Effect of short-term swim exercise on cardiac dysfunction induced by Doxorubicin in rats

Thesis

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Abstract

Background: Long-term exercise could confer protection against Doxorubicin-induced cardiotoxicity and cardiomyopathy, yet, the effect of short-term exercise just prior to exposure to doxorubicin (Dox) is still unclear. **Aim:** To investigate the effect of short-term exercise on cardiac dysfunction induced by Dox treatment, also, to evaluate heat shock protein (HSP20) and oxidative status of cardiac tissue to clarify possible underlying mechanism (s) of such effect. **Materials and Methods**: Sixty nine female albino rats were assigned into 4 groups: Group 1: control (sedentary rats, n=17), Group 2: Dox (rats received single intraperitoneal injection of Dox in a dose of 20 mg/kg, and studied 24 hours later, n=18), Group 3: Exc (rats swim exercised 1 hour/day for 3 days, n=16), Group 4: Exc +Dox (rats exercised as in group 3 and received Dox injection as in group 2 on the third day and studied 24 hours later, n=18). Rats were subjected to recording of the ECG, measurement of arterial blood pressure, echocardiograghy, analysis of serum parameters of SGOT, LDH, CPK-MB, troponin I (cTnI) and evaluation of total antioxidant capacity, malondialdehyde (MDA) and Hsp20 in the cardiac tissue. **Results**: Compared to the control, Dox-treated rats showed significant prolongation of the observed QT (QT_o) and corrected QT (QT_c) interval, with insignificant depression of the R voltage and the elevation of systolic (SBP), diastolic (DBP), mean (MAP) blood pressures were statistically insignificant. These changes were accompanied by significant elevation of serum SGOT and significant increases in cardiac tissue MDA and Hsp20. Also, compared to the control, rats exposed to 3 days exercise just before Dox injection (Exc+Dox) showed significant prolongation of both QT_o and the QT_c even more than Dox group. However, the depression of the R voltage and the elevation of the SBP, DBP, and MAP become statistically significant compared to the control. These changes were associated with significant increase in SGOT together with insignificant changes in MDA and Hsp20. However, compared to Dox group, the Exc+Dox demonstrated significant prolongation in both QT_o and the QT_c, significant reduction in both the ejection fraction and the fraction of shortening together with significant reductions in MDA and HSP20. **Conclusion: Short-term swim exercise training just prior to doxorubicin exposure is risky and makes the heart more predisposed to arrhythmia despite of the relative improvement in cardiac oxidative status.**

Key words: Doxorubicin, cardiac dysfunction, exercise, HSP20.

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List of Abbreviations

Dox	Doxorubicin
Exc	Exercise
4-HNE	4-Hydroxynonenal-modified proteins
CPK-MB	Creatine phosphokinase
cTnI	Cardiac troponin I
DPB	Diastolic blood pressure
ECG	Electrocardiogram
Echo	Echocardiograph
FoxO	Forkhead-box O
GPX	Glutathione peroxidase
H_2O_2	Hydrogen peroxide
HR	Heart rate
Hsp	Heat shock protein
I/R	Ischemia/Reperfusion
$_{i}$BW	Initial body weight
$_{f}$BW	Final body weight
EF%	Ejection fraction
FS%	Fraction of shortening
ip	Intra-peritoneal
LDH	Lactate dehydrogenase
LV	Left ventricular
LVDA	Left ventricular diastolic area
LVSA	Left ventricular systolic area
LVEDD	Left ventricular end diastolic diameter
LVESD	Left ventricular end systolic diameter
MMPs	Matrix metalloproteinase
MAP	Mean blood pressure
MAP.HR	Mean arterial blood pressure heart rate product
MDA	Malondialdehyde
MI	Myocardial infarction
O_2^-	Superoxide ion
PGC-1	peroxisome proliferator-activated receptor-gamma coactivator-1 alpha

$Q\text{-}T_o$	Observed Q-T interval
$Q\text{-}T_c$	Corrected Q-T interval
SBP	Systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
$_sHR$	Simultaneously recorded heart rate (with arterial blood pressur)
SOD	Superoxide dismutase
SR	Sarcoplasmic reticulum
T.antioxidant	Total antioxidant capacity
WH	Whole heart

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Introduction

Many scientific evidences link regular physical activity to various measures of cardiovascular health **(Fletcher et al., 2001)** and consider the sedentary lifestyle as one of the major cardiovascular risk factors.

Doxorubicin; quinone containing anthracycline antibiotic, is one of the most frequently used chemotherapeutic drug against most of solid tumors and hematological malignancies **(Cortes-Funes and Coronado, 2007)**. Unfortunately, the clinical use of this valuable drug is limited due to its dose-dependent life-threatening side effects especially on the heart **(Singal and Iliskovic, 1998)**. In this regard, it had been reported that doxorubicin (Dox) stimulates reactive oxygen species (ROS) generation by the mitochondria that leads to generation of a free radical cascade with potent oxidizing power **(Wallace, 2003)**. Regrettably, the level of Dox-induced oxidative stress on the heart is up to 10 times greater than other tissues as the liver or the kidney, because the heart exhibits low level of the antioxidant enzymes which detoxifies the H_2O_2 **(Siveski-Iliskovic et al., 1995).** Thus, the oxidative injury of the heart is the widely accepted theory presumed as a primary mechanism of Dox-induced cardiotoxicity **(Mukherjee et al., 2003)**.