tolic characteristics of RV function in HFpEF patients with and without PHT well as control subjects.
Methods: Cardiac dimension and biventricular function was evaluated by cardiac magnetic resonance imaging in 23 stable outpatients with HFpEF and 9 patients without heart failure symptoms. RV pressure volume loops were obtained with conductance catheters during basal conditions and handgrip exercise. Patients were stratified according to the presence of PHT (mean pulmonary artery pressure ≥25mmHg, PHT+ and PHT- group). Transient preload reduction was used to extrapolate the load-independent RV diastolic stiffness constant (Beta) and RV endsystolic elastance (Ees) as an estimate of load-independent RV contractility.
Results: 9 HFpEF patients and none of the control patients demonstrated PHT at rest. HFpEF PHT+ and PHT- patients were balanced in terms of baseline characteristics and impaired exercise capacity. Both groups showed similar LV and RV dimensions and ejection fractions. Invasively determined RV-Ees was numerically higher in the HFpEF PHT+ patients (P=0.10) and significantly higher as compared to controls.(p=0.01) HFpEF PHT- patients demonstrated numerically, but not statistically aignificant, elevated RV-Ees in comparison to controls.(p=0.24) However the passive RV stiffness constant Beta was comparable in both HFpEF groups (p=0.92) and significantly elevated in comparison to controls. (p<0.01.
Although pulmonary artery pressures were elevated in the HFpEF PHT+ group both at rest (p<0.01) and under exercise (p<0.01), RV filling pressures were comparable between HFpEF groups.(rest: p=0.14; exercise: p=0.44) Both HFpEF groups demonstrated a blunted increase in cardiac output under exercise (p=0.01 vs. controls) associated with prolonged RV relaxation (p=0.01 vs. controls), decrease in stroke volume (p<0.01 vs. controls) and a marked increase in the enddiastolic-pressure-volume relationship.(p<0.01 vs. controls)
Conclusion: In compensated stages of the HFpEF syndrome the presence of elevated RV afterload is balanced by an increase in RV contractility. However diastolic RV abnormalities with intrinsic RV stiffness and prolonged RV relaxation are evident independent of the presence of PHT and lead to impaired diastolic RV reserve with a blunted increase in cardiac output during exertion. Alterations of intrinsic RV myocardial properties in HFpEF patients that occur in the absence of overt pressure overload warrant further investigation.
Funding Acknowledgements: Research Fund Leipzig Heart Center

P6504
Combined exercise stress echocardiography and cardiopulmonary exercise test in assessment of diastolic function in patients successfully treated with primary percutaneous coronary intervention

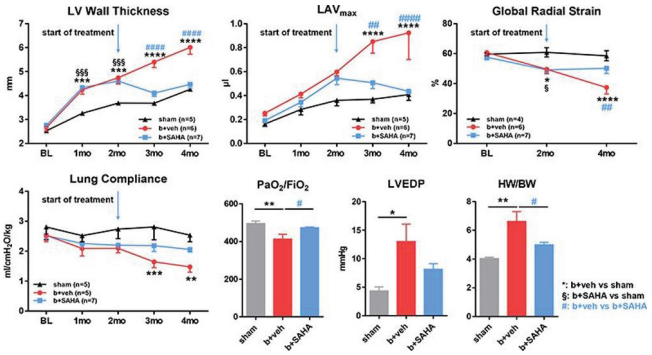
I. Nedeljkovic[1], M. Banovic[1], D. Trifunovic[1], B. Beleslin[1], G. Stankovic[1], M. Nedeljkovic[1], V. Vukcevic[1], S. Stojkovic[1], V. Giga[1], A. Djordjevic-Dikic[1], J. Stepanovic[1], M. Dobric[1], Z. Mehmedbegovic[1], M.C. Ostojic[2]. *[1]School of Medicine, Belgrade University, Division of Cardiology, CCS, Belgrade, Serbia; [2]Institute for Cardiovascular Diseases Dedinje, Cardiology, Belgrade, Serbia*

