Anthracycline-induced atrial structural and electrical remodeling characterizes early cardiotoxicity and contributes to atrial fibrillation

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October 1, 2020

Abstract

Background and Purpose: Cancer patients treated with anthracyclines are susceptible to atrial fibrillation (AF) with unknown mechanisms. Due to sudden and unpredictable features of AF, detection or prediction of anthracycline-induced AF at early phase is difficult. Experimental Approach: Breast cancer patients (post-surgery) with an anthracycline-containing regimen were recruited for echocardiography at pre-, and 3 and 6 months post-chemotherapy. Mice were injected with doxorubicin or vehicle and the following parameters were determined: left atrial diameter, electrical transmission, AF inducibility. Meanwhile, oxidative stress, cardiomyocyte size, vacuolization, inflammation and fibrosis were measured in mouse atria. The therapeutic effect of dexrazoxane on doxorubicin-induced changes in the aforementioned parameters were also determined. Key Results: Whilst ventricular parameters and functions were unchanged in cancer patients pre- and post-chemotherapy, strain and strain rate of left atrial reservoir function and conduit function were decreased at 3 months post-chemotherapy vs pre-chemotherapy. Doxorubicin-induced atrial dilatation and susceptibility to AF occurred in mice prior to onset of ventricular dysfunction. Doxorubicin-induced AF was via inducing structural remodeling (i.e. cardiomyocyte death, hypotrophy and vacuolization) and electrical remodeling (i.e. reduction and redistribution of connexin 43) in the atrium, which was effectively prevented by dexrazoxane. Atrial remodeling and AF inducibility were induced after doxorubicin injection, which can be inhibited by dexrazoxane. Conclusions and Implications: Clinically, we tested whether anthracycline-induced early atrial remodeling in patients could be detected by echocardiography. Experimentally, we investigated the mechanisms of doxorubicin-induced atrial remodeling and AF in mice, and the protective effect of the free radical scavenger dexrazoxane.

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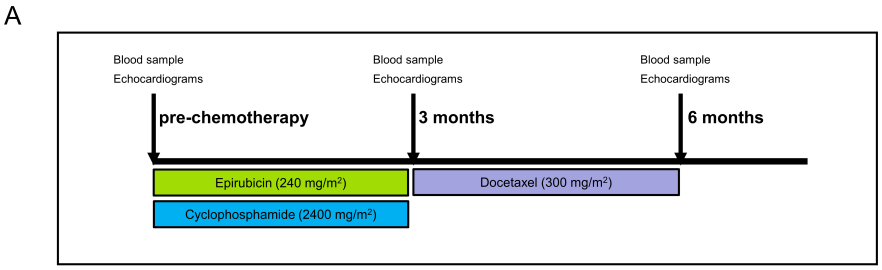

