

Effect of Spironolactone on Exercise Tolerance and Arterial Function in Older Adults with Heart Failure with Preserved Ejection Fraction

Background:

- Heart failure with preserved ejection fraction (HFpEF), a condition whose prevalence is increasing and prognosis is worsening, is largely found in older women, in whom 90% of new HF cases are HFpEF.
- Exercise intolerance is the primary chronic symptom, and previous trials have shown aldosterone antagonism (with spironolactone) may positively benefit this aspect of the disease as well as potentially improving other symptoms.

Objective:

- This study was performed to evaluate the effects of aldosterone antagonism (specifically spironolactone) on exercise intolerance in older adults with HFpEF.

Methods:

- Randomized, placebo-controlled, double-blind, prospective study over 9 months
- 80 patients enrolled (42 spironolactone, 38 placebo)
 - Inclusion: HFpEF (defined below), clinical HF NHANES score ≥ 3 , disease verification by a board-certified cardiologist
 - HFpEF – history or S&S of HF, preserved LVEF $\geq 50\%$, and no evidence of other medical conditions mimicking HF symptoms
 - Exclusion: aldosterone antagonist use within 3 months, known CI, concomitant K-sparing diuretics, concomitant K supplements, baseline K $>5.0\text{mEq/L}$, baseline SCr $\geq 2.5\text{mg/dL}$
- Spironolactone 25mg daily or matching placebo
 - Spironolactone 12.5mg daily if SCr $\geq 2.0\text{mg/dL}$ or K $>4.5\text{mEq/L}$
- Primary outcomes: exercise performance (peak VO_2), quality of life (MLHFQ score)
- Secondary outcomes: aortic distensibility, LV structure and function, carotid artery stiffness, pulse wave velocity, LV diastolic filling
- 60 patients needed for 94% power (5% change in peak VO_2) and 90% power (20% change in MLFHQ score)

Results:

- 71 patients completed the trial (37 spironolactone, 34 placebo)
- Findings:

Factor	Spironolactone			Placebo			P-Value
	Baseline	4 Months	Final	Baseline	4 Months	Final	
	Mean \pm Standard Deviation						
Peak exercise (bike)							
VO_2 , mL/min	1,141 \pm 308	1,146 \pm 385	1,167 \pm 384	1,152 \pm 338	1,180 \pm 369	1,202 \pm 383	.37
Indexed VO_2 , mL/kg per minute	13.5 \pm 2.9	13.6 \pm 3.5	13.8 \pm 3.2	13.3 \pm 2.9	13.5 \pm 3.4	13.9 \pm 3.7	.38
Time, minutes	8.1 \pm 3.0	8.5 \pm 2.9	8.4 \pm 3.1	7.9 \pm 3.1	8.2 \pm 3.1	8.3 \pm 3.0	.76
Workload, watts	63 \pm 26	67 \pm 26	68 \pm 26	60 \pm 26	64 \pm 27	66 \pm 25	.85
Heart rate, beats per minute	122 \pm 23	121 \pm 25	124 \pm 27	119 \pm 17	118 \pm 20	118 \pm 19	.88
Systolic blood pressure, mmHg	181 \pm 25	169 \pm 20	176 \pm 22	185 \pm 26	181 \pm 26	183 \pm 28	.04
Diastolic blood pressure, mmHg	83 \pm 12	76 \pm 9	78 \pm 9	81 \pm 9	80 \pm 12	82 \pm 10	<.001
Pulse pressure	98 \pm 19	94 \pm 15	98 \pm 17	104 \pm 21	101 \pm 20	101 \pm 23	.62
Respiratory rate, bpm	32 \pm 7	32 \pm 6	33 \pm 7	35 \pm 8	35 \pm 9	35 \pm 9	.94
Oxygen pulse, mL/beat	9.4 \pm 2.1	9.5 \pm 2.5	9.6 \pm 3.0	9.8 \pm 3.0	10.2 \pm 3.5	10.4 \pm 3.8	.22
VCO_2 , mL/min	1,278 \pm 394	1,338 \pm 471	1,381 \pm 485	1,281 \pm 402	1,383 \pm 454	1,363 \pm 423	.81
VE, L/min	41 \pm 13	44 \pm 17	46 \pm 17	41 \pm 12	43 \pm 13	43 \pm 13	.40
Respiratory exchange ratio	1.11 \pm 0.10	1.16 \pm 0.12	1.17 \pm 0.12	1.12 \pm 0.10	1.17 \pm 0.09	1.15 \pm 0.10	.48
VE/ VCO_2 slope	31 \pm 6	31 \pm 5	32 \pm 7	31 \pm 5	30 \pm 4	30 \pm 4	.04
Ventilatory anaerobic threshold, mL/min	683 \pm 167	703 \pm 206	669 \pm 162	719 \pm 175	725 \pm 205	708 \pm 182	.47
6-minute walk distance, feet	1,377 \pm 247	1,508 \pm 204	1,430 \pm 263	1,361 \pm 261	1,419 \pm 276	1,426 \pm 284	.96
Minnesota Living with Heart Failure Questionnaire score							
Emotional	5 \pm 5	4 \pm 4	4 \pm 4	4 \pm 4	4 \pm 5	3 \pm 4	.60
Physical	16 \pm 11	15 \pm 10	14 \pm 9	13 \pm 10	14 \pm 11	11 \pm 9	.88
Total	32 \pm 21	29 \pm 20	29 \pm 16	28 \pm 19	29 \pm 23	25 \pm 16	.91
Neurohormones							
Aldosterone	9.1 \pm 6.0	17.6 \pm 9.1	17.2 \pm 8.6	10.0 \pm 9.0	10.1 \pm 7.5	9.7 \pm 5.3	<.001
B-type natriuretic peptide	55 \pm 46	55 \pm 42	58 \pm 44	61 \pm 50	54 \pm 38	55 \pm 46	.20