Background: Heart failure with preserved ejection fraction (HFpEF) is a common complication of ST-segment elevation myocardial infarction (STEMI) even in patients successfully treated with primary percutaneous coronary interventions (pPCI). However, the role of combined stress echo cardiopulmonary exercise testing (ESE-CPX) in the detection of masked HFpEF after pPCI still remained unknown.
Objective: To unmask HFpEF with ESE-CPX, 5 years after pPCI in patients with preserved LVEF and normal diastolic echo parameters at rest.
Methods: We studied 60 pts (47 male, mean age 56±14 years) with the first STEMI treated with pPCI (TIMI 3 flow). They all underwent echo examination 3 months after pPCI, and at 5 years follow up. They all had preserved EF (LVEF >50%) and normal diastolic function at rest. ESE-CPX was performed on a supine bicycle (ramp protocol, 15 Watt/min). The marker of HFpEF was a detection of E/e'≥15 during maximal ESE-CPX.
Results: At 5 years follow-up after pPCI there was an improvement in LVEF (50.73±9.65 vs 55.76±9.44, p<0.0001). However, there is an increase in LV end-diastolic volume (117.87±33.19 vs 129.90±55.59, p<0.0001) and E/e' (5.50±2.44 vs 6.67±4.94, p<0.0001) at rest. The increase of E/e ' >15 occurred in 10/60 pts (17%) during ESE-CPX. Those patients had lower peak VO2 (p=0.002), higher VE/VCO2 slope (p<0.0001), and lower peak PetCO2 (p<0.0001). VE/VCO2 slope was an independent multivariate predictor of HFpEF (p=0.001), with a specific value of 34.95 best predictive for HFpEF.
Conclusion: Combined ESE-CPX test is a feasible and reliable test to unmask HFpEF in patients treated with pPCI for STEMI even in the presence of preserved EF and diastolic function at rest, excluding the myocardial ischemia by continuous echo monitoring. This confirms the importance of dynamic functional assessment of patients with integrated evaluation of both cardiovascular and ventilatory response.

P6505
HDAC inhibition rescues cardiac and pulmonary function in a feline model of HFpEF

M. Wallner[1], D.M. Eaton[1], R.M. Berretta[1], J. Wu[2], M.Y. Jeong[3], Y.H. Lin[3], S.T. Baker[2], M.A. Oyama[4], D. Von Lewinski[5], S. Mohsin[1], T.A. McKinsey[3], M.R. Wolfson[2], S.R. Houser[1]. *[1]Temple University School of Medicine, Cardiovascular Research Center, Philadelphia, United States of America; [2]Temple University School of Medicine, Physiology; Thoracic Medicine and Surgery; CILR, Philadelphia, United States of America; [3]University of Colorado, Division of Cardiology and Consortium for Fibrosis Research & Translation, Aurora, United States of America; [4]University of Pennsylvania, School of Veterinary Medicine, Section of Cardiology, Philadelphia, United States of America; [5]Medical University of Graz, Division of Cardiology, Graz, Austria*

Background: Heart Failure with preserved Ejection Fraction (HFpEF) is a major public health problem and there are no effective therapies, partially attributable to the lack of well-established HFpEF animal models.
Purpose: To establish a feline HFpEF model and assess the effects of histone deacetylase (HDAC) inhibition on cardiopulmonary function.
Methods: Male domestic short hair cats (n=18, aged 2mo), underwent either sham (S) procedures (n=5) or aortic constriction (n=13) with a customized preshaped band, resulting in slow progressive pressure overload during growth. 2 months post-banding banded cats were treated daily with either 10mg/kg suberoylanilide hydroxamic acid (b+SAHA) (n=7), a pan-HDAC inhibitor, or vehicle (b+veh) (n=5) for 2 months. Serial echocardiography and pulmonary function testing were performed monthly, and terminal invasive hemodynamic studies and gas exchange were conducted 4 months post-banding. Myofibril mechanics studies were performed ex vivo. Data is presented as mean±SEM.
Results: Prior to starting treatment at 2 months, all banded cats exhibited a similar HFpEF phenotype with LV hypertrophy, LA enlargement, and preserved EF. At 4 months post-banding, SAHA treated cats showed significantly reduced LV wall thickness and LA volume (LAVmax) and improved cardiac contractility compared to b+veh cats, reflected by global radial strain values (Fig). LV EF was normal in all groups at all time points. In vivo measurements of lung compliance (Fig.) demonstrated a marked time-dependent decrease in b+veh cats that was significant at 3 and 4 months post-banding compared to sham cats. Lung compliance in SAHA-treated cats did not deteriorate after 2 months of treatment, with no significant difference compared to sham cats at 3 and 4 months. Furthermore, oxygenation was only impaired in the b+veh group, but not in SAHA treated animals, reflected by a decrease in PaO2/FiO2 (Fig.). Invasively measured left ventricular end-diastolic pressure (Fig. LVEDP) at 4 months was significantly elevated in b+veh cats, but not in b+SAHA cats, compared to sham. SAHA treated cats also showed a significant reduction in heart weight to body weight ratio (Fig. HW/BW) compared to the b+veh group. Furthermore, at 4 months post-banding NTproBNP levels were significantly elevated in the b+veh group (420±223pmol/l; p<0.01), but not in the b+SAHA group (203±61pmol/l) compared to sham cats (26±1pmol/l). Efficacy of SAHA in vivo correlated with enhanced myofibril relaxation, as determined ex vivo.



