ANTIARRHYTHMIC EFFECT OF CORTICOSTEROID BY SUPPRESSING INFLAMMATION AND Ca2+ CALMODULIN-DEPENDENT PROTEIN KINASE II ACTIVATION IN AUTOIMMUNE MYOCARDITIS

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Background: The fatal arrhythmia is the important cause of death in patient with acute myocarditis. Although corticosteroid decreases the arrhythmia caused by acute myocarditis, the mechanism is not fully elucidated. This study evaluated the anti-arrhythogenic effects of corticosteroid in experimental autoimmune myocarditis (EAM).

Methods: EAM was induced by the injection of porcine cardiac myosin of 2 mg into footpads of adult Sprague-Dawley rats on day 1 and 8 (Myo group, n=15) and compared with control rats (Control, n=15). In additional rats, corticosteroid of 6 mg was injected into the gluteus muscle before the injection of porcine cardiac myosin on day 1 and 8 (MyoS group, n=15).

Results: In Myo group, 4 (27%) out of 15 rats died suddenly at 12 ± 3 days after acute myocarditis, and 5 (56%) of 9 surviving rats had arrhythmia. In contrary, no rat died and had arrhythmia in control group. The Myo group had a lower cumulative survival free of death than the control (p=0.03). In MyoS group, only one (6%) rat died and no rat had arrhythmia. Compared with control, action potential duration (APD) (98±7 vs. 152±52 ms, p=0.03), APD dispersion (13±4 vs. 43±16 ms, p=0.001), the pacing cycle length for discordant alternans (90±9 vs. 198±22 ms, p<0.001), the maximum slope of APD restitution curve (0.2±0.1 vs. 0.7±0.1, p<0.001) and the inducibility of VT (p=0.003) were increased in Myo group. However, these arrhythmogenic effects were attenuated in MyoS group. HMGB1, IL-6, and TNF-α were increased in Myo than in control group. Myo group had increased phosphated Ca2+/calmodulin-dependent protein kinase II (CaMKII), ryanodine receptor type 2 and phospholamban activity than control. However, the level of inflammatory markers and phosphorylation of CaMKII, ryanodine receptor and phospholamban was not increased in MyoS group.

Conclusion: The arrhythmogenic mechanism of myocarditis was related with the increase of APD, APD dispersion and discordant alternans. These arrhythmogenic effects were caused by the inflammation and CaMKII activation, and completely prevented by corticosteroid.