European Society of Cardiology
Heart Failure Annual Meeting

Highlights Session: Heart Failure with Preserved Ejection fraction

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DECLARATION OF INTEREST

- Consulting/Royalties/Owner/ Stockholder of a healthcare company
- Research contracts

HFpEF 2013

- Poor animal models
- Limited understanding of pathophysiology
- Heterogeneous Disorder
- Limited consensus in the HF community on etiology, diagnosis or treatment
- Can’t agree on a name
- Anecdote-Based Medicine

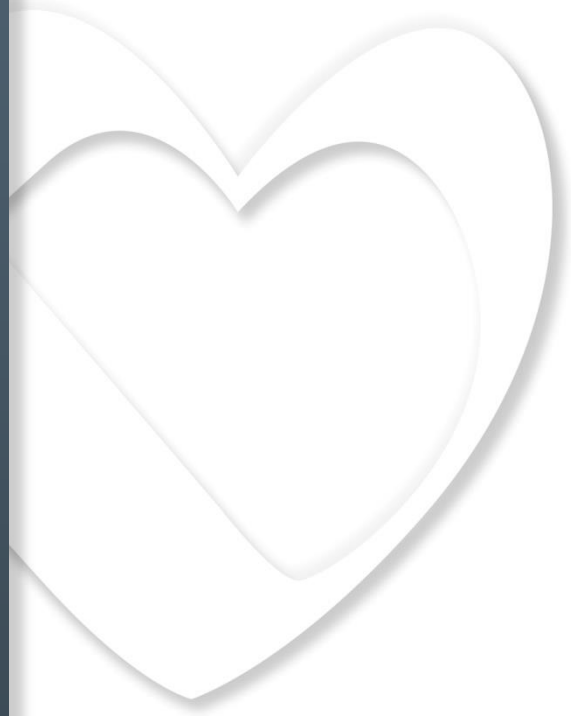
2012-2013:
An Important year for HFpEF

- **ESC 2012**
  - PARAMOUNT (LCZ696) presented
  - ALDO-DHF (Spironolactone) Presented
- **ACC 2013**
  - RELAX (Sildenafil) presented
- **AHA 2013**
  - TOPCAT to be presented
- **Q4 2013 – PARAGON-HF outcomes trial starting**

Studies in HFpEF at ESC-HF

- Epidemiology
- Pathophysiology
- Diagnosis
- Cardiac Structure and Function
- Therapy

EPIDEMIOLOGY



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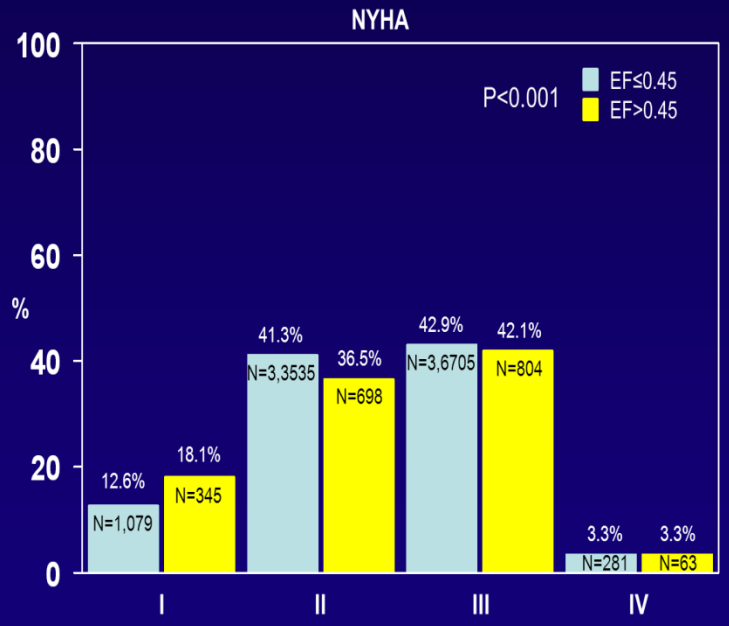
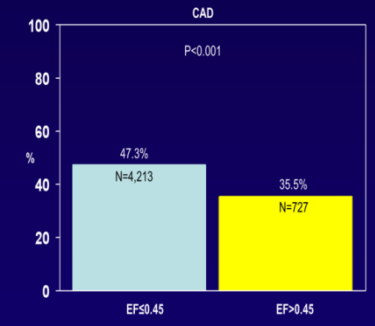
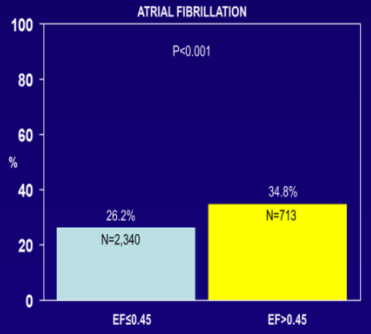
SURVIVAL IN AMBULATORY HEART FAILURE PATIENTS WITH PRESERVED EJECTION FRACTION, 1999-2011

Malcolm Arnold[1], Peter Liu[2], Marie-Hélène LeBlanc[3], Jonathan Howlett4, Andrew Ignaszewski[5], Annemarie Kaan[5], Margaret Edmonds[5], Marilyn Winkler[6], Pamela Luehr[7], Estrellita Estrella-Holder[8] *on behalf of all the nurses, dietitians, allied health care providers, and physicians in the CHFN*

10,965 ambulatory HF patients with a documented LVEF

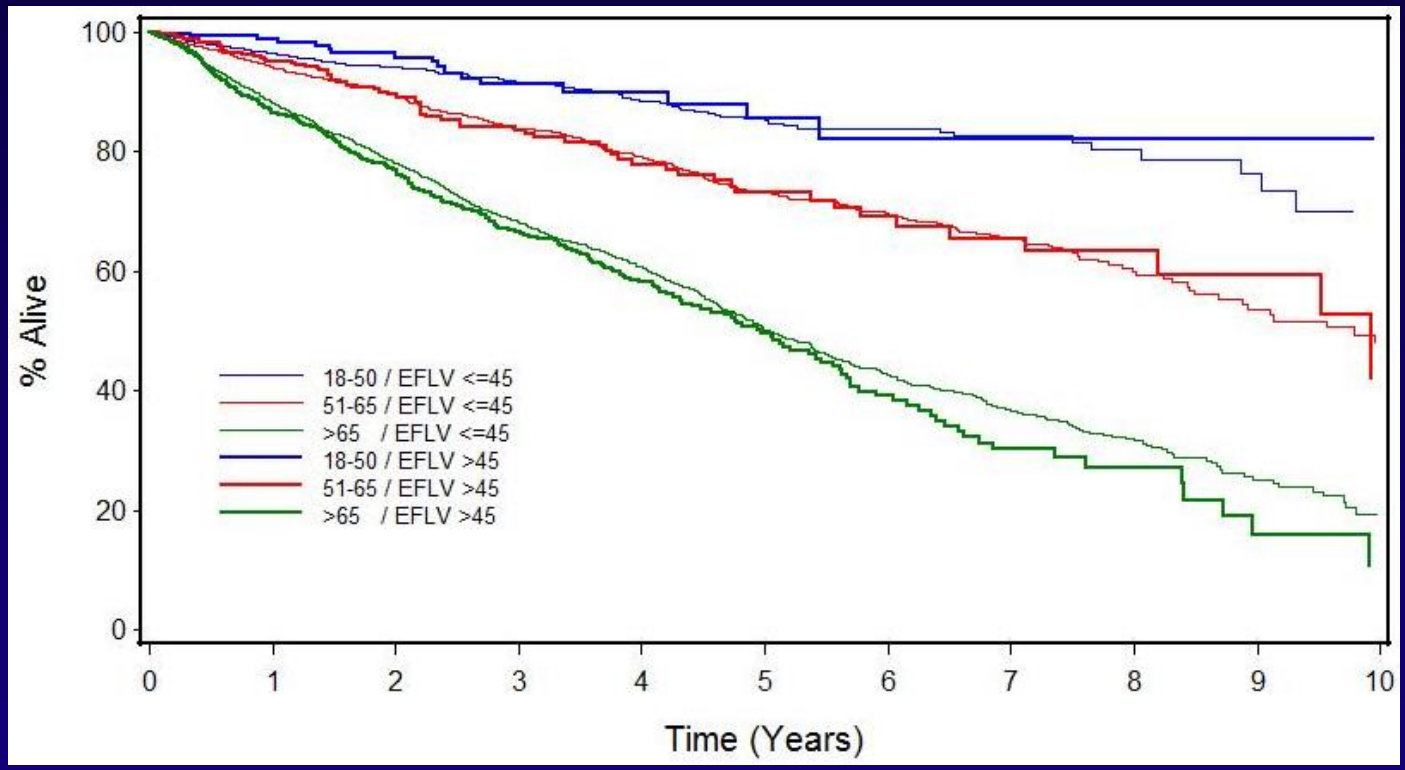






- **Distribution of NYHA class similar in HFpEF and HFrEF**
- **Prevalence of CAD slightly lower in HFpEF**
- **Prelalence of atrial fibrillation slightly higher in HFpEF**

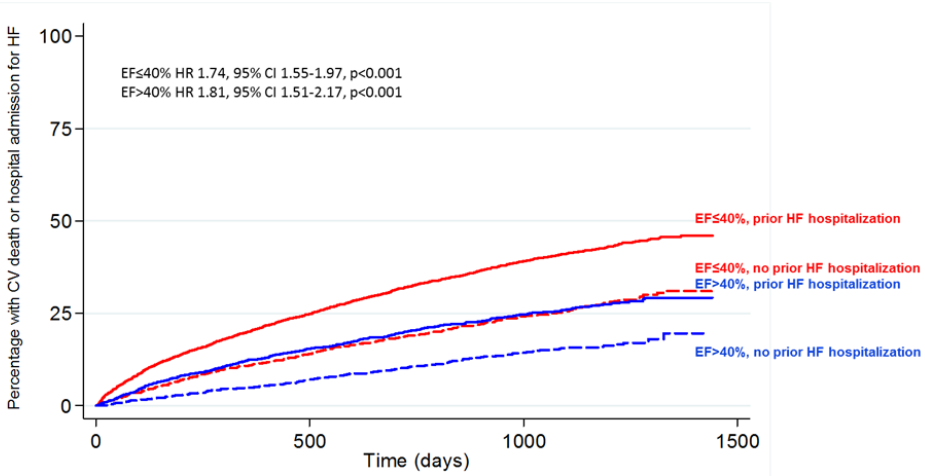
NATIONAL CHFN DATA
HEART FAILURE and LVEF

