Introduction: Thyroid hormones (TH) regulate many aspects of cells differentiation, growth and metabolism, and are critical for normal functioning of multiple organs. Heart is an important target for TH actions and marked cardiovascular changes occur in patients with acute or chronic thyroid dysfunctions. Hyperthyroidism for example leads to cardiovascular impairment. However, recent data has accumulated, highlighting also the potential beneficial effects of TH administration for clinical or preclinical treatment of different diseases. One interesting finding is the pro-remyelinating and neuroprotective effect of TH, after prolonged daily administration in animal models of multiple sclerosis. In this context, it is important to analyze undesirable secondary effects on heart during TH administration. Therefore, animal models of experimentally induced hyperthyroidism represent important tools for investigating and monitoring changes of cardiac function. In our present study we analyze the effects of such long-term hyperthyroidism on the heart with focus on left ventricular (LV) functional parameters via Magnetic Resonance Imaging (MRI).

Methods: Two groups of 8-week old female C57BL/6N mice were daily injected with either 0.3 µg T3 (3,3′,5-triiodo-L-thyronine) per g body weight (seven treated mice) or 0.9% m/v NaCl-solution (five control mice) for three weeks. The dose selected for T3 treatment was similar with the dose found to induce recovery in animal models of demyelination. T3 administration was stopped for a recovery period of three weeks and restarted for two more weeks. Longitudinal mouse heart MRI were performed (Fig. 1) using a 9.4 T small bore animal scanner (Biospec 94/20, Bruker, Germany) and a transmit/receive 1H mouse quadrature birdcage resonator. Data was acquired using an ECG-triggered and respiratory gated cine-FLASH sequence with a temporal resolution of 10 ms and a spatial resolution of 130x150 µm² (acquisition matrix of 192 x 192, 0.7 mm slice thickness, 15° flip angle, 6 averages). Four-chamber view was used to get basal, mid and apical short axis views (Fig. 1), which were used for calculation of enddiastolic volume (EDV), endystolic volume (ESV), minimum segmental wall thickness and maximum segmental wall thickness after myocardial contour segmentation. Ejection fraction (EF), global and regional wall thickening according to the 16-segment model were determined from these parameters. Statistical group analysis was performed using two-way ANOVA and Bonferroni corrections of multiple testing with * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

Results and discussion: Prolonged T3 administration in mice over a period of 3 weeks induced hyperthyroidism and significantly changed global LV function parameters of the heart, compared to control (Fig. 2). A very significant reduction of ejection fraction (EF) and global wall thickening (GWT – averaged over all 16 segments) account for impaired LV performance. Additionally, our data reveal also the recovery potential of the cardiac function after T3 treatment arrest. Improved LV performance is achieved, with an upturn of the EF and GWT to nearly control values (Fig. 2). Detailed regional and time-related analysis of wall thickening shows the same pattern of decline in the cardiac function and recovery, consistent with the timeline of the experimental design (Fig. 3). Prolonged hyperthyroidism generates an overall reduction of wall thickening in all segments with a maximum decrease in the mid septal region (segments 7 to 10) during T3 treatment. Previous clinical and preclinical studies reported initial increase in the cardiac function due to the increased cardiac metabolism induced by short-term or acute TH supplementation. Our results extend this knowledge, pointing-out the detrimental effect of the long-term hyperthyroidism on the cardiovascular system, due to sustained hemodynamic overload, that may ultimately lead to heart failure.

Conclusion: The results of this study illustrate the potential of high-field small animal MRI to assess and monitor overtime the mouse cardiac function in normal and pathological conditions. Impaired LV performance induced by long-lasting elevated values of circulating TH was assessed in mice, with reversible effects after hormonal treatment arrest. Follow-up studies are now of interest to see if long-term effects of a prolonged T3 treatment will remain or if complete recovery can be achieved. This information will be of high value for future applications of TH based remyelinating therapy in pre-clinical and clinical studies.