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Original Research Article

Beneficial Impact of Spironolactone Add-on Therapy on Cardiac Mass Index in Patients with Difficult-to-Manage Hypertension

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Abstract

Objective: Resistant hypertension (RH) is defined as uncontrolled blood pressure (BP) despite adherence to at least three optimally dosed antihypertensive medications, including a diuretic. Spironolactone is a recommended add-on therapy for RH. This study aims to evaluate the efficacy of spironolactone in BP control and its impact on cardiac mass index, assessed by left ventricular mass index (LVMI), in a South Indian population.

Materials and Methods: Sixty patients diagnosed with RH were enrolled after ethical committee approval. Spironolactone (25 mg daily) was added to their existing regimen. BP and LVMI were measured at baseline, third, sixth, and ninth months. Tolerability was assessed through biochemical investigations and clinical evaluation.

Results: Fifty-six patients completed the study (55% males, 45% females; median age: 45 years). Spironolactone significantly reduced both systolic and diastolic BP at all follow-up intervals ($p < 0.001$). LVMI regression was also significant ($p < 0.001$). Serum sodium levels decreased ($p < 0.05$), while serum potassium increased ($p < 0.001$) but remained within normal limits. Hyperkalemia occurred in 3.5% (n=2), requiring study withdrawal. Minor adverse effects included vomiting (1.7%, n=1), gastric ulcers (7%, n=4), and breast discomfort (1.7%, n=1), resolving with temporary drug discontinuation.

Conclusion: Spironolactone is an effective add-on therapy for RH, significantly improving BP control and reducing LVMI, with manageable side effects. These findings support its use in managing difficult-to-treat hypertension.

Keywords: Resistant hypertension; Difficult-to-treat hypertension;Spironolactone; Blood pressure; Left ventricular mass index.

Introduction

Resistant hypertension (RH) is defined as persistently elevated blood pressure (BP) despite adherence to a combination of at least three optimally dosed antihypertensive medications, including a diuretic. Additionally, patients requiring four or more antihypertensive medications to maintain BP control are also classified as having RH.

Studies estimate that RH affects approximately 20% of hypertensive individuals worldwide, with a prevalence of 13% in the United States and 12% in Spain. In community settings, the prevalence ranges from 5% to 40% among treated hypertensive individuals. Despite being lower than previously thought, RH remains a significant public health concern. Several factors contribute to RH, including obesity, excessive alcohol intake, obstructive sleep apnea, and poor medication adherence. The addition of spironolactone, a mineralocorticoid receptor antagonist, has been identified as an effective strategy for improving BP control in patients with RH. Beyond BP reduction, spironolactone may also provide additional cardiovascular benefits, particularly in reducing cardiac morbidity by promoting regression of the left ventricular mass index (LVMI) [1,2].

This study aims to evaluate the efficacy of spironolactone as an add-on therapy in the management of RH and assess its impact on cardiac mass index in a South Indian population. The study also investigates the safety profile of spironolactone, including potential adverse effects, to determine its role as an effective therapeutic option in RH management.

Materials and Methods

This single-center, open-labeled, prospective, interventional study was conducted over nine months at a 2500-bed government tertiary care center in Southern Tamil Nadu, India. The study aimed to evaluate the efficacy of spironolactone as an add-on therapy in patients with resistant hypertension (RH) by assessing its impact on blood pressure (BP) control and left ventricular mass index (LVMI) regression. Ethical approval was obtained (Approval No: 4105/E4/3/2013), and all participants provided written informed consent.

Study Population: A total of 100 hypertensive patients were screened, out of which 60 eligible patients were enrolled. Inclusion criteria involved adults with RH (BP ≥ 140/90 mmHg) despite treatment with at least three optimally dosed antihypertensive medications, including a diuretic. Patients with secondary hypertension, chronic kidney disease (Creatinine Clearance ≤ 60 ml/min), hyperkalemia (≥5 meq/L), hepatic dysfunction, or other contraindications were excluded.

Intervention and Follow-up: Spironolactone 25 mg was added to the existing antihypertensive regimen. Patients were reviewed every 14 days for adherence, BP monitoring, and adverse effects.