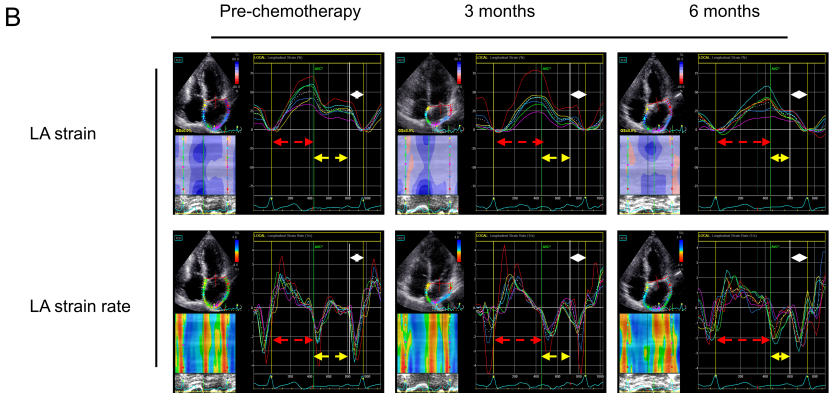

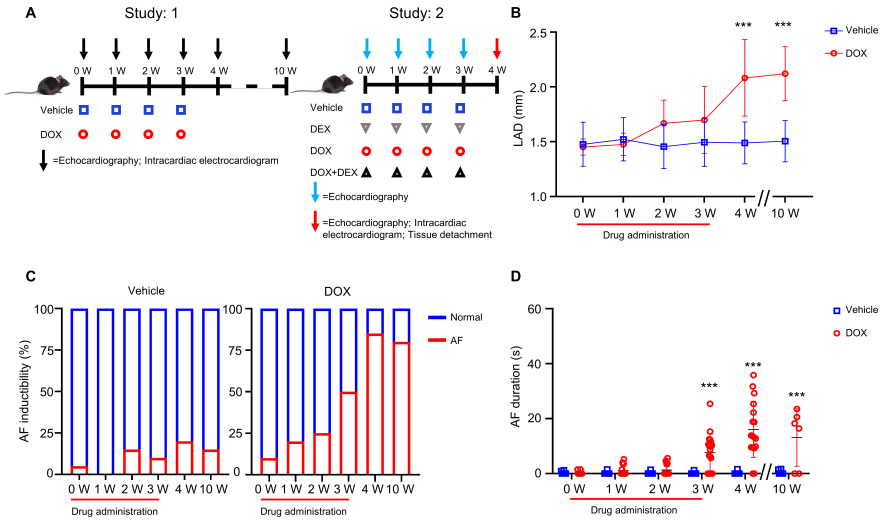

