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# Rapid Reversal of Left Ventricular Hypertrophy and Intracardiac Volume Overload in Patients with Resistant Hypertension and Hyperaldosteronism - A Prospective Clinical Study

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## Abstract

We have previously shown that patients with resistant hypertension and hyperaldosteronism have increased brain natriuretic peptide suggestive of increased intravascular volume. In the present study, we tested the hypothesis that hyperaldosteronism contributes to cardiac volume overload. Thirty-seven resistant hypertensive patients with hyperaldosteronism (urinary aldosterone ≥ 12 μg/24h and plasma renin activity ≤ 1.0 ng/ml/hr) and 71 patients with normal aldosterone status were studied. Both groups had similar blood pressure and left ventricular mass, while left and right ventricular end-diastolic volumes measured by cardiac magnetic resonance imaging were greater in high vs. normal aldosterone subjects ($p<0.05$). Spironolactone treatment (19 patients in the high aldosterone group and 15 patients from the normal aldosterone group participated in the follow up) resulted in a significant decrease in clinic systolic blood pressure, right and left ventricular end diastolic volumes, left atrial volume, left ventricular mass and brain natriuretic peptide at 3 and 6 months follow-up in patients with high aldosterone, where as in those with normal aldosterone status, spironolactone decreased blood pressure and left ventricular mass without changes in ventricular or atrial volumes or plasma brain natriuretic peptide. Hyperaldosteronism causes intracardiac volume overload in patients with resistant hypertension in spite of conventional thiazide diuretic use. Mineralocorticoid receptor blockade induces rapid regression of left ventricular hypertrophy irrespective of aldosterone status. In subjects with high aldosterone, mineralocorticoid receptor blockade induces a prominent diuretic effect compared to a greater vasodilatory effect in subjects with normal aldosterone status.

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**Disclosures:** None

**Keywords**

Resistant hypertension; Hyperaldosteronism; Cardiac volume; Cardiac hypertrophy

## Introduction

Aldosterone excess is increasingly recognized as a common cause of hypertension.[1–11] Compared to patients with similar levels of hypertension, patients with hyperaldosteronism have greater left ventricular (LV) hypertrophy, worse diastolic function and an increased rate of cardiovascular complications including myocardial infarction, stroke, and atrial fibrillation.[12–15] In such patients, echocardiographic/Doppler studies provide support for aldosterone-induced myocardial fibrosis and hypertrophy separate from changes in blood pressure (BP).[16–19]

A large body of experimental literature, including landmark studies by Brilla and Weber, clearly demonstrates that aldosterone excess in the presence of high dietary salt intake induces LV hypertrophy and fibrosis.[20–23] These effects are attributable, at least in part, to aldosterone-induced urinary and fecal loss of $Ca^{2+}$ and $Mg^{2+}$, with consequent hypocalcemia, hypomagnesima and secondary hyperparathyroidism. This secondary increase in parathyroid hormone promotes intracellular $Ca^{2+}$ overloading in various tissues, including cardiac myocytes and vascular smooth muscle cells, which has been shown to contribute importantly to increases in oxidative stress.[24,25]

In a uninephrectomized rat model, aldosterone and salt treatment has been shown to induce perivascular and myocardial inflammation characterized by monocyte and macrophage infiltration and increased expression of inflammatory markers, such as cyclooxygenase-2, osteopontin, monocyte chemoattractant protein-1 and intracellular adhesion molecule-1.[26] Inflammation and fibrosis also occur in the right ventricle (RV),[21] indicating that the changes are not BP dependent.

A recent study from our laboratory demonstrated that patients with resistant hypertension have increased aldosterone associated with brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels in the setting of a high dietary sodium ingestion indicative of intravascular volume expansion.[27] In addition, we reported that resistant hypertensive patients with hyperaldosteronism have increased levels of proteinuria associated with increases in glomerular filtration rate consistent with a hyperfiltration effect secondary to increased intravascular volume.[28]

Based on these findings, we hypothesized that hyperaldosteronism contributes to cardiac volume overload in subjects with resistant hypertension. To test this hypothesis we compared intracardiac volumes (LV, RV and left atrial volume) as measured by magnetic resonance imaging (MRI) before and after MR blockade in resistant hypertensive patients with and without hyperaldosteronism.