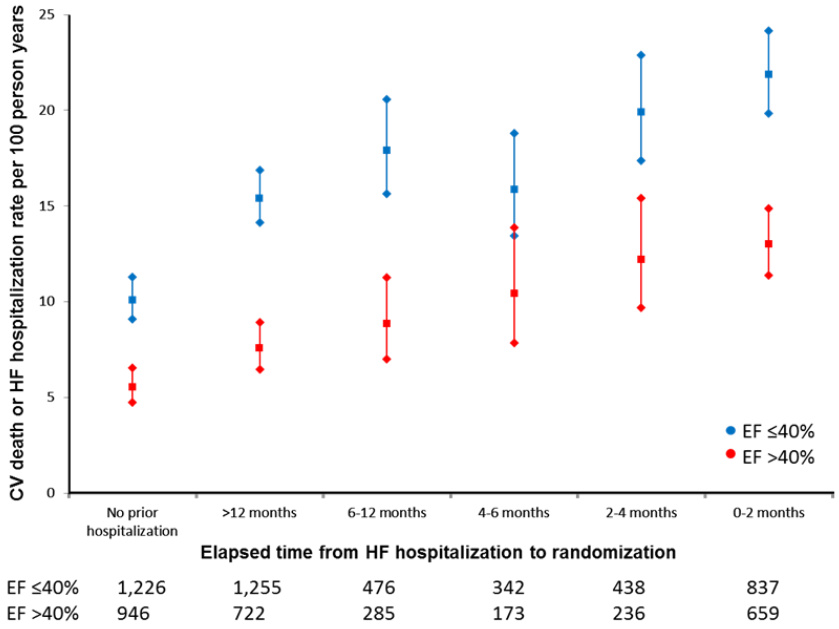


- **Preserved LVEF did not confer benefit in survival.**
- **Similar overall mortality in HFpEF and HFrEF patients**
- **Findings are similar to previously reported by Olmstead County and Toronto registry, but different from clinical trials**

Recent prior heart failure hospitalization is associated with increased risk of clinical events in patients with reduced and preserved ejection fraction in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) trials

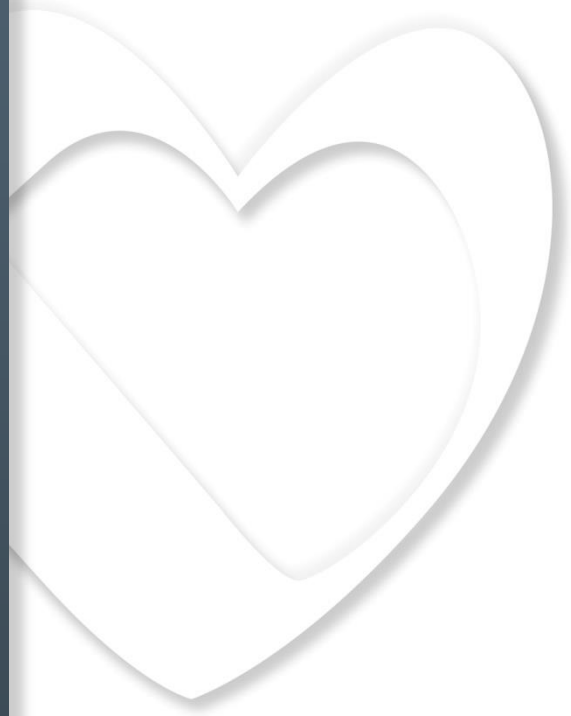
Natalie Bello[1], Akshay S. Desai[1], John J.V. McMurray[2], Christopher Granger[3], Salim Yusuf[4], Karl Swedberg[5], Marc A. Pfeffer[1], Scott D. Solomon[1]





- Risk of subsequent death or HF Hospitalization is greatest when the time from the last hospitalization is shortest
- These findings have implications for clinical trials

PATHOPHYSIOLOGY



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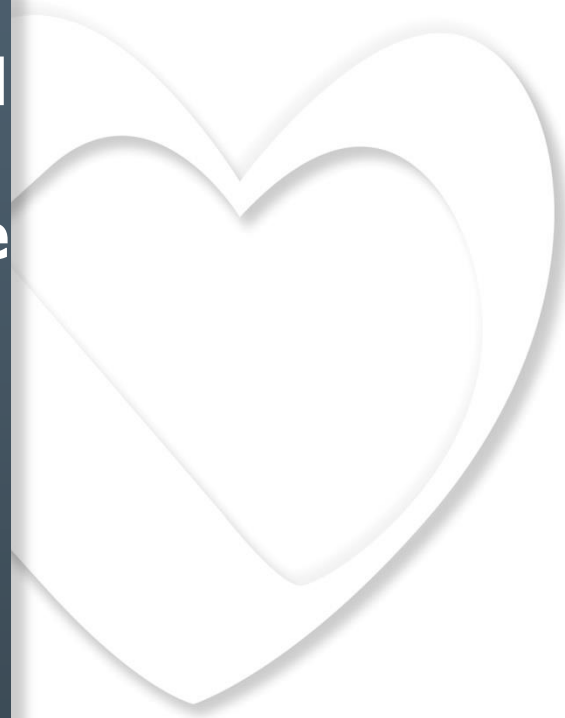
Decreased left ventricular capacitance is associated with a titin isoform shift and reduced titin phosphorylation in a porcine model of early heart failure with preserved ejection fraction.

M. Schwarzl[1], S. Seiler[1], A. Alogna[1], N. Hamdani[2], W. Linke[2], J. Verderber[1], P. Steendijk[3], BM. Pieske[1], H. Post[1]

(1) Medical University Graz, Austria
(2) Ruhr University Bochum, Germany
(3) Leiden University Medical Center, Leiden, The Netherlands



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Background & Methods

- **Aim: to establish a risk-factor based animal model of heart failure with preserved ejection fraction.**

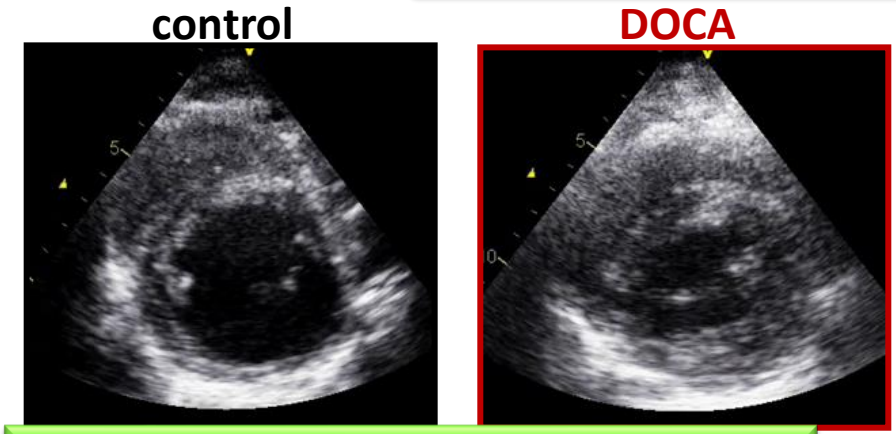
bedside to bench

- **arterial hypertension**
- **dyslipidemia**
- **physical inactivity**

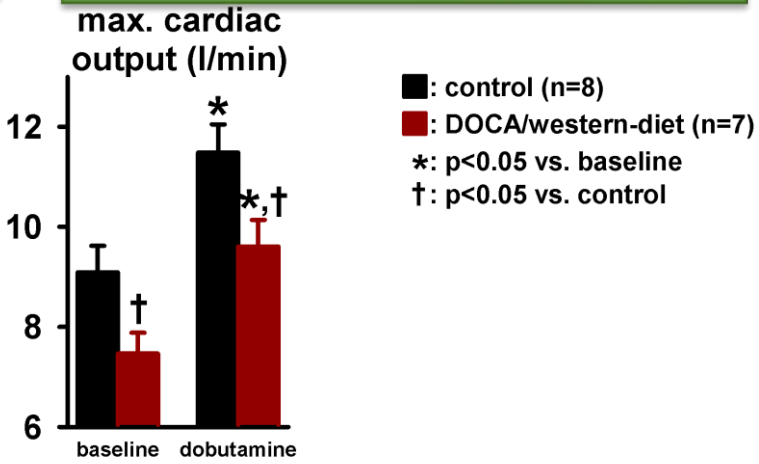
- **DOCA+salt**
- **„western-diet"**
- **physical inactivity**

