Background: Heart failure with preserved ejection fraction (HFPEF) is increasingly common but the established heart failure (HF) drugs are not effective. The underlying cellular mechanisms are incompletely understood. Therefore we investigated cardiomyocyte function and intracellular Ca\(^{2+}\) homeostasis in a model of HFPEF.

Methods: Young male Wistar rats were subjected to subtotal nephrectomy (NXT) or sham operation (SOP). Serial blood/urine samples, echocardiography and pressure-volume loops at 8 and 24 weeks were performed. After sacrifice, left ventricular (LV) hypertrophy and NCX function (Caffeine induced Ca\(^{2+}\) transient, TAU) and protein expression (Western blot) were determined. Cardiomyocyte function (Ca\(^{2+}\) transients, sarcoplasmic reticulum (SR) diastolic Ca\(^{2+}\) leak (Ca\(^{2+}\) sparks) and SR Ca\(^{2+}\) content; Fluo4-AM) were quantified in isolated LV cardiomyocytes without and with the NCX inhibitor SEA0400 (300nM).

Results: NXT rats showed stable compensated renal impairment and significantly hypertrophied LV at 8 weeks with a further increase after 24 weeks. LV systolic function (EF, dP/dt) was preserved. End diastolic pressure (EDP) volume relationship was markedly shifted left- and upwards and lung weight were significantly increased, indicating HFPEF with pulmonary congestion. LV cardiomyocytes from NXT showed no significant differences in amplitudes of Ca\(^{2+}\) transients. However, time for early (50%) relaxation of the Ca\(^{2+}\) transients at 8 weeks were significantly prolonged with a further increase after 24 weeks (RT50 17.2 ± 2.9 and 30.8 ± 2.7 vs. 27.6 ± 1.8 and 41.8 ± 2.6 ms; n ≥ 20; p < 0.05). TAU was significantly prolonged at 8 and 24 weeks indicating reduced NCX forward mode activity, while NCX protein expression was upregulated. At 8 weeks, Ca\(^{2+}\) spark frequency tended to be increased (p=0.07) while SR Ca\(^{2+}\) content was unchanged. SEA0400 accelerated Ca\(^{2+}\) transient decay but did not affect Ca\(^{2+}\) spark frequency. At 24 weeks, Ca\(^{2+}\) spark frequency was increased (4.3 ± 0.7 vs. 11.5 ± 1.8 sparks/μm\(^3\); n ≥ 20; p < 0.05) and SR Ca\(^{2+}\) content was decreased (p < 0.05). SEA0400 significantly accelerated Ca\(^{2+}\) transient decay and reduced Ca\(^{2+}\) spark frequency.

Conclusion: In this model of HFPEF, relaxation of cardiomyocytes was slower and cytosolic Ca\(^{2+}\) decay was prolonged. Diastolic Ca\(^{2+}\) leak increased significantly during diseases progression. Whereas NCX forward mode activity was already reduced early despite increased NCX protein expression. Acute treatment with NCX inhibitor SEA0400 normalized cytosolic Ca\(^{2+}\) transients in young NXT rats suggesting a role of reverse mode NCX activity and decreased Ca\(^{2+}\) leak at later time points.