HDAC inhibition in HFpEF

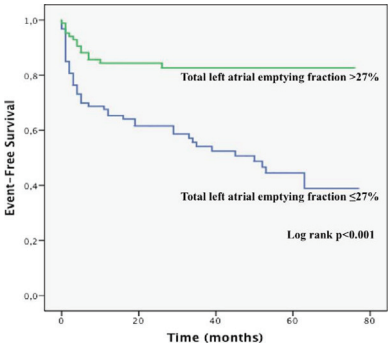
Conclusion: In a feline model of HFpEF, HDAC inhibition with SAHA rescues the established phenotype by reducing LV hypertrophy and LVEDP, decreasing LA size, improving cardiac contractility, and enhancing myofibril relaxation, which ultimately results in sustained lung compliance and improved oxygenation. Therefore, HDAC inhibition may be an interesting therapeutic strategy to treat the ever growing HFpEF population.
Funding Acknowledgements: S.R.H: NHI: 1P01HL134608-01A1, RO1 HL33920; M.R.W.: NHLBI: R01 HL118401-01A1; DoD/ONR: N000141210810; DoD/ONR: N000141210597; PA Dept of Health

P6506
Prognostic impact of left atrial function in heart failure with preserved ejection fraction

R. Schoenbauer[1], A.A. Kammerlander[2], F. Duca[2], S. Aschauer[2], C. Binder[2], C. Zotter-Tufaro[2], C. Nitsche[2], L. Fiedler[1], F.X. Roithinger[1], C. Loewe[3], C. Hengstenberg[2], D. Bonderman[2], J. Mascherbauer[2]. *[1]Landesklinikum Wiener Neustadt, Cardiology, Wiener Neustadt, Austria; [2]Medical University of Vienna, AKH – Vienna, Cardiology Clinic, Vienna, Austria; [3]Medical University of Vienna, Department of Bioimiging and Image-Guided Therapy, Vienna, Austria*

Background: Left atrial (LA) size and function have been shown to be associated with adverse events in heart failure with preserved ejection fraction (HFpEF).
Objectives: To study LA size and function and its impact on outcome in HFpEF patients in sinus rhythm versus atrial fibrillation (AF).

