



Spirinolactone and Left Ventricular Hypertrophy in End Stage Renal Disease

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Introduction

- Cardiovascular disease accounts for significant morbidity and mortality in dialysis patients.
- Left ventricular hypertrophy (LVH) increases cardiovascular risk. End Stage Renal Disease (ESRD) patients frequently develop LVH.
- Spironolactone (SPR) therapy has been shown to reduce eccentric LVH (eLVH) in heart failure patients in the RALES study (NEJM, 341: 709-717, 1999).
- SPR has been studied in patients with cLVH but to a lesser extent than patients with eLVH. SPR has shown some reduction in LVH in these patients in certain studies.
- SPR effects on LVH in dialysis patients has not been extensively studied.
- Echocardiography assessment of left ventricular mass (LVM) and geometry varies with fluctuations in volume status and limits its usefulness in patients undergoing hemodialysis.
- Cardiac magnetic resonance images (cMRI) of the heart are detailed, precise, reproducible, and independent of volume status.

Methods

- We performed a prospective, non-blinded study obtaining a cardiac MRI on 13 dialysis patients at baseline and after receiving spironolactone 25 mg daily for nine months.
- LV mass (LVM), LV mass index (LVMI), length, diameter, ejection fraction, end diastolic volumes, relative wall thickness (RWT), and sphericity index (SI) were determined using FIESTA sequences.

Table 1. Demographics of analyzed patients n=13

Age (years)	66 (35-78)
Dry Weight (Kg)	76 (54-110)
Body surface area (m ²)	1.9 (1.6-2.3)
Body mass index	26(18-39)
Female	4
Male	9
Etiology of ESRD	
Diabetes mellitus	4
Hypertension	4
Glomerulonephritis	3
Other	2
Co-morbid conditions	
Coronary artery disease	4
Diabetes Mellitus	6
Hypertension	12
Years on HD	6 (1-21)
ARB	0
ACE Inhibitor	7

Table 2. Cardiac MRI Results of 13 dialysis patients compared to 108 healthy controls

	LVM (g)	LVMi (g/m ²)	RWT	Ejection Fraction (%)	End Diastolic Volume (mL)	SI
Normal	112±27	59±11	0.35±0.1	69±6	150±31	2±0.2
Pre SPR	177±60	97±36	0.60±0.2	59±10	184±55	2.1±0.3
p value	0.002	0.001	0.0004	0.005	0.072	0.33

LVM- Left ventricular mass; LVMI- Left ventricular mass index; RWT-Relative wall thickness; SI- Sphericity Index. p value ≤ 0.05 considered statistically significant

Table 3. Cardiac MRI Results before and after spironolactone (n=13)

	LVM (g)	LVMI (g/m ²)	RWT	Ejection Fraction (%)	End Diastolic Volume (mL)	SI
Pre SPR	177±60	97±36	0.60±0.20	59±10	184±55	2.1±0.3
Post SPR	184±60	101±39	0.56±0.20	60±10	170±60	2.1±0.2
p value	0.77	0.79	0.59	0.80	0.54	0.70

LVM- Left ventricular mass; LVMI- Left ventricular mass index; RWT-Relative wall thickness; SI- Sphericity Index. p-value ≤ 0.05 considered statistically significant

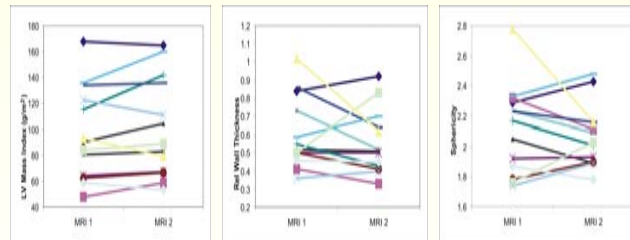


Figure 1

Figure 2

Figure 3

Definitions

- LV Mass Index = LV Mass / Body Surface Area
- End Diastolic Volume Index = End Diastolic Volume / Body Surface Area
- LV Diameter = Septum --- Posterior wall distance (short axis view in diastole)
- LV Length = Apex --- MV Annulus distance (4 chamber view in diastole)
- LV Sphericity Index = LV Length / LV Diameter
- Relative Wall Thickness = $\frac{\text{Septal Wall Thickness} + \text{Lateral Wall Thickness}}{\text{LV Diameter}}$

Results

- Table 2: Cardiac MRI revealed a relative wall thickness of 0.60, an LV cavity size of 184 mL, and an LVMI of 97 in the dialysis patients (pre spironolactone) compared to 0.35, 150 ml and 59 respectively in healthy controls.

- Table 3, Figures 1,2,3: LVM, LVMI, RWT, End Diastolic Volume and Sphericity Index were unchanged after 270 days of spironolactone

Study Limitations

- Early Study Termination
 - The original power analysis indicated that 30 patients needed to be enrolled
 - Recruiting difficulties and subject compliance with the study protocol limited the number of patients that completed the study
 - Interim analysis revealed a lack of study drug effect leading to early study termination
- Medication Compliance
 - Thirteen patients completed the study.
 - The study medication was taken by these thirteen patients at home. There was no direct observation of the study medication being consumed.

Discussion

Cardiac Geometry

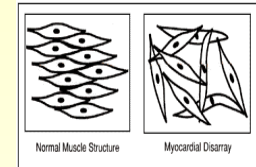
- Heart failure patients with ischemic dilated cardiomyopathy (eLVH) have a significantly enlarged LV cavity
- Hypertensive patients have a thickened LV wall and a preserved or slightly decreased LV cavity (cLVH)
- ESRD Patients have a thickened LV wall with a slightly enlarged LV cavity.



- The RALES trial demonstrated that spironolactone is effective in patients with eLVH but little data exists regarding its effect in patients with ESRD.
- Though the results in this study could be related to other issues, it is possible that the lack of response to spironolactone is related to the differences in cardiac geometry between heart failure (eLVH) and dialysis patients.

Cardiac Histology

- The lack of response to SPR could also be at the cellular level.
 - Primary histological changes in patients with LVH are intracellular and involve changes in the number and arrangement of the sarcomeres. In chronic cases of LVH widespread interstitial fibrosis occurs.



- In ischemic cardiomyopathy (eLVH) the LV responds by adding new sarcomeres in-series to existing sarcomeres, which leads to ventricular dilation. The wall thickness normally increases in proportion to the increase in chamber radius.
- In cLVH the wall thickness greatly increases as new sarcomeres are added in-parallel to existing sarcomeres. The chamber radius may not change.
- The lack of response of SPR in dialysis patients could be due to the differences in histology between dialysis patients and patients with eLVH.

Other Possible Causes for the Lack of SPR Effect

- CaPO₄ product, uremic environment, hyperparathyroidism, and chronic anemia

Conclusions

- In this study the dialysis patients had a thick left ventricular wall, an increased relative wall thickness and a slightly enlarged left ventricular cavity.
- Nine months of spironolactone did not have an effect on the geometry of the heart in this study
- This study was limited secondary to inadequate power and undocumented subject compliance with the protocol.

Future Studies

- Future studies will center around histopathological features of ESRD focusing on the mechanism of increased wall thickness, ie. hypertrophy vs massive fibrosis
- Upon determination of the mechanism of LVH in ESRD patients, pharmacologic therapy can then be tailored to treat LVH in ESRD patients