Spironolactone and Left Ventricular Hypertrophy in End Stage Renal Disease

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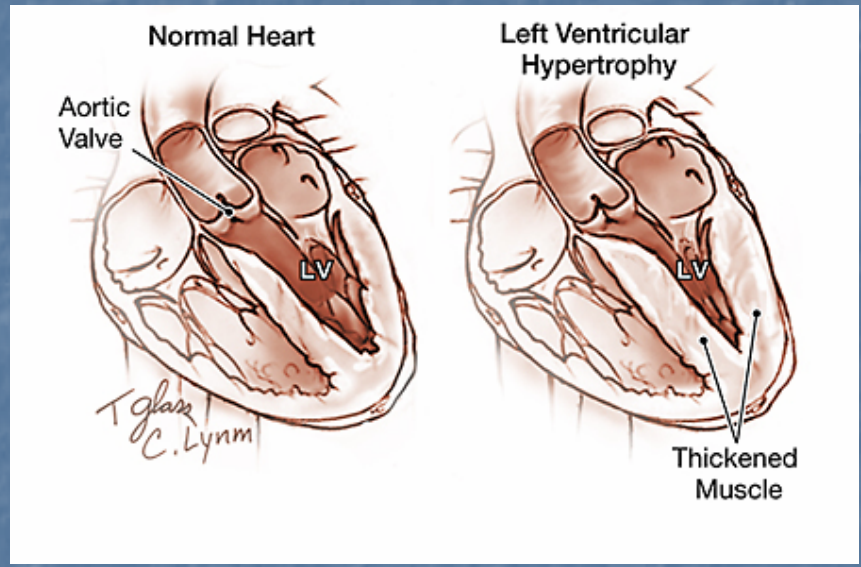
Introduction – Left Ventricular Hypertrophy

- Cardiovascular disease accounts for significant morbidity and mortality in dialysis patients
- Left ventricular hypertrophy (LVH) increases the risk of cardiovascular event
- End Stage Renal Disease (ESRD) patients frequently develop LVH
  - Noted on EKG, echocardiography, and at autopsy



Introduction – Cardiac Imaging

- 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 LVM are detailed, precise, and extremely reproducible. The images are independent of volume status.

Introduction - Spironolactone

- 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 inhibits aldosterone which is thought to play a role in myocyte fibrosis and collagen deposition
- SPR effects on LVH in ESRD patients have not been extensively studied
- SPR has been studied in patients with concentric LVH (cLVH) and has been shown to have an effect on LVH although not as significant of an effect as the RALES trial

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 9 months
- LV mass (LVM), LV mass index (LVMi), length, diameter, ejection fraction, end diastolic and end systolic volumes, relative wall thickness (RWT), and sphericity index (SI) were determined using cardiac MRI (FIESTA sequences) and were compared to 198 healthy controls (historic data)

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

$$\text{Relative Wall Thickness} = \frac{\text{(Septal Wall Thickness + Lateral Wall Thickness)}}{\text{LV Diameter}}$$

Table 1. Demographics (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 disease	4
Diabetes Mellitus	6
Hypertension	12
Years on HD	6 (1-20)
ARB	0
ACE Inhibitor	7

Results

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

	LVM (g)	LVMi (g/m2)	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

Results

- Cardiac imaging demonstrated that the typical appearance of a dialysis patient's heart is massive left ventricular hypertrophy with a profoundly thickened LV wall around a slightly enlarged left ventricular cavity.
  - Cardiac MRI revealed a left ventricular mass index and a relative wall thickness of 97 g/m^2 and 0.60 respectively in the study patients (pre spironolactone) while the normal values obtained in 108 healthy controls were a LVMi of 59 g/m^2 and a RWT of 0.35
  - End diastolic volume which is a measure of LV cavity size was 184 mL in the study patients (pre spironolactone). The LV cavity was 150 mL in the healthy controls.
  - Refer to Table 2