Serum potassium levels were assessed regularly, and echocardiography was performed at baseline, third, sixth, and ninth months to evaluate LVMI.

Outcome Measures: Primary outcomes included BP reduction and LVMI regression. Secondary outcomes involved changes in serum sodium and potassium levels and drug tolerability.

Statistical Analysis: Data were analyzed using SPSS (Version 16.0, SPSS Inc., Chicago, USA). Student's paired t-test was applied for before-and-after comparisons, with a p-value <0.05 considered statistically significant.

A summary of patient selection and study flow is depicted in Figure 1 (CONSORT Flow Diagram).

Figure 1: CONSORT Flow Diagram

Results

Demographics and Baseline Characteristics: A total of 60 patients were initially enrolled, out of which 56 completed the study. The study population comprised 55% males and 45% females, with a median age of 45 years. The age and gender distribution of the patients is depicted in Figure 2.

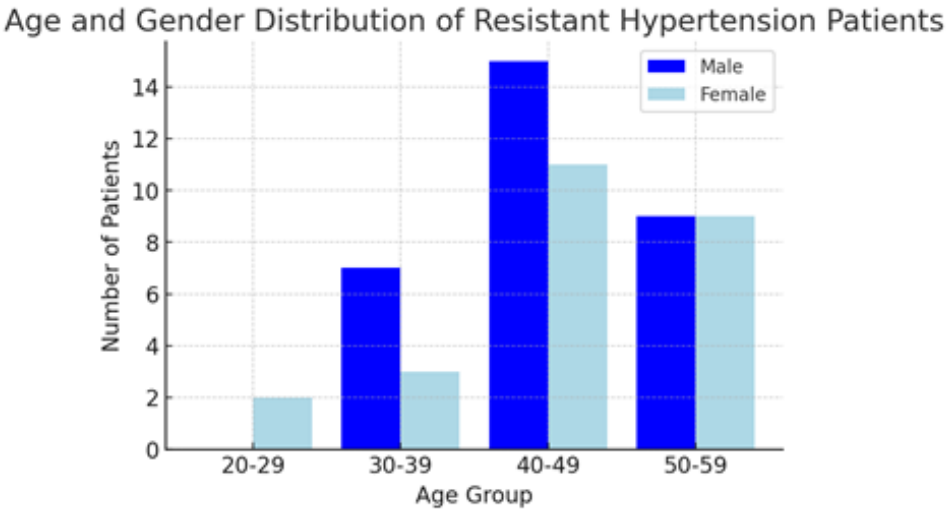

Figure 2: Age and gender distribution

BMI assessment showed that 30.35% of males and 14.28% of females had normal BMI, while 21.42% of z of females were overweight. The proportion of obese females (7.14%) was higher than obese males (1.78%). The detailed BMI and gender distribution is presented in Table 1 and Figure 3.

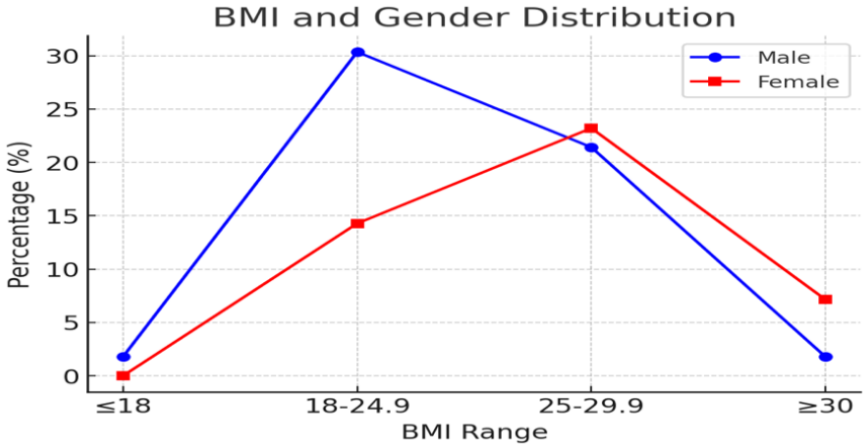

Figure 3: BMI and gender distribution

Table 1: BMI and Gender Distribution

BMI Range	Male (N, %)	Female (N, %)
≤18	1 (1.78%)	0
18-24.9	17 (30.35%)	8 (14.28%)
25-29.9	12 (21.42%)	13 (23.21%)
≥30	1 (1.78%)	4 (7.14%)