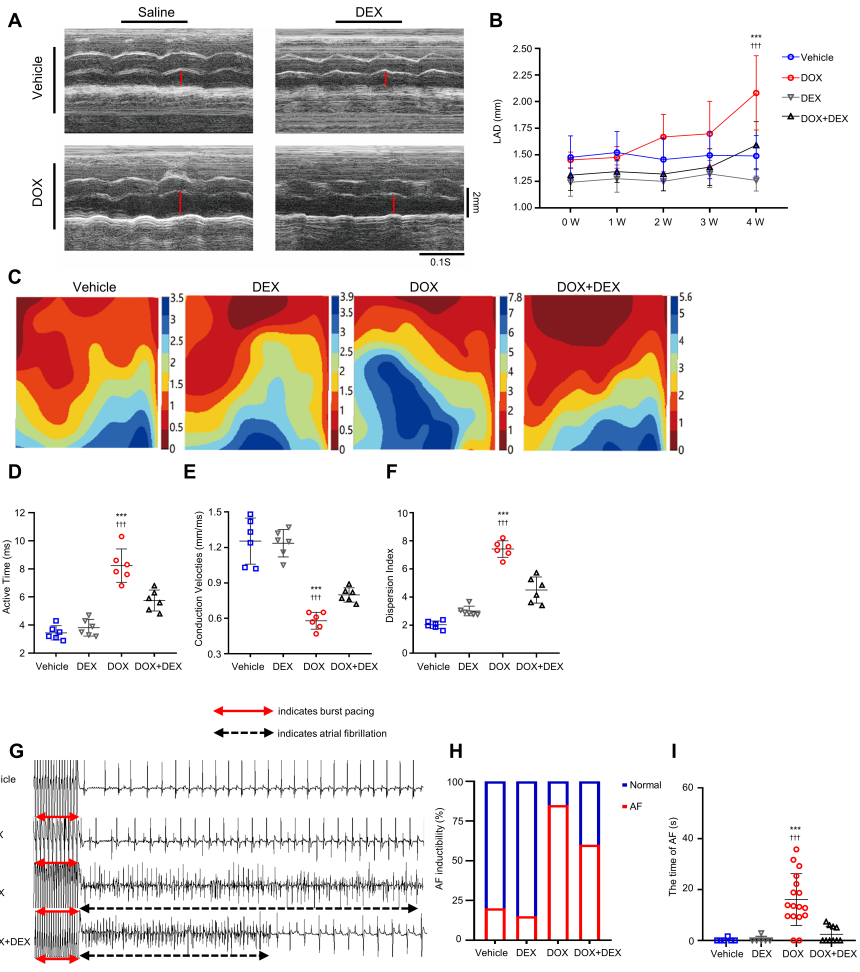

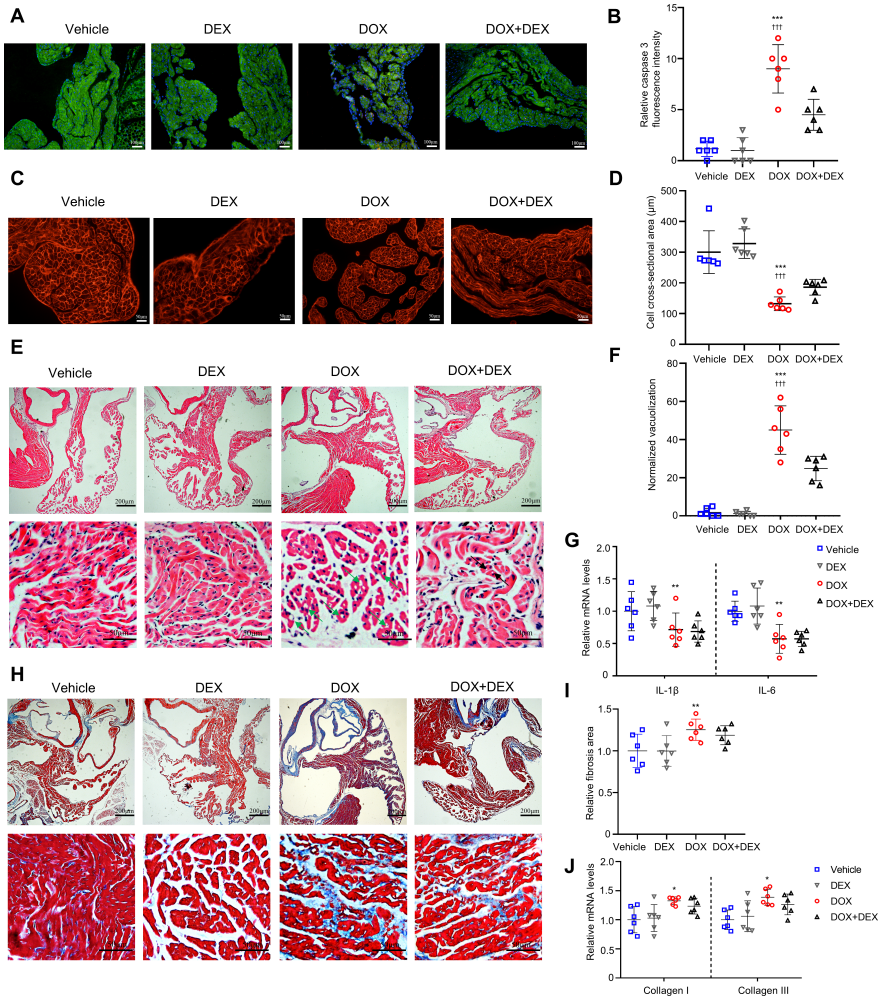