## Methods

### Subjects

This study enrolled consecutive subjects (n=108) referred to University of Alabama at Birmingham (UAB), Hypertension Clinic for resistant hypertension (defined as BP > 140/90 mmHg at 2 clinic visits, in spite of use of 3 antihypertensive medications at pharmacologically effective doses). Subjects with a history of congestive heart failure, chronic kidney disease (creatinine clearance < 60 ml/min) or chronic steroid therapy were excluded from study

participation. Secondary causes of hypertension other than hyperaldosteronism, such as renovascular hypertension, pheochromocytoma or Cushing's syndrome were excluded as clinically indicated. Patients with a known history of primary hyperaldosteronism were not included in this study; however, participants were not evaluated by suppression testing and/or adrenal imaging procedure to definitely confirm or exclude the diagnosis. All patients had been on a stable antihypertensive regimen for at least four weeks except for spironolactone, amiloride or eplerenone, which were discontinued for at least six weeks prior to biochemical evaluation. This study was approved by the UAB Institutional Review Board and was conducted according to institutional guidelines.

## Clinical and Laboratory Evaluation

Seated clinic BP was measured manually using a mercury sphygmomanometer and an appropriately-sized cuff after 5 minutes of rest. The mean of two readings were recorded as the clinic BP. All subjects underwent 24-hour ambulatory blood pressure monitoring (ABPM) (Spacelabs, Issaquah, Washington or Suntech Medical, Morrisville, North Carolina).

An early morning ambulatory plasma aldosterone concentration (PAC), plasma renin activity (PRA), BNP, serum potassium, and serum creatinine were measured. A 24-hour urine collection for aldosterone ($U_{Aldo}$), cortisol ($U_{cort}$), sodium ($U_{Na}$) and creatinine was obtained during the subject's *ad libitum* diet. Subjects with $U_{Aldo} \geq 12$ μg/24h and PRA ≤ 1.0 ng/ml/h were considered to have a high-Aldo status. All other subjects were considered to have a normal-Aldo status.

## Cardiac Magnetic Resonance Imaging

All patients underwent cardiovascular magnetic resonance imaging (CMRI) to evaluate cardiac anatomy and function. CMRI was performed with a 1.5 T clinical scanner optimized for cardiac imaging (Sigma, GE Healthcare, Waukesha, WI) using a 4-element phased array surface coil and prospective electrocardiographic triggering. Imaging was performed using a rapid steady-state free precession cine sequence (FIESTA; 10 lines per k-space segment). Standard short axis and 2- and 4-chamber images were obtained prescribed from appropriate scout images; these were used for all quantification of RV, LV and LA volumes. Cine images were reconstructed into 20 cardiac phases. Slice thickness for the short axis, 2- and 4-chamber images was 8 mm without any slice gap. The following parameters were employed: matrix size, 256×128; field of view, 40×40 cm; repetition time 3.9 ms; echo time, 1.6 ms; flip angle 45°; bandwidth 125 Hertz/pixel; typical acquired temporal resolution 39 ms.

A GE Advantage Workstation with Mass Analysis Plus (version 5.1; Medis, Leiden, The Netherlands) software was used to evaluate LV and LA volumes and function. LA contours were manually drawn on 2- and 4-chamber long axis views at ventricular end-systole; this phase corresponds to the largest LA area. The inferior LA border was defined as the plane of the mitral annulus. We excluded the pulmonary veins and the LA appendage as recommended by echocardiographic guidelines.[29] The LA base-to-mitral valve length was obtained from the middle of the plane of the mitral annulus to the posterior wall. LA volume calculated by the area-length method was determined with the formula:

$$V = \frac{8}{3\pi} \frac{A_{2CH} A_{4CH}}{L}$$

where $A_{2CH}$ and $A_{4CH}$ represent the planimetered LA area acquired from the long axis 2 and 4 chambers views respectively, and L is the shortest length from basal wall to the mitral valve annulus. Short axis cine MRI was performed and the epicardial and endocardial contours of

the LV at end-systole and end-diastole were manually drawn for each slice as previously described in our laboratory.[30] LV and LA volumes as well as LV mass were indexed to body surface area.