Effect of Spironolactone on Body Weight and BMI: After 9 months of spironolactone therapy, there was a slight reduction in body weight (62.21 ± 7.78 kg to 60.98 ± 7.94 kg) and BMI (25.15 ± 3.29 kg/m² to 24.63 ± 3.23 kg/m²), but these changes were not statistically significant ($p > 0.05$). The body weight and BMI data are summarized in Table 2.

Table 2: Body Weight and BMI Changes

Index	0 Month (Mean ± SD)	9 Month (Mean ± SD)	P Value
Weight (Kg)	62.21 ± 7.78	60.98 ± 7.94	0.40
BMI (Kg/m²)	25.15 ± 3.29	24.63 ± 3.23	0.20

Blood Pressure Reduction: Spironolactone significantly reduced both systolic and diastolic BP over 9 months. The mean systolic BP decreased from 160.32 ± 14.10 mmHg to 140.89 ± 13.67 mmHg ($p < 0.001$), while diastolic BP fell from 101.82 ± 7.06 mmHg to 92.85 ± 9.0 mmHg ($p < 0.001$). These results are presented

in Table 3 and visualized in Figure 4.

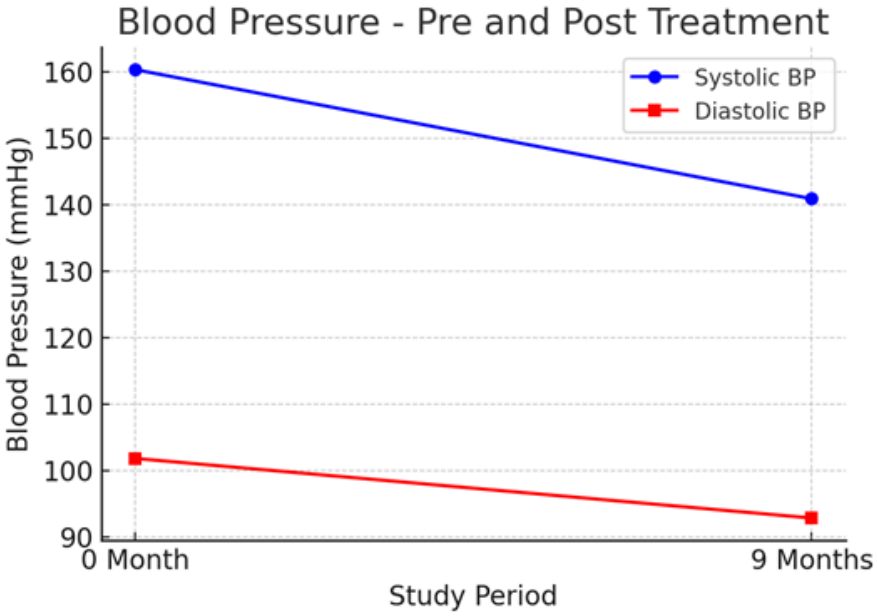

Figure 4: Blood Pressure Pre- and Post-Treatment

Table 3: Blood Pressure Pre- and Post-Treatment

Parameter	0 Month (Mean ± SD)	9 Month (Mean ± SD)	P Value
Systolic BP (mmHg)	160.32 ± 14.10	140.89 ± 13.67	< 0.001*
Diastolic BP (mmHg)	101.82 ± 7.06	92.85 ± 9.0	< 0.001*

Effect on Left Ventricular Mass Index (LVMI): LVMI showed a significant reduction from 134.69 ± 32.04 g/m² to 121.67 ± 23.49 g/m² (p = 0.001), indicating the beneficial impact of spironolactone on cardiac remodeling. The changes in LVMI are presented in Table 4 and Figure 5