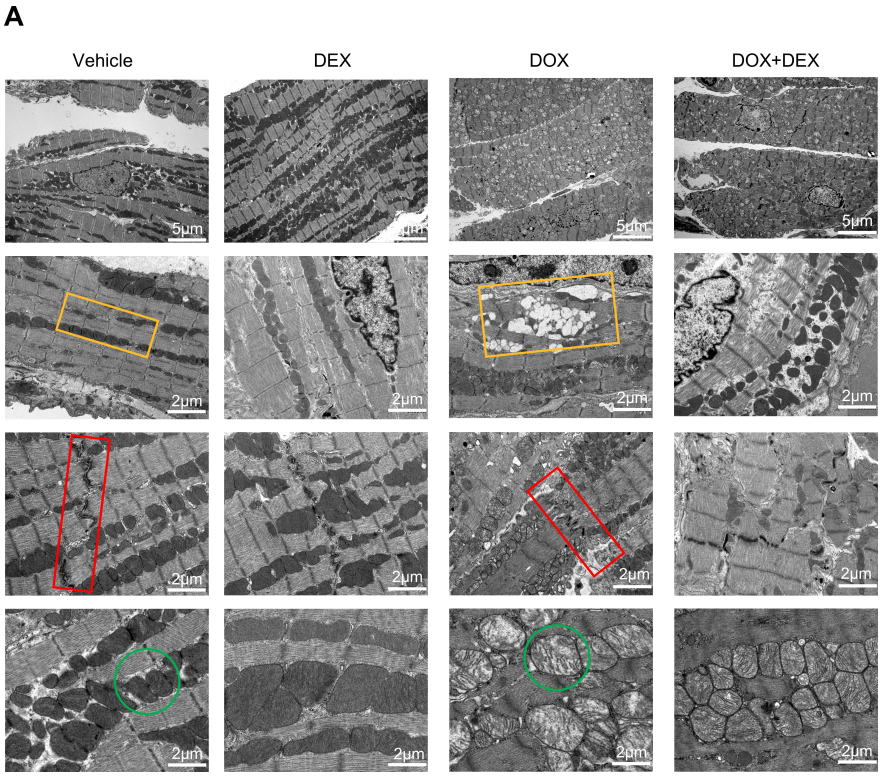

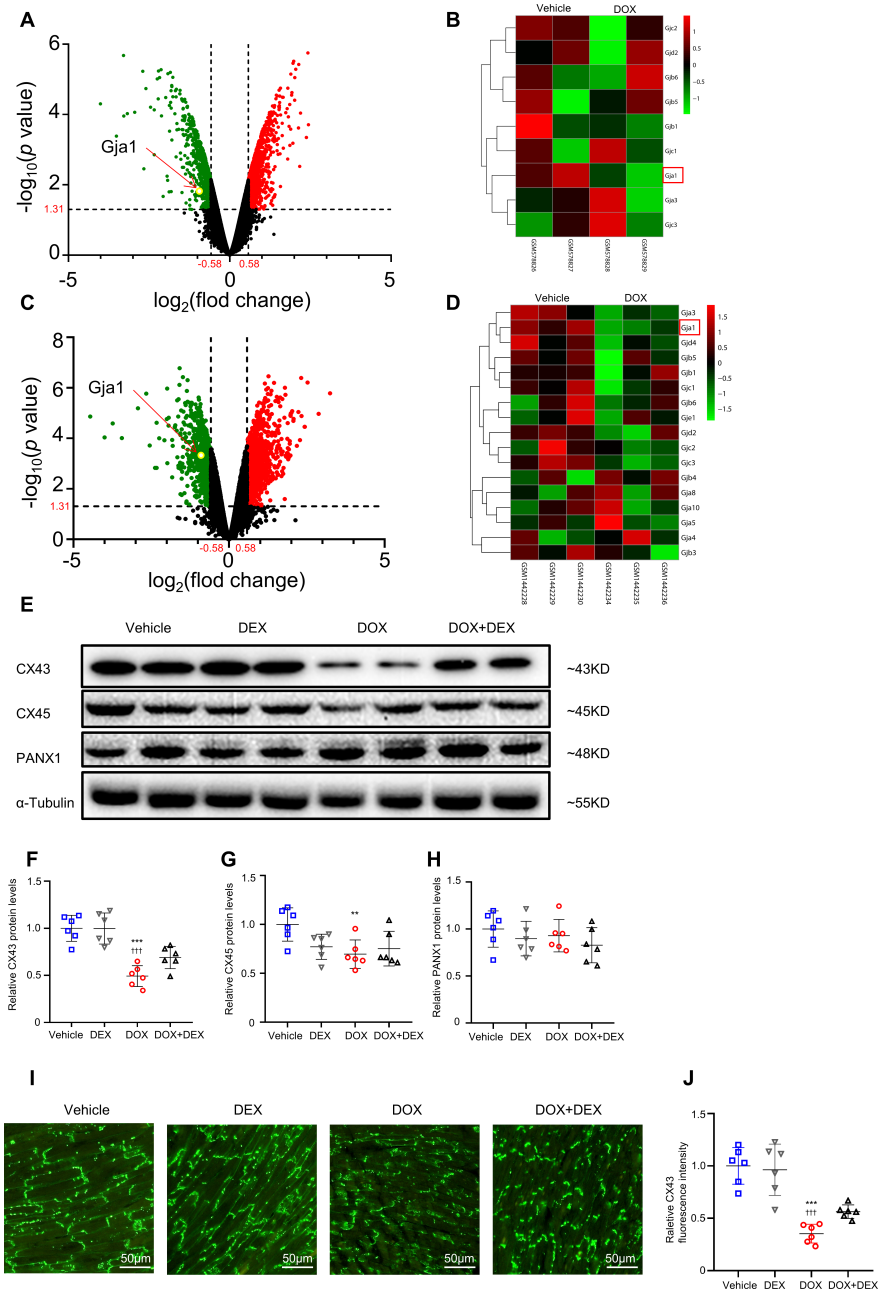