Results

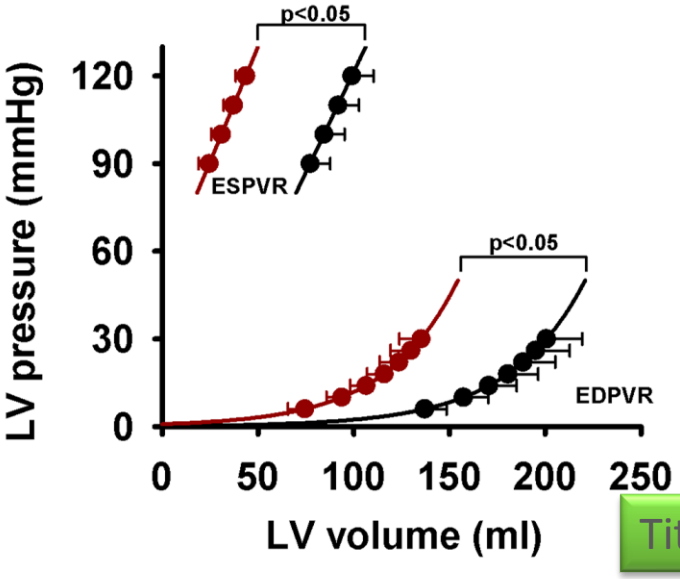
concentric LV hypertrophy

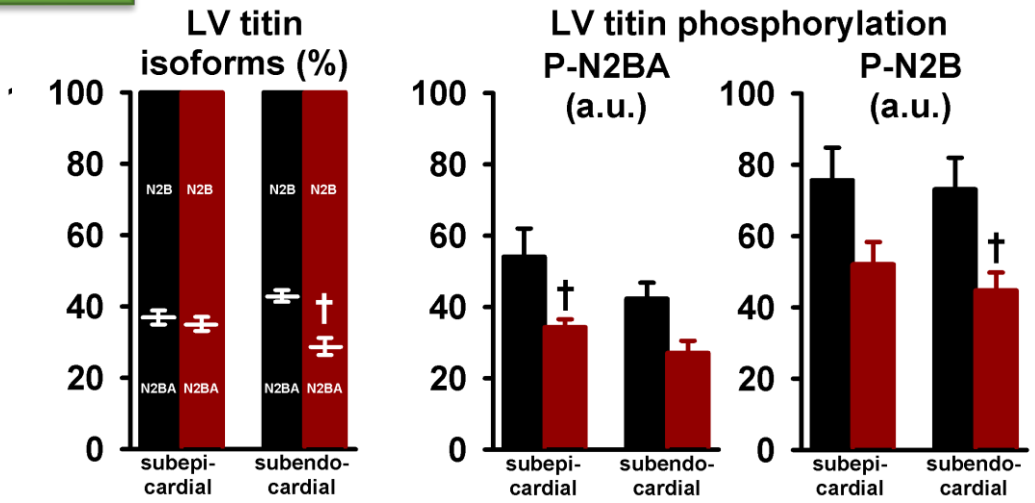


Reduced Cardiac Output Reserve



Decreased LV End-Diastolic Compliance





Titin isoform shift and reduced titin phosphorylation

Conclusion

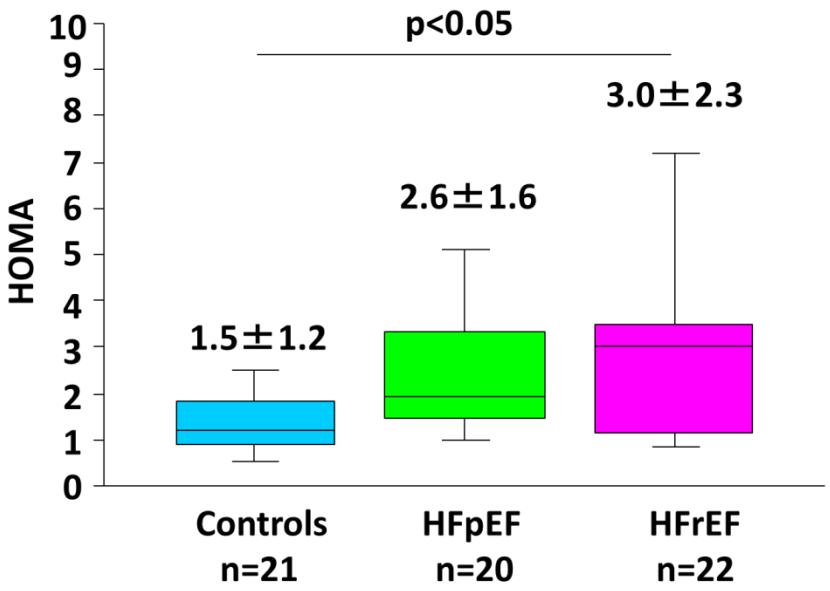
- **DOCA/western-diet treatment resulted in:**
  - concentric LV hypertrophy with
  - reduced cardiac output reserve and
  - decreased LV end-diastolic capacitance
  - titin-isoform-shift and reduced titin-phosphorylation

- **Enhancing titin-phosphorylation may improve LV dysfunction in HFpEF**

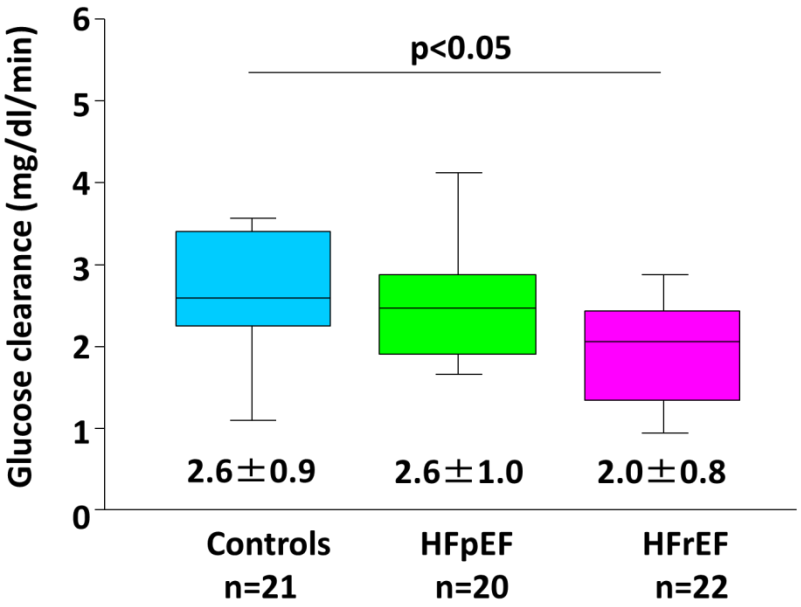
Impaired insulin resistance in systolic heart failure differs from diastolic heart failure

Nadja Scherbakov[1], Maximiliane Bauer[2], Carola Misgeld[2], Tibor Szabó[2], Agneszka Toepper[3], Stephan von Haehling[2], Stefan D. Anker[2], Hans-Dirk Duengen[3], and Wolfram Doehner[1,2]

Fasting Insulin Resistance



Short Insulin Sensitivity Test



- Fasting insulin resistance occurs in HFpEF and HFrEF
- Non diabetic patients with HFrEF showed more severe insulin resistance
- Insulin resistance observed in HFpEF as well as in HFrEF non diabetic patients
- Insulin resistance within the physiologic range of insulin/glucose interaction is seen only in HFrEF but not in HFpEF

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Galectin-3 Reflects Functional Capacity and Clinical Outcome in Heart Failure with Preserved Ejection Fraction

(The Aldo-DHF Biomarker Sub-Study)

Edelmann F, Holzendorf V, Wachter R, Durstewitz K, Schmidt AG, Kraigher-Krainer E, Duvinage A, Unkelbach I, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuß G, Götz Gelbrich G, Stough WG, and Pieske B

For the Aldo-DHF Investigators

Galectin-3 in Aldo-DHF: Objective and Aims of the Biomarker Sub-Study

Aldosterone has been implicated in the pathogenesis of HFpEF via MR-receptor mediated myocardial fibrosis, hypertrophy, and stiffening of the left ventricle.

Borlaug BA & Paulus WJ, Eur Heart J 2011;32:670–679
Edelmann F et al., Eur Heart J 2012;33:203-212

Galectin-3 is a marker of myocardial fibrosis, and it mediates aldosterone-induced vascular inflammation and fibrosis. In acutely decompensated patients with HFpEF high levels of Galectin-3 are associated with increased mortality.

de Boer RA et al., Curr Heart Fail Rep 2010;7:1-8
de Boer RA et al., Ann Med 2011;43:60-68

Aims of the Galectin-3 Sub-Study:

1) To investigate the clinical associations of galectin-3 in HFpEF.
2) To investigate the effect of chronic aldosterone receptor blockade on galectin-3 levels.
3) To investigate whether galectin-3 levels are predictive of treatment response to aldosterone receptor blockade in HFpEF.
4) To investigate whether time-dependent galectin-3 levels are related to clinical outcome in HFpEF.

Galectin-3 and Baseline Characteristics

Variable *n (%), MW (±SD)*	**Total** **n=415**	**Galectin-3** **≤ 12.1ng/ml** **n=208**	**Galectin-3** **> 12.1ng/ml** **n=207**	**P-value**
Demographics				
Age (yrs)	67 (±8)	65 (±7)	68 (±8)	**<0.001**
Female Gender	217 (52.3%)	100 (48.1%)	117 (56.5%)	*0.085*
Medical History				
Hypertension	382 (92.0%)	186 (89.4%)	196 (94.7%)	**0.048**
Diabetes mellitus	69 (16.6%)	28 (13.5%)	41 (19.8%)	*0.083*
Atrial Fibrillation	21 (5.1%)	3 (1.4%)	18 (8.7%)	**0.001**
Signs and Symptoms of HF				
NYHA III	58 (14.0%)	20 (9.6%)	38 (18.4%)	**0.010**
Edema	164 (39.5%)	68 (32.7%)	96 (46.4%)	**0.004**
Cardiovascular Medication				
ACE-Inhibitor or ARB	321 (77.3%)	153 (73.6%)	168 (81.2%)	*0.064*
Beta-Blocker	299 (72.0%)	135 (64.9%)	164 (79.2%)	**0.001**
Diuretic	226 (54.5%)	94 (45.2%)	132 (63.8%)	**<0.001**
Laboratory				
Hemoglobin (g/dL)	13.8 (±1.2)	14.0 (±1.1)	13.7 (±1.3)	**0.012**
eGFR (mL/min/1.73m²)	78.7 (±18.7)	84.7 (±17.2)	72.5 (±18.2)	**<0.001**
NT-proBNP (pg/ml)	159 (84-299)	140 (75-225)	192 (93-377)	**<0.001**

