Introduction: Structural heart disease (SHD) commonly predisposes to atrial fibrillation (AF). While progressive remodelling is implicated, direct demonstration of functional electrical endocardial-epicardial dissociation (FEEED) in humans has not been shown previously. Our study aim was to demonstrate FEEED, signal complexities and 3D activation dynamics of the human atrium with SHD.

Methods: Simultaneous intra-operative mapping of endocardial (Endo) and epicardial (Epi) lateral RA wall was performed during sinus rhythm (SR), pacing drive (600ms and 400ms CL) and premature extra-stimulation (PES) using two HD Grid catheters (16 electrodes, 3mm spacing). Filtered uni- and bipolar electrograms (EGM's) and electrode locations were exported into MATLAB for analyses. Activation (AM) and phase analyses (PM) were performed on unipolar EGM's. The finite difference technique was used to assess conduction velocity (CV). Signal fractionation and voltage analyses were performed on bipolar EGM's and comparisons made between Endo and Epi along the two orthogonal planes (horizontal [H] and vertical [V] bipolar configurations) for SR, pacing drive and PES. Signal phase at each location of the Endo surface was compared to phase timing at the opposing Epi surface. Difference of ≥20ms between paired Endo and Epi electrodes defined dissociation. Bipolar EGM's fractionation was classified based on previously described criteria.

Result: Sixteen patients with SHD (43% ischaemia, 57% valvular disease) were included. 9866 EGM's analysed. Compared to SR, PM and AM showed significant FEEED during pacing at 600ms and 400ms (PM: 22.4% vs 10%, p<0.0001; 25.8% vs 10%, p<0.0001 respectively; AM: 25.4% vs 7.8%, p<0.0001 and 27.7% vs 7.8%, p<0.0001 respectively) and PES (PM: 34% vs 10%, p<0.0001; AM: 29.5% vs 7.8%, p<0.0001). Marked CV slowing was also with PES compared to SR (Endo: 45.9 vs 56.1cm/s, p<0.0001; Epi: 41.3 vs 52.4 cm/s, p<0.0001). Signal fractionation was higher during pacing drive at 600 ms (Endo: 38.4% vs 28.9%, p=0.002; Epi: 42.1% vs 29.9%, p = 0.002), 400 ms (Endo: 44% vs 28.9%, p=0.0012; Epi: 44.3% vs 30.1%, p<0.0001) and during PES (Endo: 48.9% vs 28.9%, p<0.0001; Epi: 54% vs 28.9%, p<0.0001). Bipolar voltages differed across the two planes (V vs H: 4.3 vs 3.0mV, p=0.0008 [SR], 2.6 vs
2.0mV, p=0.03 [pacing drive] and 1.78 vs 1.06mV, p= 0.049 [PES]) and consistent with asymmetrical wavefront propagation, a decreasing trend in voltage correlation was observed between the endo- and epicardium (R2: 0.91 [SR], 0.38 [pacing drive] and 0.42 [PES]).

**Conclusion:** We have demonstrated for the first time in human atria significant FEEED with signal fractionation and CV slowing with PES on simultaneous endo-epicardial mapping. Such complex 3D interaction in electrical activation provides mechanistic insights for atrial arrhythmogenesis with SHD.