Reverse use dependence of calcium sensitizer levosimendan on action potential duration shortening prevents ventricular arrhythmia during therapeutic hypothermia

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Background: Therapeutic hypothermia (TH) increases the risk of ventricular arrhythmia (VA) by prolonging action potential duration (APD) and steepening the APD restitution (APDR). The calcium sensitizer levosimendan, a medication for heart failure treatment, has been reported to shorten APD by enhancing ATP-sensitive K current and affect the APDR.

Purpose: We hypothesized that levosimendan might shorten the already prolonged APD particularly at long pacing cycle length (PCL), thus decreases the maximal slope of APDR, and prevent VA during TH.

Methods: Langendorff-perfused isolated rabbit hearts were subjected to 15-min TH (30°C) followed by 30-min treatment with levosimendan (0.5 μM, n=9) or vehicle (n=8). Using an optical mapping system, APD was evaluated by S1 pacing and APDR curve was plotted using APD70 versus diastolic interval. Ventricular fibrillation (VF) inducibility was evaluated by burst pacing for 30 s at the shortest PCL that achieved 1:1 ventricular capture.

Results: The APD was shortened from 259±8 ms at TH to 241±18 ms after levosimendan infusion at long PCL of 400 ms (p=0.024). However, at short PCL of 280 ms, the APD was not changed before (194±19) and after (188±23) levosimendan during TH (p=0.61). Levosimendan decreases the maximal slope of APDR curve from 1.99±0.65 at TH to 1.41±0.32 after adding levosimendan (p=0.034). The VF inducibility was decreased by levosimendan from 39±30% at 30°C to 14±12% with levosimendan (p=0.023). In control hearts, the maximal slope of APDR (p=0.75) and VF inducibility (p=0.12) were not changed by vehicle during TH.

Conclusion: Levosimendan might protect the hearts against VA during TH by shortening APD at long PCL and flattening the APDR. Enhancing ATP-sensitive K current with levosimendan during TH might be a novel approach to prevent VA during TH.