Galectin-3 and Baseline Characteristics

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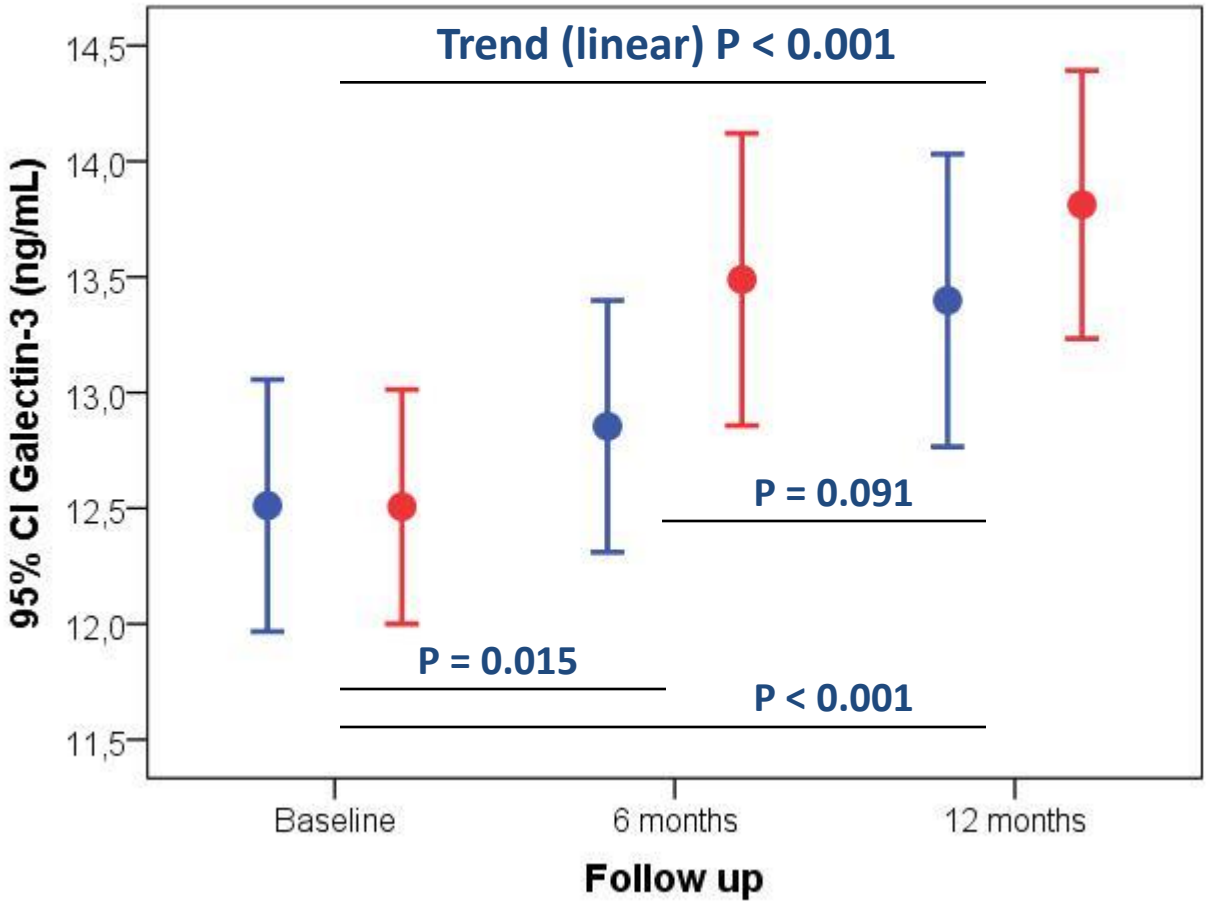
Cardiopulmonary Exercise Testing				
Peak VO_2 (mL/kg/min)	16.3 (±3.5)	16.9 (±3.2)	15.8 (±3.6)	**0.001**
AT VO_2 (mL/kg/min)	11.6 (±3.2)	12.1 (±3.3)	11.1 (±3.1)	**0.002**
VE/VCO_2 Slope	30.3 (±5.2)	29.7 (±5.3)	31.0 (±5.1)	**0.016**
6-Minute-Walk-Test				
Distance (m)	530 (±87)	546 (±83)	514 (±88)	**<0.001**
Echocardiography				
LVEF (%)	67.4 (±7.8)	67.0 (±7.7)	67.8 (±7.9)	0.268
LVMI, males (g/m^2)	117.2 (±31.0)	120.4 (±33.8)	113.4 (±27.0)	0.112
LVMI, females (g/m^2)	101.1 (±22.7)	100.6 (±24.1)	101.5 (±21.5)	0.770
LAVI (mL/m^2)	28.1 (±8.5)	27.1 (±7.4)	29.1 (±9.3)	**0.022**
E/e‘	12.8 (±4.1)	12.3 (±3.6)	13.2 (±4.4)	**0.023**

Clinical Correlates of Galectin-3

Values are B-coefficients (95%-CI) by Regression	**Model 1**	P-value	**Model 2**	P-value	**Model 3**	P-value
Peak VO_2 - mL/kg/min	-0.164 [-0.250;-0.078]	**<0.001**	-0.098 [-0.183;-0.014]	**0.023**	-0.118 [-0.219;-0.018]	**0.021**
Six-Minute Walk Distance - m	-5.92 [-8.05;-3.80]	**<0.001**	-3.95 [-6.05;-1.85]	**<0.001**	-3.87 [-6.31;-1.43]	**0.002**
SF-36 Physical Functioning Scale	-1.40 [-1.95;-0.838]	**<0.001**	-1.29 [-1.86;-0.719]	**<0.001**	-1.17 [-1.86;-0.482]	**0.001**
NYHA Class	+0.016 [0.007;0.025]	**<0.001**	+0.012 [0.003;0.021]	**0.009**	+0.014 [0.004;0.024]	**0.007**
LV Ejection Fraction - %	+0.147 [-0.049;0.343]	0.142	+0.079 [-0.124;0.282]	0.445	+0.139 [-0.107;0.386]	0.268
E/e' (medial) Velocity Ratio	+0.130 [0.029;0.232]	**0.012**	+0.067 [-0.036;0.171]	0.203	+0.027 [-0.091;0.145]	0.653
LA Volume Index - mL/m²	+0.313 [0.102;0.524]	**0.004**	+0.232 [0.019;0.444]	**0.033**	+0.148 [-0.078;0.375]	0.199
LV Mass Index – g/m²	-0.465 [-1.17;0.244]	0.198	-0.539 [-1.24;0.164]	0.133	-0.543 [-1.39;0.306]	0.209

Model 1: Gal-3 only.
Model 2: Gal-3 adjusted for Sex, Age.
Model 3: Gal-3 adjusted for Sex, Age, Atrial Fibrillation, Blood Pressure (mean arterial pressure), eGFR [mL/min/1.73m^2], Hemoglobin [g/dL].

