Increase in Cardiac Ischemia-Reperfusion Injuries in Opa1+/- Mouse Model

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BACKGROUND:
Recent data suggests the involvement of mitochondrial dynamics in cardiac ischemia/reperfusion (I/R) injuries. Whilst excessive mitochondrial fission has been described as detrimental, the role of fusion proteins in this context remains uncertain.

OBJECTIVES:
To investigate whether Opa1 (protein involved in mitochondrial inner-membrane fusion) deficiency affects I/R injuries.

METHODS AND RESULTS:
We examined mice exhibiting Opa1delTTAG mutations (Opa1+/-), showing 70% Opa1 protein expression in the myocardium as compared to their wild-type (WT) littermates. Cardiac left-ventricular systolic function assessed by means of echocardiography was observed to be similar in 3-month-old WT and Opa1+/- mice. After subjection to I/R, infarct size was significantly greater in Opa1+/- than in WTs both in vivo (43.2±4.1% vs. 28.4±3.5%, respectively; p<0.01) and ex vivo (71.1±3.2% vs. 59.6±8.5%, respectively; p<0.05). No difference was observed in the expression of other main fission/fusion protein, oxidative phosphorylation, apoptotic markers, or mitochondrial permeability transition pore (mPTP) function. Analysis of calcium transients in isolated ventricular cardiomyocytes demonstrated a lower sarcoplasmic reticulum Ca2+ uptake, whereas cytosolic Ca2+ removal from the Na+/Ca2+ exchanger (NCX) was increased, whilst SERCA2a, phospholamban, and NCX protein expression levels were unaffected in Opa1+/- compared to WT mice. Simultaneous whole-cell patch-clamp recordings of mitochondrial Ca2+ movements and ventricular action potential (AP) showed impairment of dynamic mitochondrial Ca2+ uptake and a marked increase in the AP late repolarization phase in conjunction with greater occurrence of arrhythmia in Opa1+/- mice.

CONCLUSION:
Opa1 deficiency was associated with increased sensitivity to I/R, imbalance in dynamic mitochondrial Ca2+ uptake, and subsequent increase in NCX activity.

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