### Treatment and Follow-Up

Forty-four subjects enrolled in the follow-up study. Spironolactone was added to their ongoing antihypertensive regimen at 25 mg/day and force titrated to 50 mg/day at four weeks. Subjects were followed-up at 3 and 6 months for repeat clinical, biochemical and MRI evaluation. Following addition of spironolactone, other antihypertensive agents were withdrawn as needed in an attempt to minimize the change in blood pressure. Centrally acting agents or vasodilators were withdrawn first, followed by β blockers then calcium channel blockers and finally renin angiotensin antagonists (ACEI or ARBs). Twenty-four hour ABPM was repeated at 6 months.

Ten subjects did not complete the follow-up study after enrolling: 1 subject did not tolerate spironolactone, 1 subject was withdrawn due to an increase in creatinine which returned to baseline after stopping spironolactone, 3 subjects were withdrawn at 3 months due to uncontrolled BP, 1 subject developed angina and underwent revascularization at 2 months, 4 subjects were withdrawn due to scheduling conflicts. One subject developed hyperkalemia (serum potassium > 5.1 mmol/L) at the final visit that normalized upon lowering the spironolactone dose to 25 mg daily.

### Statistics

Comparison of the two groups (high- vs. normal-Aldo) was done using unpaired *t*-tests for continuous variables. Wilcoxon Rank Sum test was applied if the data did not follow a normal distribution. For categorical variables, Fisher exact test was used to compare the two groups. Repeated mixed model analysis using SAS MIXED procedure was performed separately to compare the effects of spironolactone in high-Aldo or normal-Aldo patients at 3 and 6-months to baseline. The model allows for comparison of the three time points while adjusting for the within patient correlation due to repeated measures. Left ventricular mass, LVEDV, RVEDV and LA volume were the primary outcomes with other parameters being analyzed secondarily. All *P* values < 0.05 were considered significant.

## Results

### High- and Normal-Aldo patients

There were no significant differences in age, gender, race, BMI, duration of hypertension, and clinic and ambulatory BP levels in high- vs. normal-Aldo patients (Table 1). Heart rate was lower in the high-Aldo group likely secondary to greater use of beta blockers in this group compared to the normal-Aldo group (97% vs. 69%; P < 0.0001). Other than the difference in use of beta blockers, there were no differences in antihypertensive medication use between the 2 groups. By definition $U_{Aldo}$ and PAC were significantly higher and PRA was significantly lower in the high- vs. normal-Aldo group. The high-Aldo group had a significantly higher $U_{cort}$. Both groups were routinely ingesting a high salt diet as indicated by the urinary sodium excretion (>180 mEq/24-hr).

Baseline characteristics of the high- and normal-Aldo subjects that participated in the interventional protocol with spironolactone were similar to baseline characteristics of the high- and normal-Aldo subjects who did not participate in the interventional protocol except for clinic systolic BP (141 vs. 152 mm Hg, p=0.03), 24-hr ambulatory systolic BP (140 vs. 158 mm Hg, p=0.04) and plasma potassium levels (3.6 vs. 4.0 mmol/L, p=0.002) being lower in the treated high-Aldo compared to the untreated high-Aldo group and clinic diastolic BP being lower in the treated normal-Aldo (81 vs. 89, p=0.008) compared to the untreated normal-Aldo

group. Importantly, all MRI parameters were similar in the treated compared to the respective untreated groups.

### High-Aldo patients have cardiac volume overload

LV end-diastolic volume index (LVEDVI) and RV end-diastolic volume index (RVEDVI) were significantly higher in the high- vs. normal-Aldo group (Table 2), consistent with intracardiac volume expansion in high-Aldo patients, despite almost all subjects (89% of the high-Aldo and 94% of normal-Aldo) receiving thiazide diuretics. Plasma BNP was significantly higher in high- vs. normal-Aldo patients, indicative of increased cardiac filling pressures (Table 1). Left atrial volume index (LAVI) and LV mass index (LVMI) did not differ between the 2 groups. LV ejection fraction was well preserved (>65%) in both groups.

### Effect of MR blockade

Spironolactone significantly decreased clinic systolic BP in both high-and normal-Aldo patients (Table 3) while clinic diastolic BP and ambulatory BP tended to be lower in both groups in spite of having withdrawn approximately 1.5 antihypertensive medications in both groups after the addition of spironolactone. LVMI was significantly reduced at both 3 and 6 months follow-up in both the high- and normal-Aldo subjects. The degree of regression tended to be greater in the high-Aldo group (22 vs. 12%, respectively, at 6 months follow-up). Posterior wall thickness (PWT) and septal wall thickness also decreased in both Aldo groups, but without achieving statistical significance in the normal-Aldo group. Importantly, LVEDVI, RVEDVI, LAVI and BNP were all significantly reduced with spironolactone treatment in the high-Aldo patients; whereas in the normal-Aldo patients, these same parameters were unchanged with spironolactone. There was a significant decrease in LV and RV stroke volume index in high-Aldo patients, while heart rate was unchanged. In the normal-Aldo patients, both LV and RV stroke volume index and heart rate were unchanged consistent with a stable cardiac output.

