

Gao W, Y Liu, E Marban. Selective effects of oxygen free radicals on excitation-contraction coupling in ventricular muscle. *Circ* 1996;94: 2597-2604.

BACKGROUND: Oxygen free radicals (OFRs) have been implicated in the pathogenesis of myocardial stunning, but the precise mechanism by which OFRs foster stunning remains unclear. We investigated the pathophysiology of the contractile dysfunction that occurs after direct exposure of OFRs to cardiac muscle and compared the results with the pathophysiology of stunned myocardium. METHODS AND RESULTS: Trabeculae from the right ventricles of rat hearts were loaded iontophoretically with fura-2 to determine $[Ca^{2+}]_i$. Steady-state force- $[Ca^{2+}]_i$ relations were obtained by rapid electrical stimulation in the presence of ryanodine. Two exogenous OFR-generating systems were used: $H_2O_2 + Fe(3+)$ -nitrilotriacetic acid ($H_2O_2 + Fe^{3+}$) to produce hydroxyl radical, and xanthine oxidase+purine (XO + P) to produce superoxide. In muscles exposed to $H_2O_2 + Fe^{3+}$ for 10 minutes, both twitch force and Ca^{2+} transients were decreased (eg, in 1.5 mmol/L external $[Ca^{2+}]_o$, force decreased from 41 ± 7 to 23 ± 4 mN/mm², $P < .05$, and Ca^{2+} transient amplitude from 0.96 ± 0.09 to 0.70 ± 0.05 μ mol/L, $P < .05$). Maximal Ca^{2+} -activated force (F_{max}) decreased slightly, from 103 ± 5 to 80 ± 12 mN/mm² ($P = NS$). Neither the $[Ca^{2+}]_i$ required to achieve 50% of F_{max} (Ca_{50}) nor the Hill coefficient was changed. In muscles exposed to XO + P for 20 minutes, twitch force was reduced (in 1.5 mmol/L external $[Ca^{2+}]_o$) from 50 ± 9 to 39 ± 8 mN/mm² ($P < .05$). Ca^{2+} transients, on the other hand, were not affected. F_{max} decreased insignificantly from 100 ± 16 to 81 ± 14 mN/mm². Ca_{50} increased from 0.71 ± 0.06 to 1.07 ± 0.07 μ mol/L ($P < .05$), with no change in the Hill coefficient. CONCLUSIONS: These results indicate that exposure to the $H_2O_2 + Fe^{3+}$ free radical-generating system reduces activator Ca^{2+} availability, whereas XO + P decreases the Ca^{2+} sensitivity of the myofilaments. Exogenously generated OFRs, particularly those produced by XO + P, mimic the effects of myocardial stunning on cardiac excitation-contraction coupling.