Aldosterone-Receptor Blockade and the Course of Galectin-3 Levels



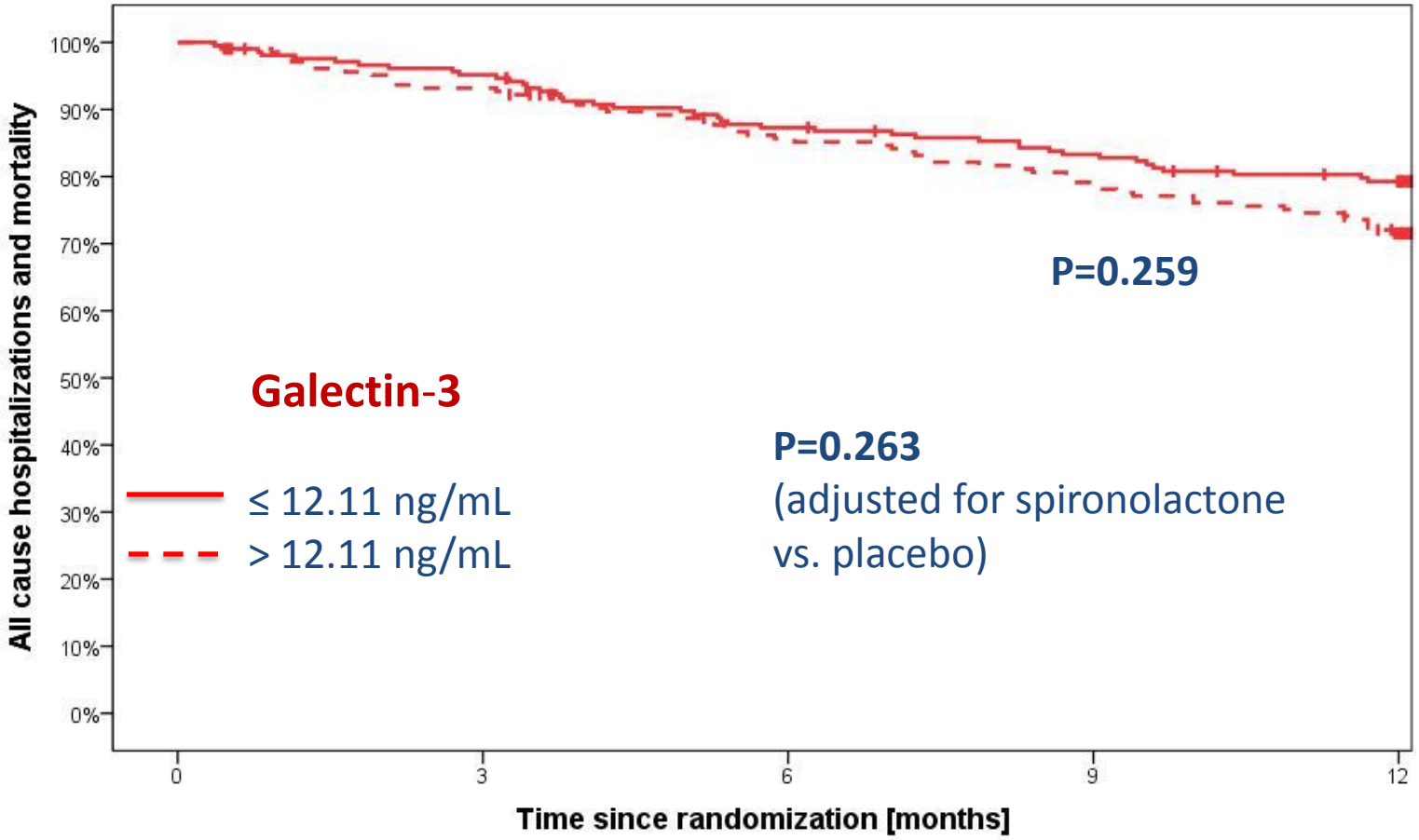
No Treatment-effect
P = 0.175

No Interaction
Galectin-3 * Treatment
P = 0.356

Spironolactone

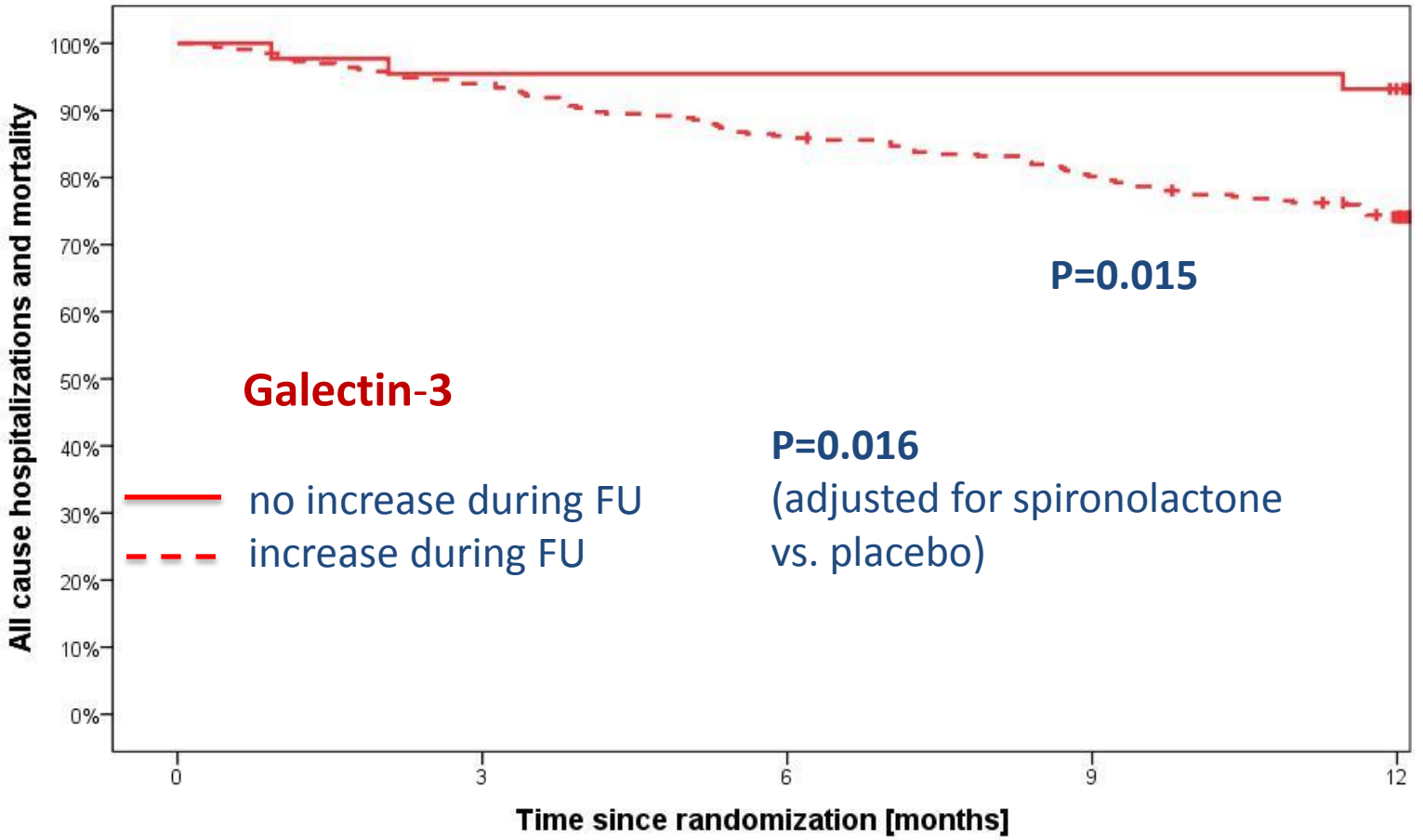
Placebo

Galectin-3 at Baseline and Clinical Outcome



Pts. at Risk	208		196	177	
	167	154			
Pts. at Risk	207	191	170		156
	137				

Course of Galectin-3 and Clinical Outcome



Pts. at Risk	44	42	42	42	39
Pts. at Risk	333	313	287	266	239

Summary

Galectin-3 concentrations are modestly elevated in patients with well-compensated HFpEF, and they are related to different subjective and objective measures of physical performance.

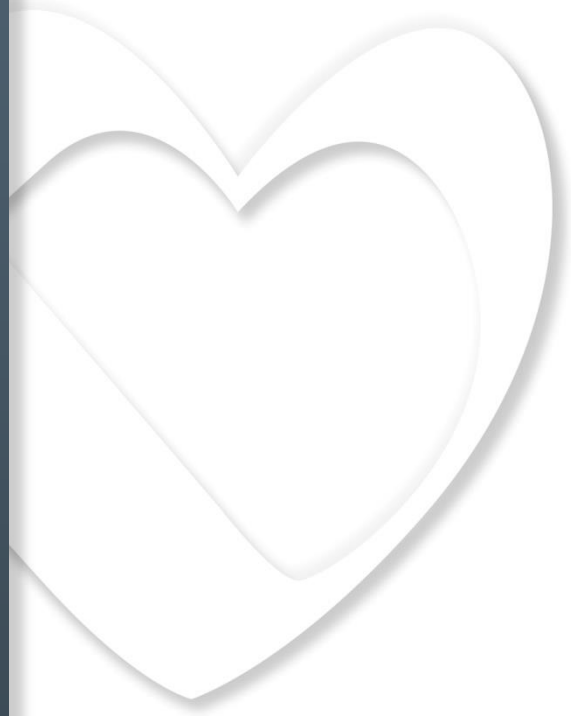
in these patients Galectin-3 levels increases over time. This increase predicts subsequent outcome independent of other factors including NT-proBNP.

There is no evidence from this study that spironolactone modulates the observed increase in galectin-3 over time, although spironolactone did improve echocardiographic measures reflective of diastolic filling and ventricular remodeling and did decrease NT-proBNP levels in Aldo-DHF.

Conclusions

These findings especially regarding the prognostic value of galectin-3 provide the foundation for future studies to further evaluate the contribution of galectin-3 to HFpEF pathophysiology and to determine if it is a viable target for therapeutic intervention.

DIAGNOSIS



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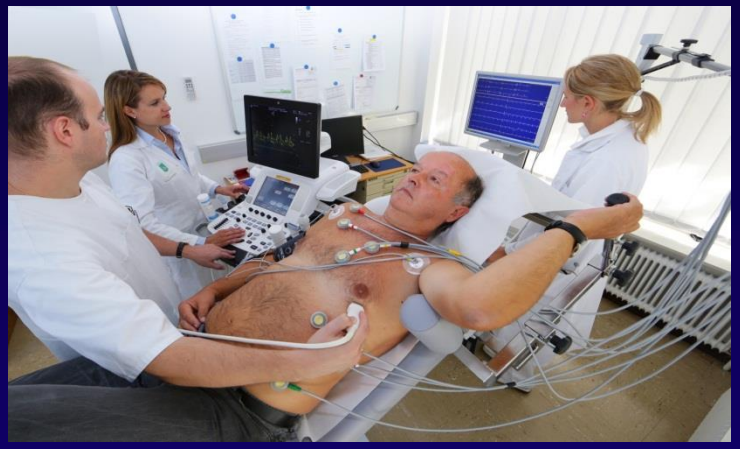
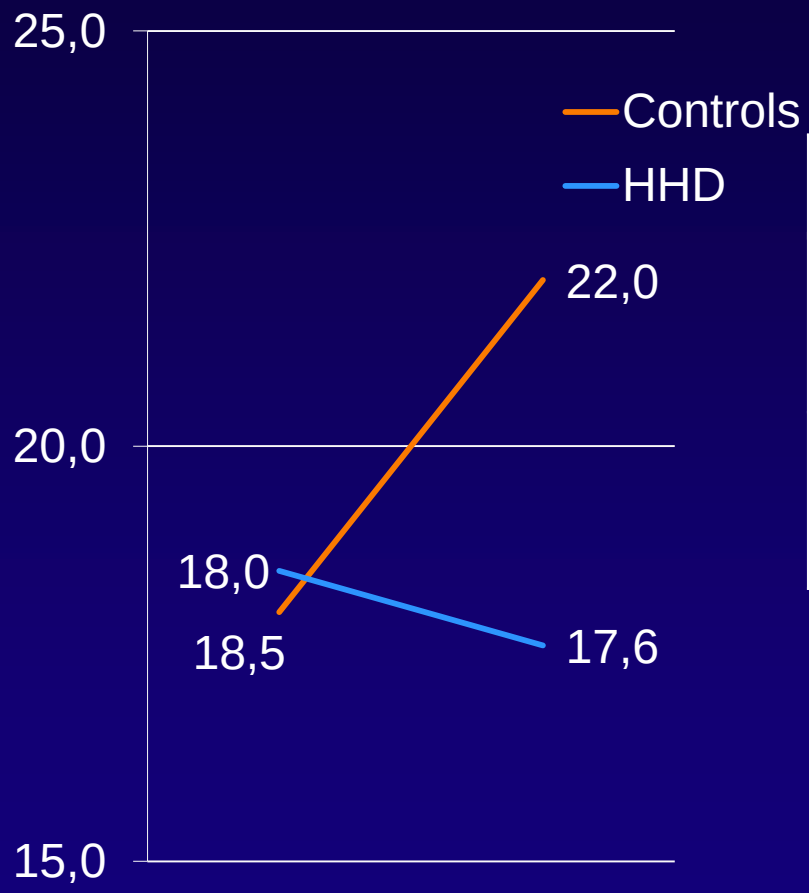
Exercise test with echocardiography (diastolic stress test)

Ha et al. JASE. 2005; 18: 63-8

- Supine bike
- 25 Watts increments
- Assess systolic function
- Mitral inflow (E, A and DT)
- Mitral annulus velocity
- E/e´
- TR velocity
- Recovery



Alterations in global longitudinal strain (GLS) during the test



	HHD	Controls
GLS rest	-18,5±3,8	-18,0±1,3
GLS test	-17,6±2,4	-22,0±3,8

p > 0,05 vs. rest

GLS increased in controls, but decreased in hypertensive heart disease.

