Doxorubicin and dysregulation of cytosolic calcium dynamics in heart

PRALOY CHAKRABORTY
Mohammed Ali Azam
Keith Dadson
Stéphane Massé
Patrick F. H. Lai
Phyllis Billia
Kumaraswamy Nanthakumar

Introduction: Anthracyclines are the most commonly used antineoplastic drugs to treat a host of hematological and solid tumors. The most feared complication of this group of antineoplastic agents is cardiotoxicity, characterized by systolic dysfunction and heart failure. Myocyte loss due to apoptosis is the hallmark of anthracycline induced cardiomyopathy. Calcium (Ca2+) is essential for excitation–transcription (ET) coupling pathways. Disturbances in cellular Ca2+ handling has been shown to be critically involved in structural and functional remodeling processes associated with heart failure. Doxorubicin has been shown to alter the expression and function of proteins associated with cytosolic calcium handling. However, there is limited published data on the effect of doxorubicin in cardiac cytosolic calcium dynamics physiology. The study was planned to determine the effects of doxorubicin in cardiac cytosolic calcium dynamics in an in vivo mouse model.

Methods: A single dose of doxorubicin (10mg/kg) (n=12) or saline (n=10) was administered intraperitoneally in mice. Fourteen days later, the mice were sacrificed, and hearts were perfused in a Langendorff setup. After stabilization, Rhod-2AM and blebbistatin were infused and ventricular epicardial calcium fluorescence was optically measured following a pace-and-pause protocol. Calcium transient duration 50 (CaTD50) (Figure 1A), calcium transient duration 80 (CaTD80) (Figure 1B), calcium alternans ratio (1C), and spontaneous calcium elevation (Figure 1D) were measured using custom MATLAB codes.

Result: Diastolic spontaneous calcium elevation (p=0.034)(1D) and calcium alternans (p=0.002) (1C) were higher in doxorubicin-treated mice hearts compared to controls. In vivo treatment with doxorubicin prolonged both CaTD50 (p=0.016)(1A) and CaTD80 (p=0.005)(1B) and decreased CaTD50-to-CaTD80 ratio (p=0.016) compared to control hearts.

Conclusion: Doxorubicin treatment is associated with abnormal cytosolic calcium handling characterized by spontaneous diastolic calcium release, decreased diastolic clearance and calcium alternans. The pattern of abnormality suggests dysfunction of both Ryanodine Receptor and SERCA2a. Apart from abnormal excitation contraction and extraction excitation–transcription coupling, the abnormal calcium handling may also play crucial role in genesis of arrhythmia, a complication of heart failure.