## Discussion

This study provides several novel and clinically important results. In subjects with resistant hypertension we demonstrate that: 1) high-Aldo status is clearly associated with intracardiac volume overload as indicated by increased RV and LV end-diastolic volumes and plasma BNP levels in spite of chronic thiazide diuretic use; 2) MR blockade induces significant regression of LV hypertrophy in both high- and normal-Aldo patients within 3 months of treatment; 3) MR blockade produces a prominent diuretic effect in high-Aldo patients as indicated by significant reductions in intracardiac volumes and BNP, whereas normal-Aldo patients do not manifest such a large diuretic effect. The reduction in BP in the normal-Aldo group in the absence of a prominent diuretic effect and no change in cardiac output (stroke volume and heart rate were unchanged) suggests greater vasodilation. These findings demonstrate in patients with resistant hypertension a dichotomous effect depending on the underlying aldosterone status: in patients with high aldosterone levels, intravascular and intracardiac volume overload is evident; in patients with normal or low aldosterone levels, volume overload is less prominent, suggesting that hypertension is more dependent on vascular stiffening.

In the current study, high-Aldo status is clearly associated with intracardiac volume overload. This finding contrasts with earlier human studies that did not find differences in intracardiac volumes in high- compared to normal-Aldo patients when measured by echocardiography.[15,17,19] However, the current findings are consistent with animal studies that demonstrate an association of aldosterone excess with volume overload, particularly in the setting of high dietary salt intake.[31,32] Magnetic resonance imaging is more accurate than 2-D echocardiography in measuring cardiac volumes, thus facilitating detection of subtle but significant alterations in intracardiac volume status, as shown in our study.

As we have observed in other studies of patients with resistant hypertension[27], the high-Aldo group had a significantly higher $U_{cort}$ compared to the normal-Aldo group. Possible explanations for this difference include: 1) the presence of adrenal adenomas/hyperplasia that secrete both aldosterone and cortisol 2) excess of adreno-corticotrophic hormone (ACTH) or some other as yet unrecognized stimulus for both aldosterone and cortisol secretion in high-Aldo patients, and 3) sympathetic nervous system activation, which may stimulate aldosterone and cortisol release.[33,34] Additional studies will be needed to distinguish among these possibilities.

The volume overload present in the high-Aldo subjects was largely reversed by low doses of spironolactone, consistent with a prominent diuretic effect of MR blockade. This resulted in substantial reductions in intracardiac volumes, including LA volumes, which would be anticipated to significantly reduce cardiovascular risk, including risk of incident heart failure and atrial fibrillation.[35–37] Importantly, the higher cardiac volumes in the high-Aldo subjects were present in spite of chronic thiazide diuretic use in almost all subjects (33 of 37). This suggests that volume overload in high-Aldo patients is refractory to hydrochlorothiazide (HCTZ) at conventional dosing (25 mg daily). Additional studies are needed to determine if higher doses of HCTZ or more potent diuretics than HCTZ, such as chlorthalidone or furosemide, could overcome this fluid retention. However, either of these options is more likely to induce unfavorable metabolic effects, particularly hypokalemia, as opposed to spironolactone which is potassium sparing.

