題名:Aging increases pulmonary veins arrhythmogenesis and susceptibility to calcium regulation agents.

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摘要:BACKGROUND: Aging and pulmonary veins (PVs) play a critical role in the pathophysiology of atrial fibrillation. Abnormal Ca(2+) regulation and ryanodine receptors are known to contribute to PV arrhythmogenesis. OBJECTIVE: The purpose of this study was to investigate whether aging alters PV electrophysiology, Ca(2+) regulation proteins, and responses to rapamycin, FK-506, ryanodine, and ouabain. METHODS: Conventional microelectrodes were used to record action potential and contractility in isolated PV tissue samples in 15 young (age 3 months) and 16 aged (age 3 years) rabbits before and after drug administration. Expression of sarcoplasmic reticulum Ca(2+) ATPase (SERCA2a), ryanodine receptor, and Na(+)/Ca(2+) exchanger was evaluated by western blot. RESULTS: Aged PVs had larger amplitude of delayed afterdepolarizations, greater depolarized resting membrane potential, longer action potential duration, and higher incidence of action potential alternans and contractile alternans with increased expression of Na(+)/Ca(2+) exchanger and ryanodine receptor and decreased expression of SERCA2a. Rapamycin (1,10,100 nM), FK-506 (0.01, 0.1, 1 microM), ryanodine (0.1, 1 microM), and ouabain (0.1, 1 microM) concentration-dependently increased PV spontaneous rates and the incidence of delayed afterdepolarizations in young and aged PVs. Compared with results in young PVs, rapamycin and FK-506 in aged PVs increased PV spontaneous rates to a greater extent and exhibited a larger delayed

afterdepolarization amplitude. In PVs without spontaneous activity, rapamycin and FK-506 induced spontaneous activity only in aged PVs, but ryanodine and ouabain induced spontaneous activity in both young and aged PVs. CONCLUSION: Aging increases PV arrhythmogenesis via abnormal Ca(2+) regulation. These findings support the concept that ryanodine receptor dysfunction may result in high PV arrhythmogenesis and aging-related arrhythmogenic vulnerability.