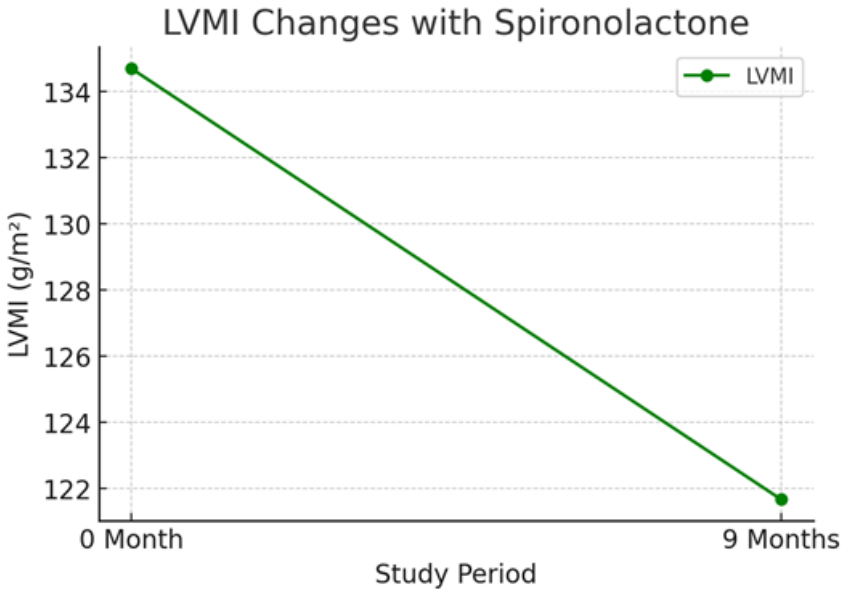

Figure 5: LVMI Changes with spironolactone

Table 4: LVMI Changes with Spironolactone

Period	Mean	SD	P Value
0 Month	134.696	32.04	0.001*
9 Months	121.679	23.49	

Serum Electrolyte Changes: A significant decrease in serum sodium levels was observed (137.70 ± 6.69 meq/L to 133.82 ± 7.76 meq/L, p = 0.03). Conversely, serum potassium levels increased from 3.44 ± 0.43 meq/L to 3.78 ± 0.75 meq/L (p = 0.004) but remained within the normal range. These findings are shown in Table 5, Figure 5 (serum sodium), and Figure 6 (serum potassium).

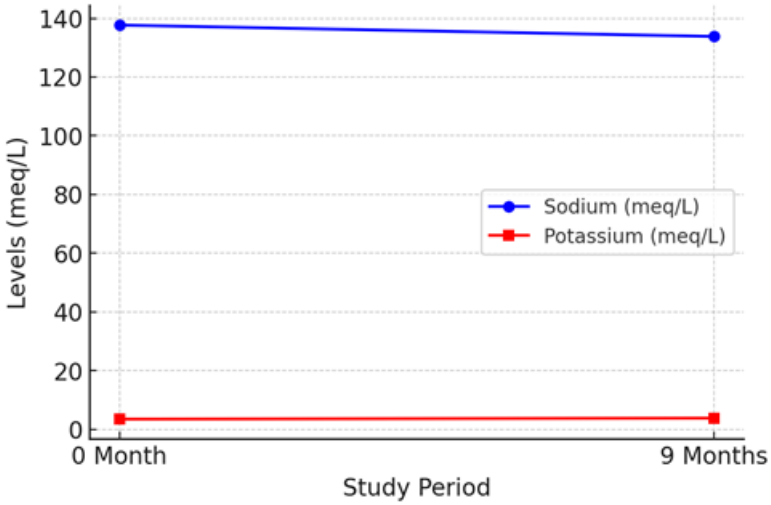

Figure 6: Serum sodium and potassium levels – Pre and Post treatments

Table 5: Serum Sodium & Potassium Levels

Parameter	Baseline (Mean ± SD)	End of Study (Mean ± SD)	P Value
Sodium (meq/L)	137.70 ± 6.69	133.82 ± 7.76	0.03*
Potassium (meq/L)	3.44 ± 0.43	3.78 ± 0.75	0.004

Adverse Effects and Tolerability: Among the 56 patients, 3.5% (n=2) developed hyperkalemia, necessitating their withdrawal from the study. Minor adverse effects included gastric ulcers (7%, n=4), vomiting (1.7%, n=1), and breast discomfort (1.7%, n=1). The percentage distribution of adverse effects is illustrated in Figure 7.

