Cardiac resynchronization therapy (CRT) has become a standard of care for patients with heart failure (HF) associated with left ventricular (LV) dyssynchrony. CRT benefits are heterogeneous between patients and approximately one third of patients are clinically and/or echocardiographically non-responders. Thus, guidelines restrict CRT to HF patients with both mechanical dyssynchrony and wide QRS.

The relationship of mechanical dyssynchrony and QRS widening has been described among populations. However, the temporal evolution of this relationship occurring during cardiac function degradation has not been characterized. The dog model of dilated cardiomyopathy (DCM) induced by rapid ventricular pacing is a predictive and translational model to investigate HF mechanism. Using healthy and DCM dogs, this study investigates the interplay of the mechanical dyssynchrony and the different phase of the action potential (observed by electrocardiogram), especially on ventricular depolarization and repolarization, *i.e*, QRS complex, JTp interval and Tp-Te interval.

Mechanical dyssynchrony was assessed by the measurement of septal to posterior wall motion delay (SPWMD) using echocardiography and the QRS complex, JTp interval and Tp-Te interval durations were monitored on electrocardiogram (ECG). Three series of experiments were conducted: firstly, mechanical dyssynchrony and QRS complex duration were observed along the degradation of LV on dogs were implanted with a right ventricular pacemaker and underwent rapid ventricular pacing for seven weeks at 240 bpm (n=6). Secondly, dyssynchrony was evoked on healthy dogs by flecainide (Class Ic anti-arrhythmic, fast sodium channels blocker, infused i.v. at 10mg/kg over 45 minutes, n=6). Finally, the HMR1556 (blocker of the slow delayed rectifier potassium current IKs, administered at 30 mg/kg, P.O, n=4) on healthy dogs and dogs with moderate and severe heart failure.

In pacing-induced DCM dogs, SPWMD progressively increased and became significant after 14 days of pacing to reach 122 ± 2.7 ms on day 42 of pacing vs 35 ± 8.4 ms before pacing ($p=0.0001$) while QRS duration progressively increased from 39 ± 2 ms to 48 ± 3 ms after 21 days of pacing ($p<0.0001$). In healthy dogs, the block of INa and IKs channels modified ECG duration and increased SPWMD. Flecaïnid widened QRS complex (+ 30±7%) and increased SPWMD by 40±10% ($p <0.01$ vs baseline). HMR1556 elongated the late repolarization evaluated by the ECG index (Tp-Te/QT and Tp-Te/JTp) and increased SPWMD by 46%. Whereas, in pacing-induced DCM dogs, HMR1556 decreased by 13% SPWMD with a pronounced effect on early repolarization (JT/QT increased).

In pacing-induced DCM dogs, mechanical dyssynchrony preceded QRS widening and QRS complex duration started to increase after SPWMD had reached a plateau. QRS widening is a marker of dyssynchrony severity. The ventricular depolarization and repolarization modulation on healthy and DCM dogs impacted the mechanical dyssynchrony especially in DCM dogs where HMR1556 decreased the SPWMD. In conclusion, mechanical dyssynchrony in HF patients could be treated earlier with new “resynchronizing” drugs addressing mechanisms of action dissociated from electrophysiological correction.

Key words: dyssynchrony, electrocardiogram, echocardiography, dog, dilated cardiomyopathy, flecaïnid, HMR1556, repolarization