = 0.12$ ,  $R^2 = 0.0373$ ).

**Graph 2. Regression of Change in LVMI VS Change in ARR**



## **Discussion**

Average left ventricular mass was the greatest in patients with a low renin but high aldosterone levels, coinciding with our stated hypothesis that patients with greater free aldosterone will have consequently greater LVMI. However, upon closer analysis of aldosterone-renin ratios, we saw there were not significantly different LVMI in patients with greater ARR. As such, the hypothesis regarding a positive relationship between serum aldosterone and left ventricular remodeling could not be validated.

Current science has been suggesting that serum aldosterone has some effect on left ventricular mass. However, physicians have had a hard time getting conclusive and repetitive results. The EPHESUS and RALES trials provided a strong basis to support the novel approach of utilizing aldosterone receptor blockers to treat heart failure and MI [10, 20]. Studies regressing

LVH with primary aldosteronism have also suggested some connection between cardiac remodeling and serum aldosterone levels [6]. However, studies with similar research models to the current investigation have suggested that aldosterone does in fact have an insignificant relationship to cardiac structure [21]. Other studies imply a more complex system linking aldosterone and LVM. A recent investigation found that post-saline load aldosterone levels, as opposed to baseline aldosterone levels, are good predictors of LVM, implying some role of sodium in aldosterone-mediated cardiac remodeling [12]. Overall, the literature is inconclusive and calls for more research to be done on the topic.

### **Limitations**

The current study is a retrospective study and was therefore limited in the number and types of patients that were investigated. Few subjects were found to have elevated aldosterone levels or aldosterone-renin ratios, therefore greatly limiting the breadth of the sample. This limitation could be accounted for through a research model in which there was active enrollment of patients with elevated serum aldosterone, rather than leaving it up to retrospective chance.

All patients enrolled were required to have some form of left ventricular hypertrophy. As such, the investigation was limited to studying the relationship between aldosterone and LVH severity, as opposed to LVH incidence.

The sample size was limited by the small portion of subjects that actually completed up until the 52 week follow up. A large portion of the data had to be neglected due to incomplete data sets involving LVMI and aldosterone. The gaps in data also restricted the different variables controlled for in the multivariate regression.

## **Conclusion**

In this investigation, we could not find a significant and independent relationship between serum aldosterone and left ventricular mass. Based on our data, there cannot be any conclusions made as to whether aldosterone-related therapy would be effective in treating patients with left ventricular hypertrophy. Further study is necessary to investigate other significant factors that may play a role in left ventricular remodeling in conjunction with elevated serum aldosterone levels, such as kidney function and sodium loading. The current study provides another building block in determining the direct effect of aldosterone on the heart.

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