Factor	Mean \pm Standard Deviation		P-Value
	Spironolactone	Placebo	
Diastolic measures			
Ea, cm/s			
Lateral	7.0 \pm 2.1	7.0 \pm 2.1	
Septal	6.3 \pm 1.2	5.9 \pm 1.4	
Early deceleration time, ms	235 \pm 57	242 \pm 59	
E, cm/s	80 \pm 19	78 \pm 21	
Atrial mitral flow velocity, cm/s	88 \pm 20	87 \pm 19	
Early/atrial mitral flow velocity ratio	0.91 \pm 0.2	0.89 \pm 0.2	
E/a	12.2 \pm 4.5	12.1 \pm 4.9	
Lateral	13.3 \pm 4.2	14.0 \pm 5.2	
Septal	13.3 \pm 5.6	13.9 \pm 5.4	
14.0 \pm 4.5	14.0 \pm 4.5	13.8 \pm 5.0	
12.6 \pm 4.2	12.6 \pm 4.2	12.6 \pm 4.2	
Left ventricular and arterial functional measures			
Left ventricular function (CMRI)			
Mass, g	126 \pm 45	124 \pm 39	
Mass/ventricular volume ratio	1.8 \pm 0.4	1.7 \pm 0.4	
End diastolic volume, mL	73 \pm 21	73 \pm 20	
End systolic volume, mL	29 \pm 10	28 \pm 8	
Stroke volume, mL	45 \pm 14	45 \pm 15	
Ejection fraction, %	61 \pm 7	62 \pm 8	
Aortic function (CMRI)			
Phasic area change, mm ²	44 \pm 28	59 \pm 45	
Distensibility, 10 ⁻³ /mmHg	0.88 \pm 0.45	1.20 \pm 0.86	
Aortic compliance, mm ³	0.72 \pm 0.42	1.03 \pm 0.95	
Systolic blood pressure, mmHg	139 \pm 18	134 \pm 15	
Diastolic blood pressure, mmHg	76 \pm 11	74 \pm 8	
Pulse pressure, mmHg	62 \pm 12	60 \pm 12	
Pulse pressure/stroke volume	1.46 \pm 0.43	1.44 \pm 0.43	
Carotid arterial compliance, 10⁻³/mmHg			
Carotid arterial distensibility, 10 ⁻³ /mmHg	0.49 \pm 0.05	0.44 \pm 0.05	
Carotid arterial distensibility, 10 ⁻³ /mmHg	1.81 \pm 0.20	1.64 \pm 0.19	
Carotid-femoral pulse wave velocity, mm/s	1,142 \pm 118	1,137 \pm 123	
1,195 \pm 98	1,195 \pm 98	1,296 \pm 142	

- Exercise Performance: no significant difference
 - Spironolactone -0.4 mL/kg/min (95% CI, -1.1-0.4mL/kg/min, P = 0.38)
- Quality of Life: no significant difference (P = 0.81)
- LV Structure and Function: no significant difference
- Arterial Function: no significant difference
- Neurohormones: significant difference with aldosterone, not with BNP
 - Spironolactone 17.2 +/- 8.6 vs. 9.7 +/- 5.3 ng/dL Placebo (P < 0.001)
- Blood Pressure: significant difference for both SBP and DBP
 - SBP (P = 0.04), DBP (P < 0.001)
- Authors concluded that in older adults with stable compensated HFpEF, 9 months of spironolactone 25mg daily was well tolerated and reduced BP but did not improve exercise capacity, QoL, LV mass, or arterial stiffness.

Strengths:

- Employed a study sample that more accurately reflects HFpEF in the population
- Utilized CMRI over Echo due to its increased sensitivity
- Strong study design with adequate power achieved

Limitations:

- Failed to include patients with more severe disease (higher BNP, decompensated HF, other comorbidities that contribute to exercise intolerance)
- Type II error was possible given the noticeable difference in treatment effect despite the nonsignificance calculated
- Only provided power for the two primary outcomes but did not address the myriad of secondary outcomes assessed
- Study duration may not be adequate to determine long-term benefit
- Treatment groups had a noticeable difference in baseline characteristics despite nonsignificance calculated
- Relatively small study confined to one specific location

Conclusions:

- Aligning with other published studies, spironolactone has not shown benefit in reducing exercise intolerance. However, it does benefit blood pressure to a lesser extent which can positively impact the progression of heart failure. It is possible that use over a time period much longer than 9 months could result in a slowing of the major chronic symptoms of the disease and even the progression of the disease itself.
- In current practice, spironolactone could be considered in patients with HFpEF and a blood pressure above goal as long as it is tolerated and does not prevent the use of other, more necessary medications.

*Eric Kinney, PharmD Candidate 2018
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