In the normal-Aldo subjects, intracardiac volumes are lower at baseline compared to the high-Aldo subjects, and there is no change in LV and RV volumes with spironolactone treatment. The BP lowering and LV regression in the normal-Aldo group could be explained by a predominant vasodilator effect and a resulting improvement in cardiac afterload and diastolic function. This interpretation is further supported by lack of change in cardiac output (no change in heart rate or stroke volume) in the normal-Aldo group. The mechanisms by which aldosterone may function as a vasoconstrictor are multiple. Secondary hyperparathyroidism resulting from increased urinary and fecal excretion of $Ca^{2+}$ and $Mg^{2+}$ in hyperaldosteronism and consequent intracellular $Ca^{2+}$ overloading leads to oxidative stress in various tissues, including cardiac myocytes and vascular smooth muscle cells, and thus endothelial dysfunction, vasoconstriction, and vascular stiffening.[24,25] Spironolactone has been shown to block the increased urinary and fecal excretion of $Ca^{2+}$ and $Mg^{2+}$ and thus could potentially block the cascade of events leading to vascular stiffening and vasoconstriction.[38] Separately, we and others have demonstrated that spironolactone, even in patients with normal aldosterone levels, significantly improves endothelial function, resulting in enhanced vasodilation as indexed by flow-mediated dilation of the brachial artery.[39] Such an effect would be consistent with the current findings of lower BP secondary to reductions in vascular resistance during spironolactone treatment.

An important clinical finding of the current study is the rapid regression of LVH both in high- and normal-Aldo patients, with a larger effect observed in the high-Aldo patients (21% vs. 12% reduction at 6 months). Because baseline LVM was the same in high- and normal-Aldo patients, it can be argued that higher aldosterone levels may not contribute to greater LV hypertrophy. It is possible that chronic use of RAS blockers by the current study group blunted aldosterone-induced progression of LV hypertrophy. However, the greater degree regression observed in the high-Aldo patients with MR blockade does suggest a greater role of aldosterone in causing LVH either through direct effects on cardiomyocytes or indirectly through increases in intracardiac volumes and the accompanying increases in wall stress.

Classical studies of thiazide diuretics indicate that acutely, thiazides are associated with decreases in extracellular fluid volume, preload, and cardiac output. [40,41] However, these

effects tend to be transient, with return of intravascular volume and cardiac output toward baseline. As this occurs, however, reductions in BP persist largely because of decreases in systemic vascular resistance. The mechanism of this vasodilatory effect remains obscure but it is speculated that it may involve alterations in smooth muscle cell ion content and/transport, i.e., a reduction in intracellular sodium content. Based on the presumed reduction in vascular resistance induced by MR blockade in the current evaluation, it may be that spironolactone has a similar effect in causing a reduction in total body sodium content including in vascular smooth muscle cells, with a consequential arterial vasodilation. If true, it would suggest that even low or normal circulating levels of aldosterone promote a small but physiologically significant degree of sodium retention that induces increases in vascular resistance prior to development of frank fluid overload.

### Perspectives

It is estimated that 10–20% patients with hypertension are resistant to treatment. The current results suggest that aldosterone at high levels contributes to intravascular and intracardiac volume overload, while at lower levels, it contributes to increases in vascular resistance. Increases in fluid retention and peripheral resistance raise blood pressure while increases in intracardiac volumes would be expected to contribute to increased risk of atrial fibrillation and congestive heart failure. Importantly, the current study indicates both effects are overcome with low-doses of spironolactone, thus demonstrating benefit of aldosterone blockade regardless of underlying aldosterone status.

This study also raises an important clinical question. To what degree is spironolactone-induced reductions in blood pressure and LV mass attributble to direct vascular and/or tissue effects versus a natuiretic/diuretic effect, particularly in patients with seemingly normal aldosterone levels? Controlled studies comparing spironolactone with other antihypertensive agents such as more potent thiazide or loop diuretics are needed to determine if the current findings are specific to aldosterone blockade or are attributable to more effective diuresis regardless of agent.

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## Table 1

Baseline values in the high- and normal-aldosterone (Aldo) groups.

