LDL electronegativity and male predominance in early ventricular tachyarrhythmias following ST-elevation myocardial infarction: evidence of sexual dimorphism associated reduction of sodium currents

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Background: Early ventricular tachycardia/fibrillation (VT/VF) in patients with ST-elevation myocardial infarction (STEMI) was associated with a higher morbidity and mortality rate. We sought to investigate the gender-specific risk and explore the underlying mechanisms of early VT/VF in STEMI patients.

Methods: We analyzed the clinical and laboratory data among 2965 consecutive STEMI patients between Jan 1, 2008 and Dec 31, 2021. Early VT/VF was defined as occurrence of spontaneous VT/VF of ≥30 seconds or requirement of immediate cardioversion/defibrillation due to hemodynamic compromise within the first 48 hours after onset of symptoms. To explore the mechanisms underlying early VT/VF, ex vivo ischemic-reperfusion experiments were conducted in 8-week-old ApoE-/- mice fed a high-fat diet for 8 weeks to promote atherogenesis.

Results: Of the 2965 STEMI patients studied, 256 (8.6%) experienced early VT/VF. Patients who developed early VT/VF were younger (58 ± 13 vs. 61 ± 13 years old, P = 0.012) and had a higher proportion of males (87% vs. 83%, P = 0.043). Notably, some patients with early VT/VF had significantly higher plasma levels of L5, the most electronegative subclass of low-density lipoprotein (LDL), compared to those without early VT/VF (n = 19, L5: 10.14 ± 3.09% vs. n = 43, L5: 2.11 ± 0.23%, P = 0.006). In animal study, we have previously showed that male mice have higher plasma L5 concentrations than female mice. In this study, all male mice (n = 4) developed VT/VF following the sham operation, whereas none of the female mice (n = 3) did. Moreover, male mice had significantly slower heart conduction velocity than female mice in whole heart preparations (13.37 ± 3.81 cm/s vs. 40.70 ± 4.97 cm/s, P < 0.001), despite having similar action potential duration (61.00 ± 7.07 vs. 50.33 ± 4.16 ms, P = 0.999). In addition, isolated ventricular myocytes from male mice exhibited markedly lower sodium current density (-29.20 ± 3.04 pA/pF, n = 6) compared to those from female mice (-114.05 ± 6.41 pA/pF, n = 6, P < 0.001). The reduced sodium current density was accompanied by lower membranous Nav1.5 protein expression (0.38 ± 0.06 vs. 0.89 ± 0.09 A.U., P < 0.001) and higher cytosolic Nav1.5 levels (0.59 ± 0.06 vs. 0.29 ± 0.04 A.U., P < 0.01) in male mice.

Conclusions: Our study demonstrates that male STEMI patients with early VT/VF have higher levels of L5, the most electronegative LDL subclass. This gender disparity in the susceptibility of early VT/VF may be caused by compromised sodium channel trafficking, likely linked to increased LDL electronegativity.