Inflammatory mediators in a short-time mouse model of doxorubicin-induced cardiotoxicity

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Doxorubicin (DOXO) is commonly used in therapy for a wide range of malignant tumors, but its clinical use is limited by acute and chronic cardiotoxicity. The precise mechanism underlying DOXO-induced cardiotoxicity is still not completely elucidated, but cardiac inflammation seems to be involved. Numerous studies showed that cardiac expression of proinflammatory cytokines, infiltration of inflammatory cell, and necrosis are increased in hearts of chronic DOXO treated mouse (Ikegami et al., 2007; Li et al., 2006; Riad et al., 2009). To note, it is believed that the activation of the innate immune system with the ensuing proinflammatory cytokines release are at the basis of the pathogenesis of DOXO-induced cardiotoxicity (Hadi et al., 2012). Inflammatory cytokines have been proved to be involved in several cardiac diseases in that they affect heart rate, have negative inotropic effect and induce deleterious left ventricular remodelling (Zhu et al., 2009).

Many studies report the long-term cardiotoxic effects of DOXO; but, the weakness in these studies is that cardiac damage is usually detected only when a functional impairment has already occurred, which leaves little room for early, preventive strategies (Cardinale and Sandri, 2010).

Starting from the evidence that the damage caused by anthracyclines on cardiomyocytes is immediate after each injection (Robert 2007), in the present study, a short-time model of DOXO-induced cardiomyopathy was established. C57BL/6j female mice were randomly divided in groups and injected with DOXO for 1-3 or 7 days once every other day. Cardiac function was assessed using VEVO instrument before sacrifice and after that the heart was removed and frozen for biochemical analysis.

The results of our study demonstrated alterations in Ejection Fraction (EF), Fraction Shortening Index (FS), Left Ventricular End-Diastolic – Diameter (LVEDP), and Left Ventricular End- Systolic Diameter (LVDs) already in mice sacrificed 24 hours after a single injection of DOXO. DOXO administration caused production of proinflammatory cytokines (such as TNF-α and IL-6) with a concomitant reduction of IL-10, a well-known antiinflammatory cytokine. Furthermore, overexpression of inducible nitric oxide synthase (iNOS) in heart tissue and increased levels of nitrite in serum of DOXO-treated mice were detected. Notably, DOXO administration significantly increased the expression of nitrotyrosine in mouse heart. All these proinflammatory parameters progressively increased from 1 to 7 days. We can hypothesize that these inflammatory molecular events could be responsible for the trigger of the deleterious remodelling of myocardium, inducing cardiomyopathy, when DOXO is administered during a long-term clinical protocol.

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