| Characteristic | High-Aldo (n = 37) | Normal-Aldo (n = 71) |
|---|---|---|
| Age (y) | 55.1 ± 1.3 | 54.7 ±1.2 |
| Male/female (n) | 23/14 | 36/35 |
| Whites/Non-whites (n) | 20/17 | 38/33 |
| Body mass index (kg/m$^2$) | 32.2 ± 0.8 | 33.1 ± 0.7 |
| Duration of hypertension (y) | 18 ± 2 | 17 ± 1 |
| Heart Rate | 67 ± 2$^*$ | 72 ± 1 |
| Clinic systolic BP (mm Hg) | 146 ± 3 | 146 ± 2 |
| Clinic diastolic BP (mm Hg) | 87 ± 2 | 88 ± 1 |
| 24-hr systolic BP (mm Hg) | 148 ± 3$^‡$ | 143 ± 2 |
| 24-hr diastolic BP (mm Hg) | 85 ± 2$^‡$ | 81± 1.5 |
| No. of antihypertensives | 4.6 ± 0.2 | 4.3 ± 0.1 |
| Plasma renin activity (ng/ml/h) | 0.6 ± 0.0$^†$ | 3.1 ± 0.6 |
| Plasma aldosterone (ng/dl) | 16.3 ± 1.4$^†$ | 8.8 ± 0.6 |
| Aldosterone renin ratio | 29 ± 3$^†$ | 8 ± 1 |
| Serum creatinine (mg/dl) | 1.1 ± 0.0 | 1.1 ± 0.0 |
| 24-hr urinary aldosterone (μg/24h) | 18.7 ± 1.2$^†$ | 10.7 ± 1.3 |
| 24-hr urinary cortisol (μg/24h) | 151 ± 15$^*$ | 107 ± 7.4 |
| 24-hr urinary sodium (mEq/24h) | 182 ± 17 | 184 ± 9.1 |
| 24-hr urinary potassium (mEq/24h) | 78 ± 7.7$^*$ | 59 ± 3.2 |
| Serum potassium (mmol/L) | 3.8 ± 0.1 | 3.95 ± 0.0 |
| Brain natriuretic peptide (pg/ml) | 42.7 ± 6.1$^*$ | 28.1 ± 3.3 |

Values are mean ± SE.

$^*$ $P < 0.05$ compared to normal-Aldo;

$^†$ $P < 0.001$ compared to normal-Aldo;

$^‡$ 33 subjects in the high-Aldo and 56 subjects in the normal-Aldo group completed ambulatory blood pressure monitoring at baseline.

BP, blood pressure.

## Table 2

Baseline MRI parameters in the high- and normal-aldosterone (Aldo) groups.

| Characteristics | High-Aldo (n=37) | Normal-Aldo (n=71) |
|---|---|---|
| LVEDVI (ml/m$^2$) | 74 ± 2* | 68 ± 2 |
| LVESVI (ml/m$^2$) | 24 ± 1 | 22 ± 1 |
| LVSVI (ml/m$^2$) | 49 ± 2 | 46 ± 1 |
| LVEF (%) | 67 ± 1 | 69 ± 1 |
| RVEDVI (ml/m$^2$) | 78 ± 3* | 69 ± 2 |
| RVESVI (ml/m$^2$) | 34 ± 2* | 28 ± 1 |
| RVSVI (ml/m$^2$) | 45 ± 2 | 41 ± 1 |
| RVEF (%) | 58 ± 1 | 60 ± 1 |
| LAVI (ml/m$^2$) | 39 ± 2 | 36 ± 1 |
| LVMI (gm/m $^2$) | 81 ± 3 | 77 ± 2 |
| PWT (mm) | 10.6 ± 0.4 | 10.3 ± 0.3 |
| IVS (mm) | 12.4 ± 0.4 | 12.7 ± 0.3 |

Values are mean ± SEM.

* $P < 0.05$ compared to normal-Aldo; LVEDVI, LV end diastolic volume index, LVESVI, LV end systolic volume index; LVSVI, LV stroke volume index; LVEF, LV ejection fraction; RVEDVI, RV end diastolic volume index, RVESVI, RV end systolic volume index blood pressure; RVSVI, RV stroke volume index; RVEF, RV ejection fraction; LAVI, LA volume index; LVMI, LV mass index; PWT, posterior wall thickness, IVS, interventricular septal thickness.

**Table 3**

Effects of spironolactone in high-aldosterone (high-Aldo) or normal-aldosterone (normal-Aldo) patients at 3- and 6-months follow-up.