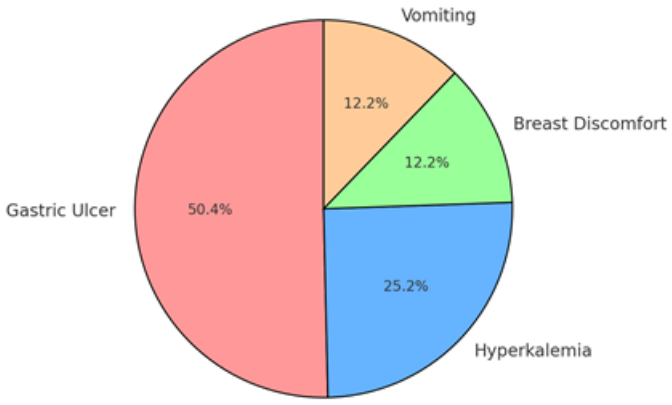

Figure 7: Percentage distribution of side effects to spironolactone Add-on Thearpy

Spironolactone was effective in significantly reducing BP and LVMI, with manageable side effects. Though minor changes in body weight and BMI were observed, they were not statistically significant. The increase in serum potassium levels was within a safe range, reinforcing the safety of spironolactone as an add-on therapy in resistant hypertension.

Discussion

Resistant Hypertension and the Role of Spironolactone: Resistant hypertension (RH) is a challenging clinical condition characterized by persistently elevated blood pressure (BP) despite the use of at least three optimally dosed antihypertensive medications, including a diuretic. Uncontrolled hypertension increases the risk of cardiovascular events such as left ventricular

hypertrophy, heart failure, stroke, and chronic kidney disease. Aldosterone excess has been identified as a key contributor to RH, leading to sodium retention, potassium excretion, and vascular remodeling, which further exacerbates BP elevation. Spironolactone, a mineralocorticoid receptor antagonist, has been widely studied for its role in BP reduction and cardiac protection in RH patients [3,4].

Efficacy of Spironolactone in BP Reduction: Our study demonstrated a significant reduction in both systolic and diastolic BP with spironolactone add-on therapy over nine months. The mean systolic BP decreased from 160.32 ± 14.10 mmHg to 140.89 ± 13.67 mmHg ($p < 0.001$), while the mean diastolic BP reduced from 101.82 ± 7.06 mmHg to 92.85 ± 9.0 mmHg ($p < 0.001$). This reduction is consistent with global studies, such as the ASPIRANT (Addition of Spironolactone in Patients with Resistant Arterial Hypertension) trial, which reported a similar decline in BP levels with spironolactone therapy. The findings reinforce the effectiveness of spironolactone in RH management, especially in patients with elevated aldosterone levels. [5,6]

Impact on Left Ventricular Mass Index (LVMI): Beyond BP control, the study assessed the impact of spironolactone on left ventricular mass index (LVMI), a key marker of hypertensive heart disease and cardiac morbidity. The LVMI significantly reduced from 134.69 ± 32.04 g/m² to 121.67 ± 23.49 g/m² ($p = 0.001$) over nine months. This suggests that spironolactone plays a crucial role in left ventricular remodeling and regression of hypertrophy in RH patients. Our results align with the findings of Krishna Gaddam et al., who demonstrated rapid LVMI reduction with mineralocorticoid receptor antagonists in patients with resistant hypertension and hyperaldosteronism. [7,8]

Changes in Body Weight and BMI: Spironolactone therapy led to a slight reduction in body weight (62.21 ± 7.78 kg to 60.98 ± 7.94 kg, $p = 0.40$) and BMI (25.15 ± 3.29 kg/m² to 24.63 ± 3.23 kg/m², $p = 0.20$). However, these changes were not statistically significant. This contrasts with some Western studies, where significant weight reduction was observed after long-term spironolactone use, possibly due to better adherence to lifestyle modifications in those populations. [9,10]

