**CALPAIN-MEDIATED DYSTROPHIN DISRUPTION MAY BE A POTENTIAL STRUCTURAL CULPRIT BEHIND CHRONIC DOXORUBICIN-INDUCED CARDIOMYOPATHY**

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The critical importance of dystrophin to cardiomyocyte contraction and sarcolemmal and myofibers integrity, led us to test the hypothesis that dystrophin reduction/loss could be involved in the pathogenesis of doxorubicin-induced cardiomyopathy, in order to determine a possible specific structural culprit behind heart failure. Rats received total cumulative doses of doxorubicin during 2 weeks: 3.75, 7.5, and 15 mg/kg. Controls rats received saline. Fourteen days after the last injection, hearts were collected for light and electron microscopy, immunofluorescence and western blot. The cardiac function was evaluated 7 and 14 days after drug or saline. Additionally, dantrolene (5mg/kg), a calcium-blocking agent that binds to cardiac ryanodine receptors, was administered to controls and doxorubicin-treated rats (15 mg/kg). This study offers novel and mechanistic data to clarify molecular events that occur in the myocardium in doxorubicin-induced chronic cardiomyopathy. Doxorubicin led to a dose-dependent marked reduction/loss in dystrophin membrane localization in cardiomyocytes correlated with dose-dependent left ventricular dysfunction, which may constitute, in association with sarcomeric actin/myosin proteins disruption, the structural basis of a dose-dependent doxorubicin-induced cardiac depression. Moreover, increased sarcolemmal permeability suggests functional impairment of the dystrophin-glycoprotein complex in cardiac myofibers and/or oxidative damage. Increased expression of calpain, a calcium-dependent protease, was markedly increased in cardiomyocytes of doxorubicin-treated rats. Dantrolene strikingly improved survival rate and preserved myocardial dystrophin and calpain levels, which supports the opinion that calpain mediates dystrophin loss and myofibrils degradation in doxorubicin-treated rats. Studies are needed to further elucidate this mechanism, which may provide new interventional pathways to prevent doxorubicin-induced cardiomyopathy.