Methods: 189 HFpEF patients were prospectively enrolled and underwent baseline clinical and echocardiographic assessment, cardiac magnetic resonance imaging (CMR) and invasive hemodynamic assessment. Coronary artery disease was ruled out by coronary angiography. 90 patients were in persistent AF, 24 in paroxysmal AF and 71 in sinus rhythm. LA size and function were assessed by CMR.
Combined endpoint was defined as hospitalization for heart failure or cardiac death.
Results: Patients in AF had significantly larger endsystolic LA volume indices (LAVI) (81±27 vs. 55±18ml/m^2, p<0.001), larger enddiastolic LAVI (68±25 vs. 35±17ml/m^2, p<0.001), lower total LA emptying volume (24±11 vs. 41±14ml, p<0.001) and fraction (16±7 vs. 39±11%, p<0.001) as well as lower fraction of longitudinal shortening (5±4 vs. 14±7%, p<0.001). Among patients in sinus rhythm passive LA emptying volume and fraction were 21±10ml and 20±7%. Active LA emptying volume and fraction were 21±13ml and 20±11%, respectively.
After 31±24 months, 64 patients reached the combined endpoint. By multivariate cox regression analysis including all LA parameters, only reduced total LA emptying fraction was significantly associated with adverse outcome (p<0.001, HR 0.962, 95% CI 0.944–0.981). After adjustment for sex, age, presence of persistent AF, NTproBNP, right ventricular ejection fraction by CMR and pulmonary capillary wedge only elevated NTproBNP (p=0.022, HR 1.078, 95% CI 1.011–1.150) and reduced total LA emptying fraction (p=0.004, HR 0.969, 95% CI 0.949–0.990) were predictive for adverse events.



Kaplan-Meier plot

Conclusion: Impaired LA function plays a key role in HFpEF. Reduced total LA emptying fraction outperforms LA size and presence of persistent AF in prediction of adverse events in HFpEF.

P6507
Factors associated with troponin elevation and risk of cardiac events in patients with heart failure and preserved ejection fraction

P. Myhre[1], E. O'Meara[2], S. De Denus[2], I. Beldhuis[1], B.L. Claggett[1], P. Jarolim[3], J.L. Rouleau[2], S.D. Solomon[1], M.A. Pfeffer[1], A.S. Desai[1]. *[1]Brigham and Women's Hospital, Division of Cardiovascular Medicine, Boston, United States of America; [2]Montreal Heart Institute, Montreal, Canada; [3]Brigham and Women's Hospital, Clinical Chemistry, Boston, United States of America.* On behalf of TOPCAT study group

Background/Introduction: Cardiac troponins (cTn) are frequently elevated in patients with chronic heart failure and reduced ejection fraction (HFrEF) and correlate with the risk for death and HF hospitalization. However, identification of factors associated with elevation of cTn concentrations and our understanding of the association of cTn levels with cardiovascular (CV) events in patients with HF and preserved ejection fraction (HFpEF) are limited.
Purpose: To determine the clinical correlates of cTn elevation and the relationship of cTn levels with the risk of specific CV events in patients with HFpEF.
Methods: Of 1767 subjects in the TOPCAT trial with symptomatic HFpEF randomized in the Americas, 236 had baseline measurements of high sensitivity troponin I (hs-cTnI) by the Abbott ARCHITECT STAT assay. We identified clinical correlates of hs-cTnI elevation at baseline in multivariable linear regression models and correlated baseline hs-cTnI levels with adjudicated CV outcomes over mean follow-up time of 2.6±1.5 years using multivariable Cox models. Model discrimination was assessed using the Harrell C statistics.
Results: The median concentration of hs-cTnI at baseline was 6.2 ng/L (interquartile range 3.4–12.9) and levels were detectable in 99.8% of the patients. In multivariable models, higher hs-cTnI concentrations were associated with male gender, black race, lower estimated glomerular filtration rate (eGFR) and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (R2=0.26). After adjustment for these predictors, baseline hs-cTnI level was associated with elevated risk for all-cause mortality, cardiovascular death and composite CV death or HF hospitalization (Figure). In this adjusted model, C statistics for hs-cTnI in discriminating time to CV death or HF hospitalization was 0.76 (95% CI 0.70–0.81). Patients in the highest quartile of hs-cTnI demonstrated a 4-fold risk of the composite CV death or HF hospitalization compared to the 1st quartile (HR 3.64 (95% CI 1.53–8.68), p=0.004) in the adjusted model.