Serum Electrolyte Changes and Tolerability: As expected, spironolactone significantly influenced serum sodium and potassium levels. Serum sodium levels decreased from 137.70 ± 6.69 meq/L to 133.82 ± 7.76 meq/L ($p = 0.03$), while serum potassium increased from 3.44 ± 0.43 meq/L to 3.78 ± 0.75 meq/L ($p = 0.004$). Although potassium levels rose, they remained within the normal range, reinforcing the safety profile of spironolactone when used with appropriate monitoring. [11,12]

Adverse Effects and Safety Profile: A small percentage of patients (3.5%) developed hyperkalemia, requiring discontinuation of spironolactone. Other minor adverse effects included gastric ulcers (7%), vomiting (1.7%), and breast discomfort (1.7%), which were managed with temporary drug discontinuation and symptomatic treatment. These side effects are consistent with previous studies, highlighting the need for routine biochemical monitoring, particularly for potassium levels, to ensure patient safety. [13,14]

Clinical Implications: This study confirms that spironolactone is a highly effective and well-tolerated add-on therapy for resistant hypertension. Beyond BP reduction, it offers cardioprotective benefits by reducing left ventricular hypertrophy, which is a major predictor of adverse cardiovascular events. The findings also emphasize the importance of serum potassium monitoring to prevent hyperkalemia-related complications. [15]

Limitations of the Study: Despite its strengths, our study has some limitations. Firstly, it was a single-center study, which may limit the generalizability of results. Secondly, the study duration was only nine months, whereas long-term effects of spironolactone in RH patients require further investigation. Additionally, aldosterone levels were not measured, which could have provided better insight into the subgroup of patients who benefit the most from spironolactone therapy.

Future Directions: Future studies should include a larger patient population, a longer follow-up period, and a randomized controlled trial design to validate these findings. Additionally, exploring the role of genetic factors and aldosterone levels in treatment response could pave the way for personalized therapy in resistant hypertension.

Conclusion

In conclusion, spironolactone significantly reduces BP and LVMI in patients with resistant hypertension, demonstrating both antihypertensive and cardioprotective effects. While mild electrolyte disturbances and minor adverse effects were observed, spironolactone remains a safe and effective add-on therapy when used with appropriate monitoring. Given its proven benefits, spironolactone should be considered an integral component of RH management to reduce long-term cardiovascular risks.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this study.

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References

1. Segura J, Sierra ADL, Ruilope LM. Detection and treatment of resistant hypertension. Curr Hypertens Rep. 2010; 12:325-330.
2. Viera AJ. Resistant Hypertension. J Am Board Fam Med. 2012; 25:487-495.
3. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. 2011; 57:1076–80.
4. De la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011; 57:898–902.
5. Gupta R. Trends in hypertension epidemiology in India. J Hum Hypertension. 2004;18(2):73-8.
6. Feely J, Mahmud A. Spironolactone in resistant hypertension. Hypertension. 2007; 50:57.
7. Lariviere R, Thibault G, Schiffrin EL. Increased endothelin I content in blood vessels of deoxycorticosterone acetate-salt sensitive hypertensive but not in spontaneously hypertensive rats. Hypertension. 1993; 21:294-300.
8. Duprez DA. Aldosterone and the vasculature: Mechanisms mediating resistant hypertension. J Clin Hypertens.2007;9:13–18.
9. Theodore LG, David AC. Resistant hypertension, obesity, sleep apnea and aldosterone: Theory and therapy. Hypertension. 2004; 43:518-524.
10. Vaclavik J, Sedlak R, Plachy M, Navratil K. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT). Hypertension. 2011; 57:1069-1075.
11. Chapman N, Dobson J, Wilson S, Dahlof B, Wedel H, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007; 49:839-845.
12. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. Am J Hypertens. 2003; 16:925-930.
13. de Souza F, Muxfeldt E, Fiszman R. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension. 2010; 55: 147-152.
14. Nicola CE, Richard PS, Paul MS, Charles JF, Jonathan NT. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease. JACC. 2009; 54(6):505-511.
15. Gaddam K, Corros C, Pimenta E. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism. Hypertension. 2010; 55:1137-1142.