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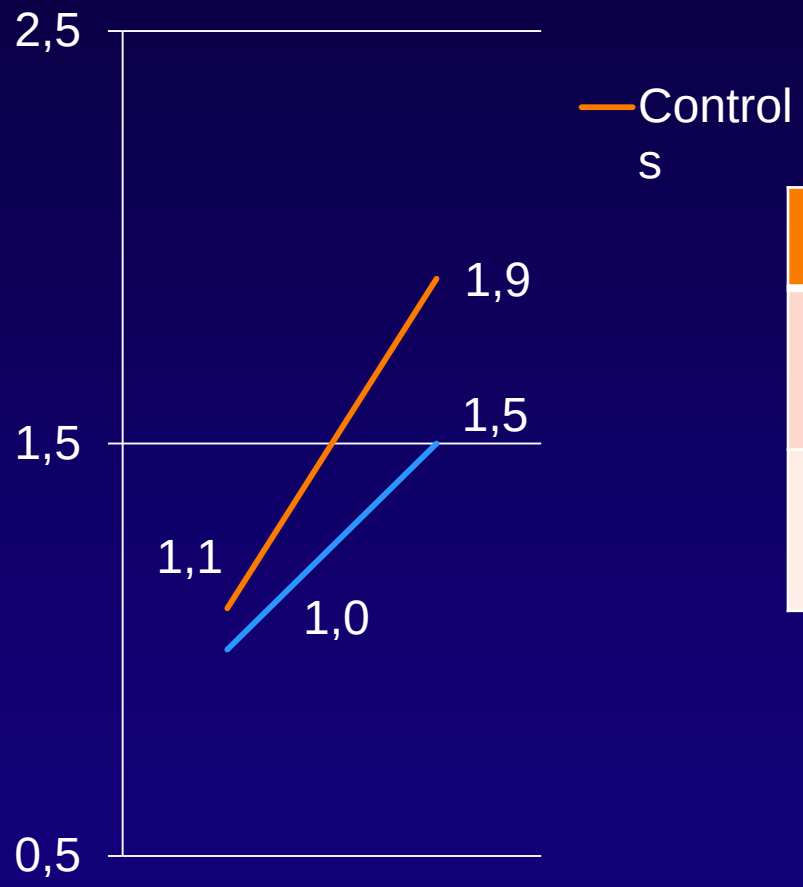
Alterations in early diastolic strain rate (e_DSR) during the test



	HHD	Controls
e_DSR rest	1,1±0,3	1,0±0,2
e_DSR test	1,9±0,7*	1,5±0,3*

* p < 0,05 vs. rest

Early diastolic strain rate improved during exercise in controls, but a lesser extent in HHD group.

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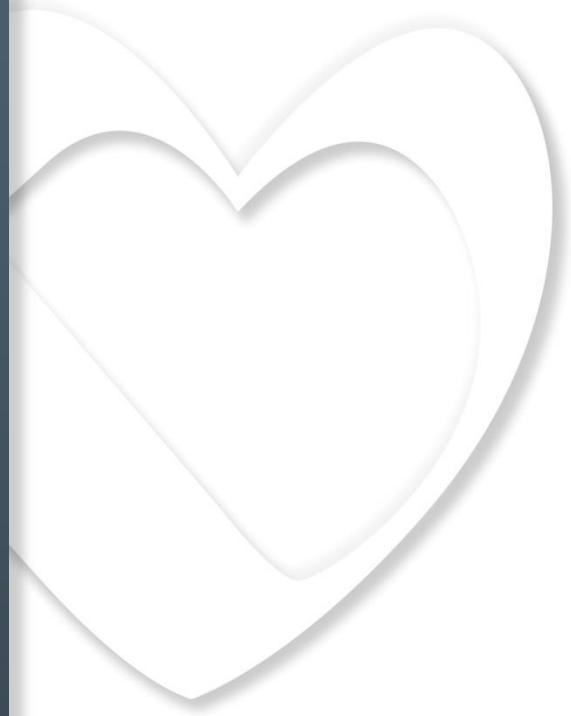
CARDIAC STRUCTURE AND FUNCTION



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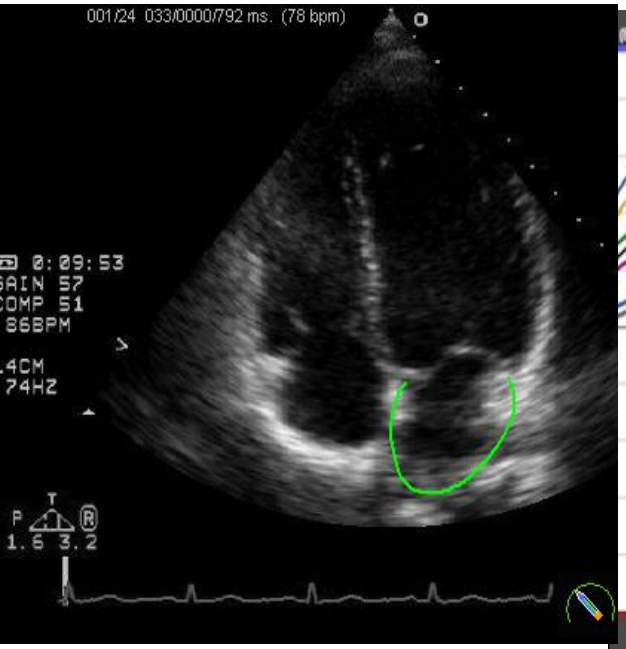
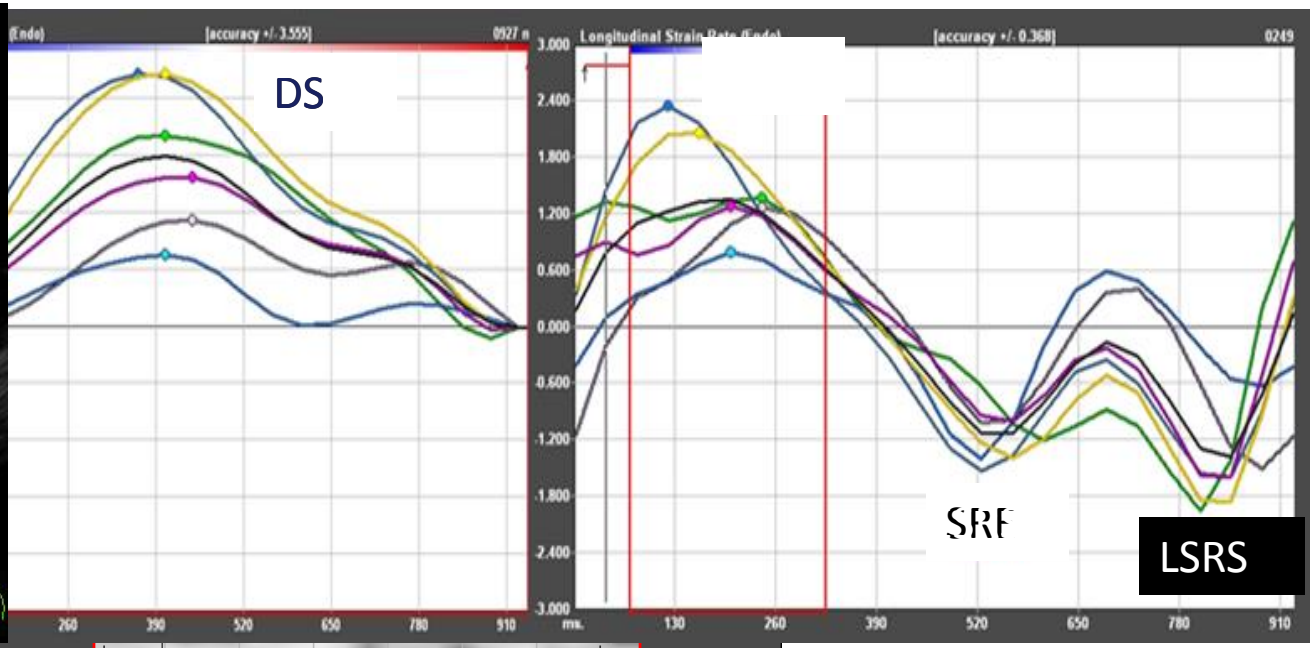
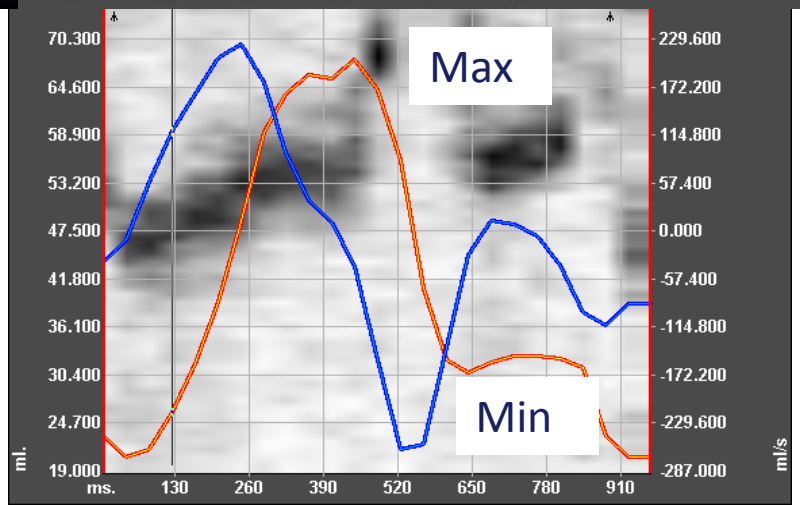
LA deformation and volumetric function

Kraigher-Krainer E. Et al.