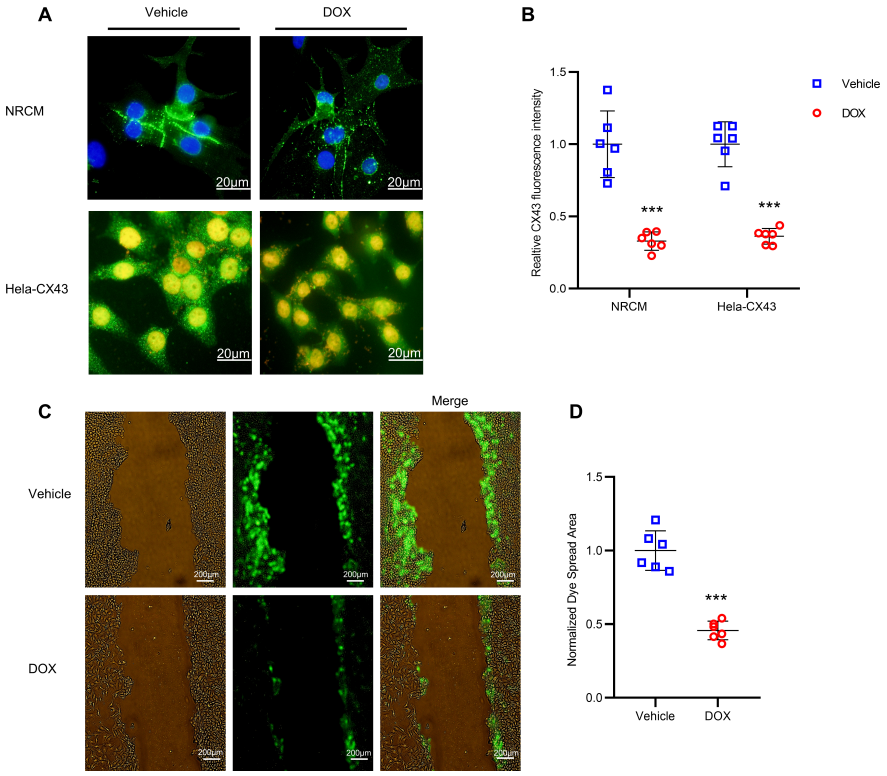

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