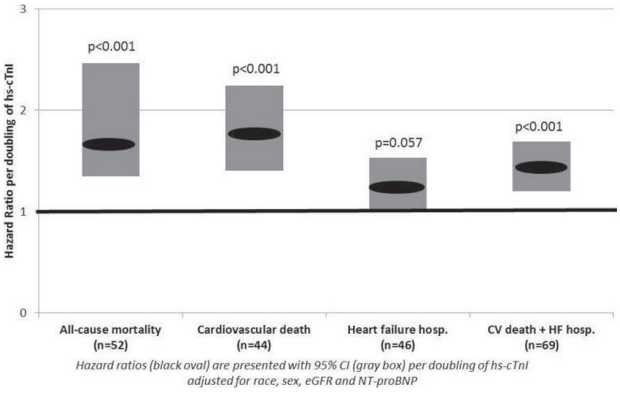


Figure 1

Conclusion: In ambulatory patients with HFpEF, elevations in hs-cTnI are associated with male gender, black race, lower eGFR, and higher NT-proBNP. Levels of hs-cTnI are independent predictors of all-cause mortality and CV mortality or HF hospitalization in this patient population.
Funding Acknowledgements: Supported by a contract from the National Heart, Lung, and Blood Institute, National Institutes of Health (HHSN268200425207C)

P6508
Balance of risk and benefit of spironolactone according to renal function in heart failure patients with preserved ejection fraction

I.E. Beldhuis[1], P.L. Myhre[1], B. Claggett[1], K. Damman[2], J.C. Fang[3], E.F. Lewis[1], E. O'Meara[4], B. Pitt[5], S.J. Shah[6], A.A. Voors[2], M.A. Pfeffer[1], S.D. Solomon[1], A.S. Desai[1]. *[1]Brigham and Women's Hospital, Cardiovascular Division, Boston, United States of America; [2]University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands; [3]University of Utah School of Medicine, Salt Lake City, United States of America; [4]Montreal Heart Institute, Montreal, Canada; [5]University of Michigan School of Medicine, Ann Arbor, United States of America; [6]Northwestern University Medical Center, Division of Cardiology, Chicago, United States of America*

Background: Guidelines now suggest that spironolactone may be useful to reduce heart failure hospitalization (HFH) in heart failure with preserved ejection fraction (HFpEF) patients. However, spironolactone may increase the risk for hyperkalaemia and worsening renal function, particularly in patients with severe renal dysfunction.
Purpose: We investigated the influence of baseline renal function on clinical outcomes and the balance of safety and efficacy of spironolactone in HFpEF patients.
Methods: Among patients enrolled in the Americas region of the TOPCAT trial (N=1767), we examined the association between baseline renal function categories (CKD-EPI eGFR <45, 45–60, ≥60 mL/min/1.73m^2) and the primary efficacy outcome of cardiovascular (CV) death, HFH, or aborted cardiac arrest and safety outcome of drug discontinuation for adverse events (AE). Variation in the efficacy and safety according to baseline renal function was examined in Cox proportional hazard models.
Results: Incidence rates for the primary efficacy outcome and drug discontinuation for AE increased with declining eGFR, with highest rates in those with severe renal dysfunction (eGFR<45). Compared to placebo, across all eGFR categories, spironolactone was associated with lower relative risk (RR) for the primary endpoint (interaction p=0.13) and higher RR for drug discontinuation (interaction p=0.46). Over 4-year follow-up, efficacy of spironolactone remained consistent across the range of eGFR, but the difference in absolute risk for drug discontin-

Abstract P6508 – Table 1. Treatment effect of spironolactone

	Efficacy CV Death, HFH, or Aborted Cardiac Arrest				Safety Permanent Drug Discontinuation			
	Incidence Rate (per 100py)		Treatment Effect		Incidence Rate (per 100py)		Treatment Effect	
	Placebo	Spironolactone	HR	4-year Absolute Risk Difference	Placebo	Spironolactone	HR	4-year Absolute Risk Difference
eGFR (ml/min/1.73m^2)								
≥60	11.1	7.3	0.66 (0.50, 0.88)	–9% (–17%, –2%)	1.7	4.3	2.50 (1.38, 4.53)	+8% (+3%, +14%)
45–60	10.6	10.5	0.99 (0.73, 1.36)	+1% (–8%, +11%)	2.7	10.7	3.80 (2.24, 6.45)	+24% (+14%, +33%)
<45	19.5	17.4	0.89 (0.66, 1.21)	–9% (–21%, +3%)	9.4	21.0	2.12 (1.41, 3.19)	+27% (+12%, +42%)
Interaction P-value			0.13	0.23			0.46	0.003