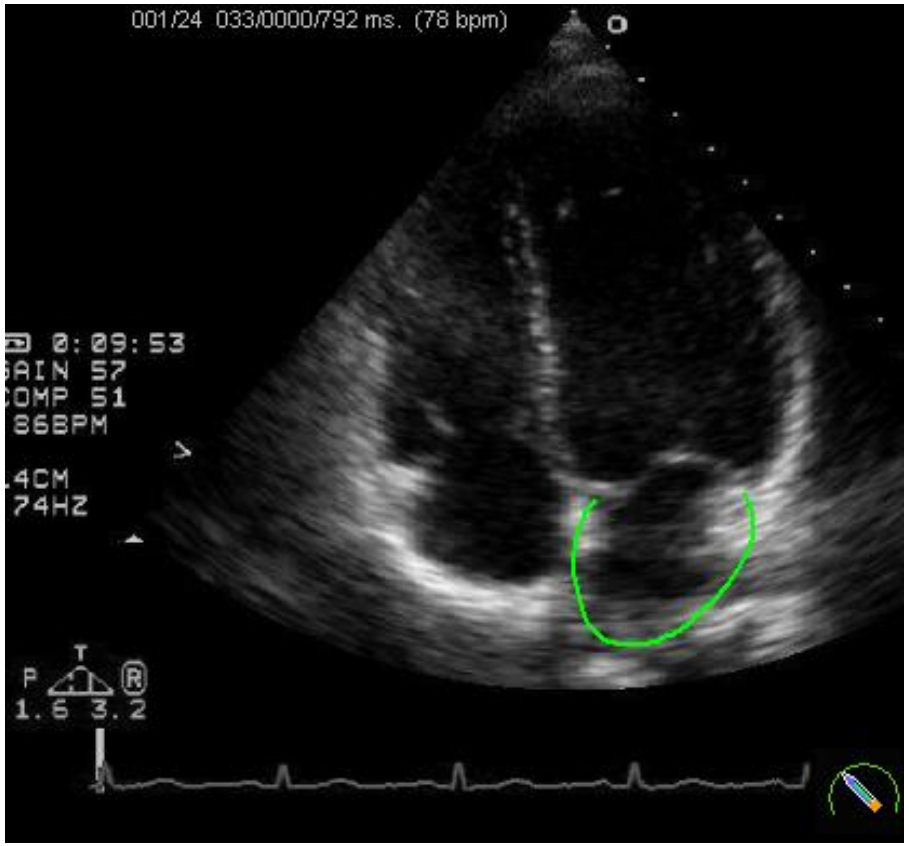






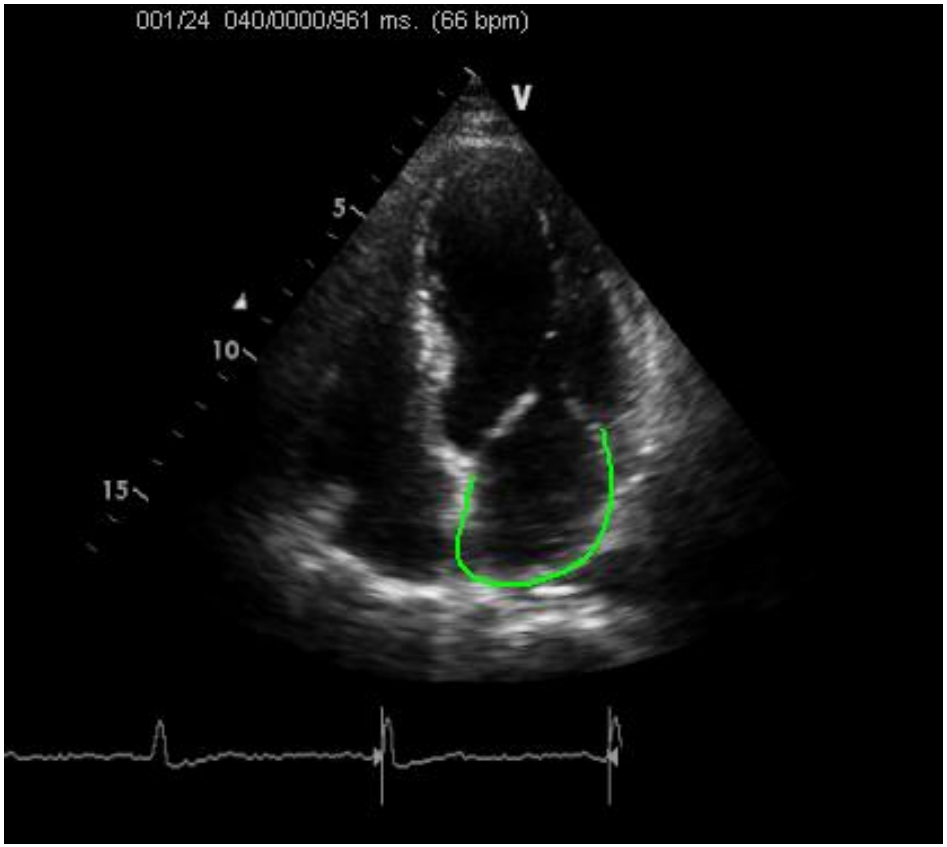
- LAEF
- LA passive EF
- LA active EF

Left Atrial Strain



Normal Control

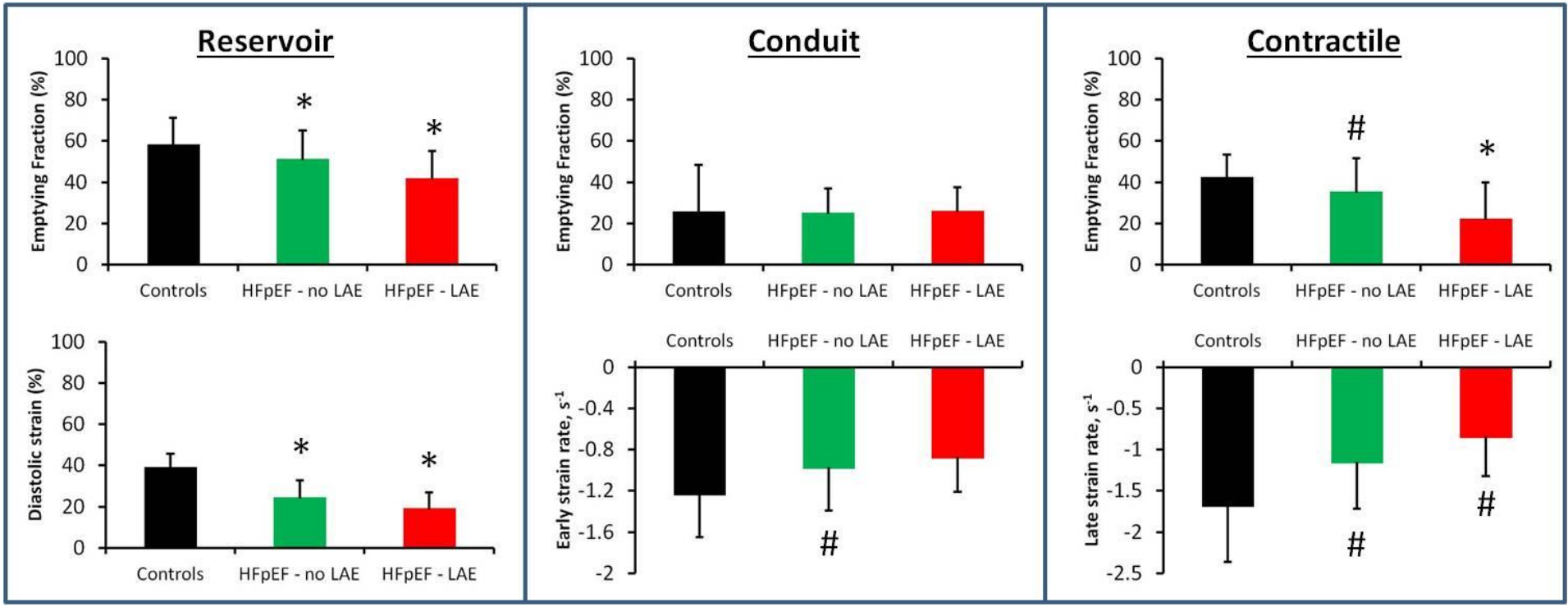
LA Strain: 46.2 %



HFpEF

LA Strain: 20.1 %

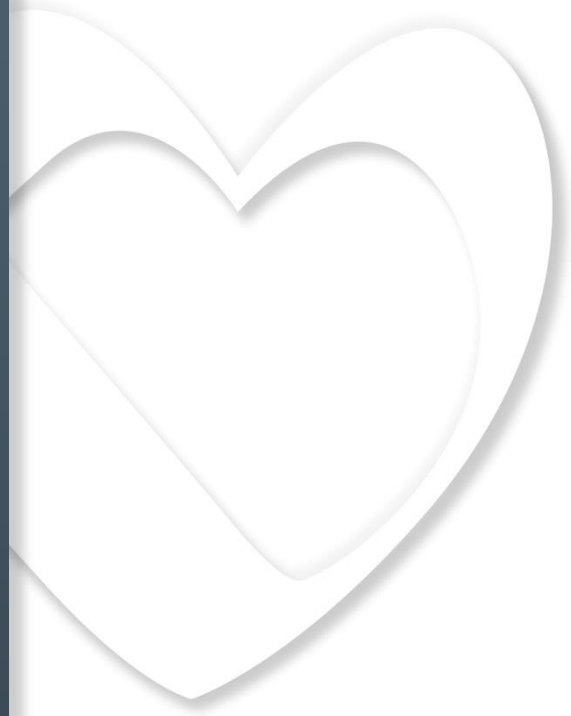
Phases of LA strain and phasic volume stratified by LA size



- P < 0.001; # p ≤ 0.01; LAE = left atrial enlargement;
- Left atrial enlargement defined as LA volume index (to BSA=body surface area) ≥ 29ml/m^2.

