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.

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**Figure 1.**

A. Spontaneous VT/VF

B. Conduction velocity

C. Sodium currents and Nav1.5 proteins in 4 groups of ApoE-/- mice model. Abbreviations: E2, 17β-estradiol; OVx, ovariectomy; m, membranous; c, cytosolic.