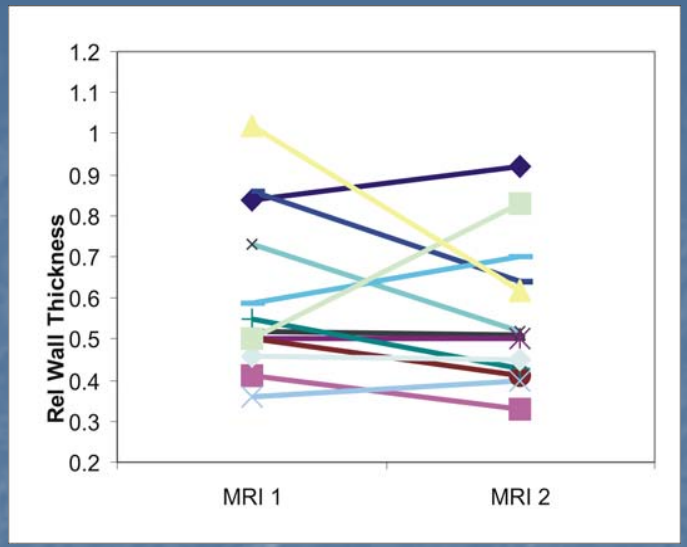
Results

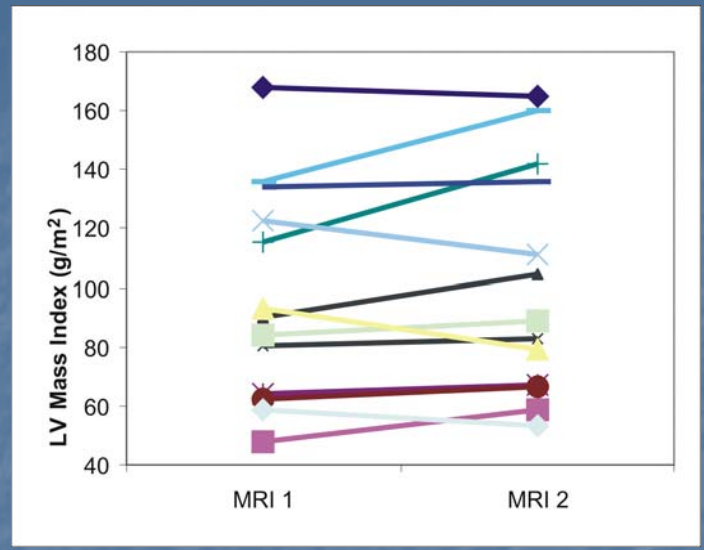
Table 3. Cardiac MRI Results before and after spironolactone (n=13)

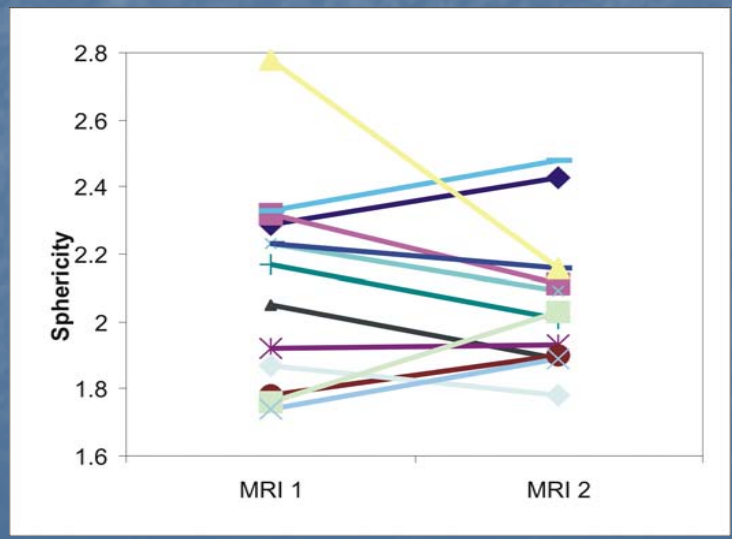
	LVM (g)	LVMi (g/m^2)	RWT	Ejection Fraction (%)	End Diastolic Volume (mL)	SI
Pre SPR	177±60	97±36	0.60±0.2	59±10	184±55	2.1±0.3
Post SPR	184±60	101±39	0.56±0.2	60±10	170±60	2.1±0.2
p value	0.77	0.79	0.59	0.80	0.54	0.70

LVM- Left ventricular mass; LVMi- Left ventricular mass index; RWT-Relative wall thickness; SI- Sphericity Index

p value < 0.05 considered statistically significant


Rel Wall Thickness
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
MRI 1
MRI 2


LV Mass Index (g/m²)
180
160
140
120
100
80
60
40
MRI 1
MRI 2


Sphericity
2.8
2.6
2.4
2.2
2
1.8
1.6
MRI 1
MRI 2

Results

- There was no change in LVMi, RWT, End Diastolic Volume, and sphericity index in dialysis patients by cardiac MRI after receiving 270 days of spironolactone
  - Refer to Table 3

Discussion – Study Limitations

- Early Study Termination
  - The original power analysis indicated that 34 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

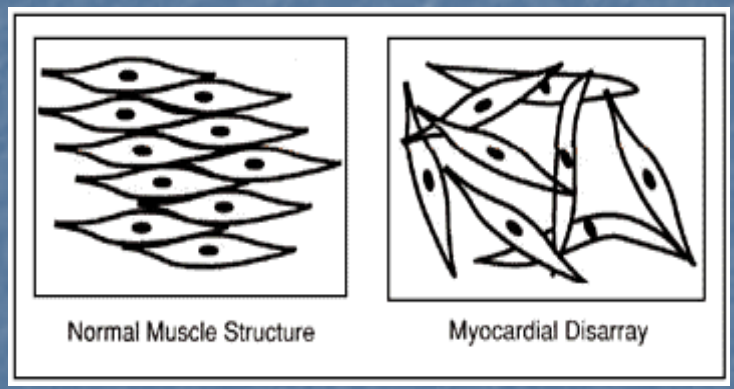
Discussion – Cardiac Geometry

- 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

Discussion – 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. The actual number of myocardial cells is unchanged.

Sarcomere arrangement



Discussion – Cardiac Histology

- 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.

Discussion – Other possible causes for the lack of response of SPR

- Calcium phosphorous product
- Hyperparathyroidism
- Uremic environment

Conclusions

- In this study the dialysis patients had a thick left ventricular wall with 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 however this study was not adequately powered
  - Compliance of the patients could have played a major role in the results of this study

Future Studies

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