Kraigher-Krainer E, Solomon SD et al. Presented at HFA 2013

THERAPY



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The Effects of Inspiratory Muscle Training in Patients With Heart Failure With Preserved Ejection Fraction

P. Palau Sampio[1], E. Dominguez Mafe[2], B. Mascarell Gregori[1], E. Nuñez Botero[1], JM. Ramon Ferrandis[1], P. Vergara Lozano[3], J. Sanchis Fores[1], FJ. Chorro Gasco[1], J. Nuñez Villota[1]

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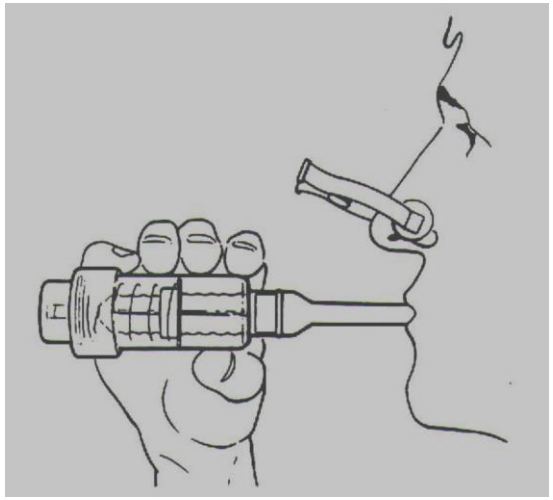
ClinicalTrials.gov Identifier: NCT01707277

Objective

- A simple and low intensity IMT protocol
- 12-week
- Home-based



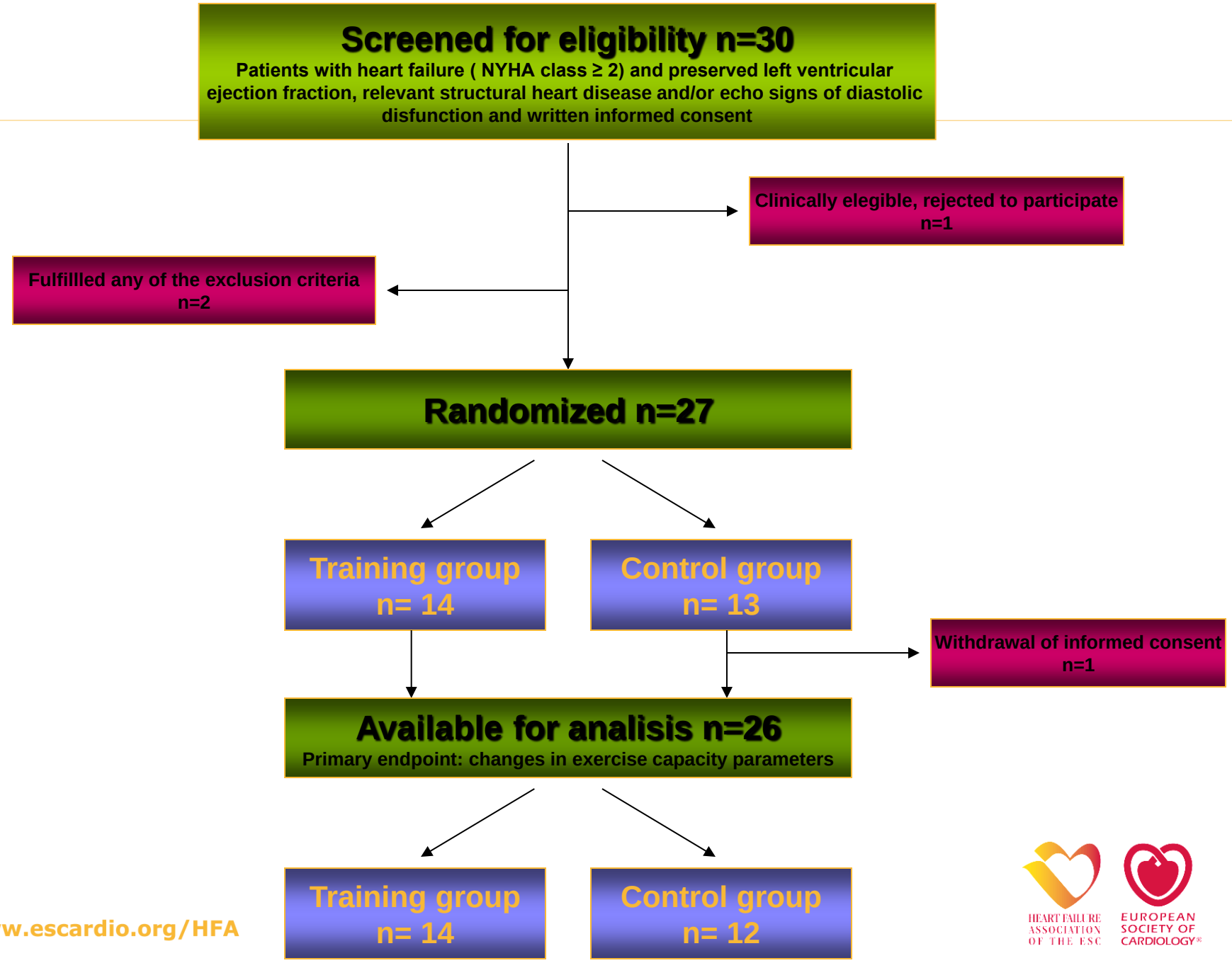
Primary endpoint: exercise capacity parameters

- **Peak VO2**
- VO2 at anaerobic threshold
- VE/VCO2 slope
- METs
- 6-MWT

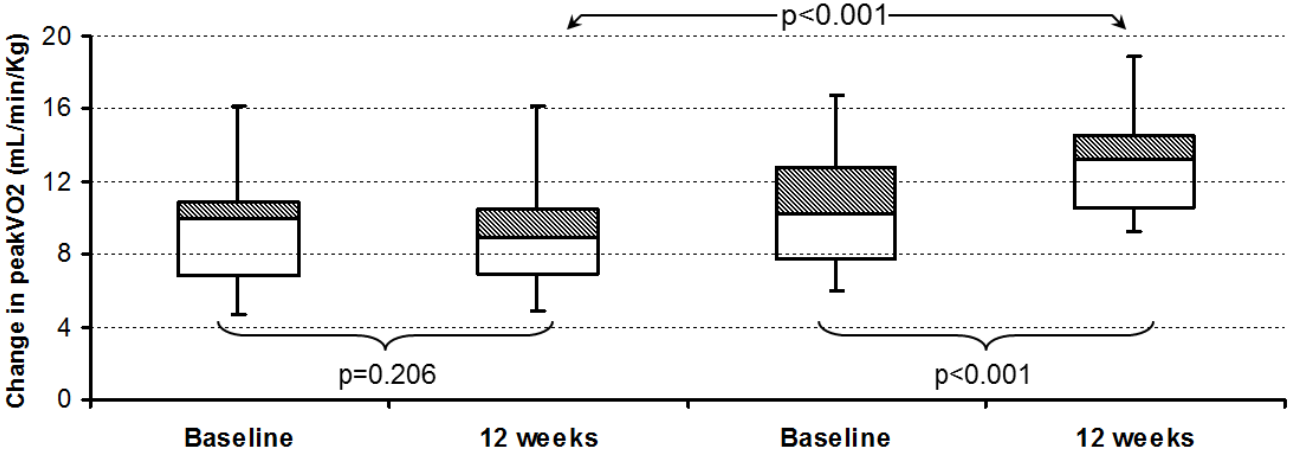
Secondary endpoint:

- QoL
- Echo
- Biomarkers (NT-proBNP and CA125)

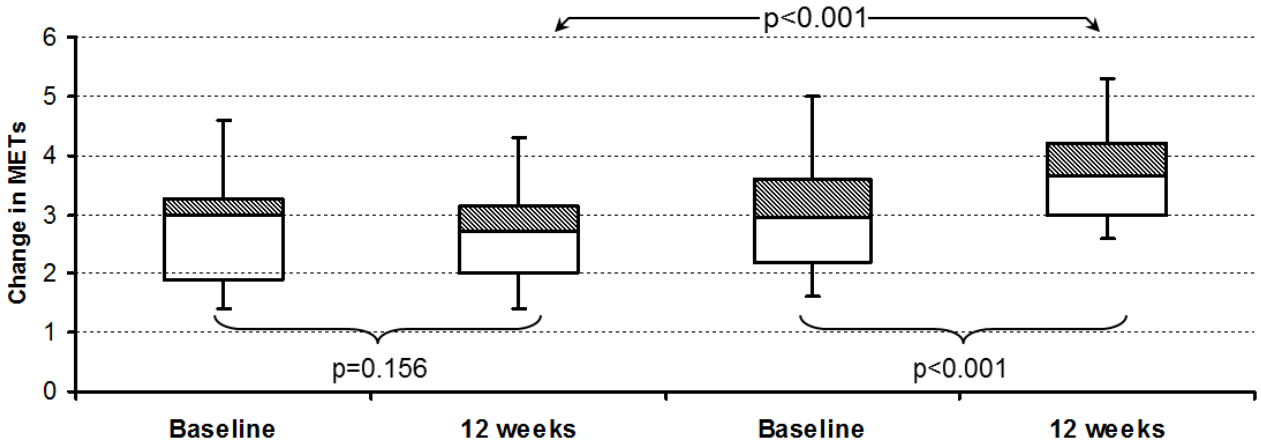
Advanced HFpEF and reduced aerobic capacity



Results at 12 weeks



Peak VO2



METs

Conclusions

- **In patients with advanced HFpEF, IMT was associated with marked improvement in exercise capacity and QoL.**
- **These results provide evidence to suggest that IMT may be considered as a promising therapy in these patients**