The goal of this research is to studying doxorubicin-induced metabolic alterations and the protective role of dexrazoxane. This strategy leading to an oxidative stress causing apoptosis or necrosis in cardiomyocytes, clinically expressed by a progressive heart failure from subclinical myopathy to patient’s death.

2. Metabolic effects of doxorubicin

Doxorubicin-induced oxidative stress was assessed by a fluorimetric assay, using DCFH-DA probe. Briefly, H9C2 cells were seeded in a 96 wells plate and kept growing during 48 hours. Cells were exposed to different doxorubicin doses during 2 hours. A preincubation of 30 min. with dexrazoxane was also assessed. DCFH-DA probe was added to a final concentration of 100 μM during 30 min. at 37 °C in dark. Fluorescence was read at 490 nm (EX)/510-570 nm (EM). Results show that the ROS production is proportional to doxorubicin concentration and that a 10 times higher dose of dexrazoxane can reduce significantly the ROS production.

3. Metabolic effects of doxorubicin

Results of the metabolomic study suggest an oxidative stress-induced impairment of the Krebs cycle, resulting in a metabolic switch to anaerobic conditions with glycolysis as main ATP production pathway: Pyruvate is metabolized mainly into lactate and amino acids. A decrease of proteins synthesis and an increase of anti-oxidant defenses are suggested too.

4. Metabolic effects of pre-incubation with dexrazoxane

Dexrazoxane reduces the doxorubicin-induced oxidative stress, leading to a recovery of mitochondrial metabolism with a decrease of lactate production and an increase of proteins synthesis. Choline metabolism is highly stimulated for membranes synthesis and an important secretion of succinate is noticed.

References