| | High-Aldo (n = 19) | | | Normal-Aldo (n = 15) | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **Baseline** | **3-months** | **6-months** | **Baseline** | **3-months** | **6-months** |
| Body mass index (Kg/m$^2$) | 31.7 ± 1.1 | 30.9 ± 1.2 | 31.9 ± 1.2 | 35.5 ± 1.2 | 35.2 ± 1.2 | 35.6 ± 1.2 |
| No. of antihypertensives | 4.5 ± 0.2 | 4.3 ± 0.2¶ | 3.8 ± 0.3¶ | 4.4 ± 0.3 | 4.3 ± 0.2¶ | 3.9 ± 0.3¶ |
| Heart Rate | 63 ± 3 | 74 ± 3 | 70 ± 3 | 71 ± 2 | 68 ± 3 | 73 ± 3 |
| Clinic systolic BP (mm Hg) | 141 ± 3 | 124 ± 3* | 130 ± 4* | 139 ± 4 | 122 ± 3* | 127 ± 4* |
| Clinic diastolic BP (mm Hg) | 85 ± 3 | 78 ± 2 | 80 ± 2 | 81 ± 3 | 75 ± 3† | 77 ± 3 |
| 24-hr systolic BP (mm Hg) | 140 ± 3‡ | | 130 ± 3 | 143 ± 4§ | | 135 ± 4 |
| 24-hr diastolic BP (mm Hg) | 81 ± 3‡ | | 78 ± 2 | 80 ± 3§ | | 74 ± 4* |
| Serum Potassium (mmol/L) | 3.6 ± 0.1 | 4.5 ± 0.1† | 4.2 ± 0.1† | 3.9 ± 0.08 | 4.3 ± 0.1* | 4.3 ± 0.1* |
| Serum Creatinine (mg/dl) | 1.0 ± 0.0 | 1.1 ± 0.1* | 1.1 ± 0.1* | 1.1 ± 0.1 | 1.25 ± 0.1 | 1.23 ± 0.1 |
| Plasma renin activity (ng/ml/h) | 0.6 ± 0.0 | | 12.2 ± 4.1† | 1.8 ± 0.5 | 10.5 ± 3.3† | |
| Brain natriuretic peptide (pg/ml) | 46.6 ± 9.3 | | 18.4 ± 4.1* | 17.6 ± 4.4 | | 12.6 ± 3.2 |
| LVEDVI (ml/m$^2$) | 77 ± 4 | 70 ± 4* | 68 ± 4* | 68 ± 3 | 72 ± 3 | 71 ± 4 |
| LVESVI (ml/m$^2$) | 25 ± 2 | 25 ± 2 | 23 ± 2 | 22 ± 2 | 25 ± 2 | 23 ± 2 |
| LVSVI (ml/m$^2$) | 52 ± 3 | 45 ± 2* | 45 ± 2* | 46 ± 2 | 47 ± 2 | 48 ± 3 |
| LVEF (%) | 67 ± 1 | 65 ± 2 | 67 ± 2 | 68 ± 2 | 65 ± 2 | 68 ± 2 |
| RVEDVI (ml/m$^2$) | 83 ± 6 | 73 ± 4* | 70 ± 4* | 73 ± 3 | 77 ± 3 | 73 ± 3 |
| RVESVI (ml/m$^2$) | 35 ± 3 | 32 ± 2.5 | 30 ± 3* | 30 ± 2 | 34 ± 2 | 32 ± 2 |
| RVSVI (ml/m$^2$) | 48 ± 3 | 41 ± 2* | 40 ± 2* | 43 ± 2 | 44 ± 2 | 41 ± 2 |
| RVEF (%) | 59 ± 1 | 57 ± 2 | 58 ± 2 | 59 ± 2 | 57 ± 2 | 57 ± 1 |
| Gaddam *et al.* | | | | 25 | | |
| LA VI (ml/m$^2$) | 40 ± 3 | 34 ± 3* | 33 ± 3* | 37 ± 3 | 34 ± 3 | 35 ± 3 |
| LVMI (gm/m$^2$) | 80 ± 4 | 67 ± 3† | 63 ± 3† | 81 ± 4 | 73 ± 3† | 71 ± 3† |
| IVS (mm) | 11.9 ± 0.5 | 11.7 ± 0.4 | 10.7 ± 0.6* | 12.6 ± 0.8 | 11.7 ± 0.4 | 12 ± 0.7 |
| PWT (mm) | 11.0 ± 0.6 | 10.1 ± 0.5 | 9.3 ± 0.5* | 10.4 ± 0.6 | 10.1 ± 0.4 | 9.4 ± 0.5 |

Values are mean ± SEM.

*$P < 0.05$ compared to baseline;

†$P < 0.001$ compared to baseline. Abbreviations are same as in Tables 1 and 2.

‡15 subjects completed ambulatory blood pressure monitoring at baseline and at 6 months follow up;

††12 subjects completed ambulatory blood pressure monitoring at baseline and at 6 months follow up;

¶includes spironolactone