

## **Doxorubicin-induced cardiomyopathy: Prevention and treatment by a coronary specific vasodilator Chromonar**

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### Objectives:

- To explore the possibility of using a known coronary vasodilator as a treatment for doxorubicin induced cardiomyopathy.
- To propose a way how doxorubicin can lead to heart failure
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Doxorubicin is an anthracycline class chemotherapeutic agent that is used with other medications to treat cancers. Doxorubicin works by slowing the growth of cancer cells due to its toxic effects mediated through redox cycling that produces oxidative injury to cells. One side effect of doxorubicin treatment is doxorubicin-induced cardiomyopathy (DiC). DiC typically has the morphological and functional abnormalities of dilated cardiomyopathy, with all cardiac chambers dilated. This dilation occurs as a result of reductions in diastolic and systolic dysfunction leading to impaired ejection and reduced cardiac output. DiC can progress to congestive heart failure. Currently there is no treatment or prevention for DiC. Our goal is to test the hypothesis that Chromonar, a coronary specific vasodilator, will prevent and treat DiC. We have observed that some types of heart failure are associated with evidence of coronary insufficiency, and Chromonar has a beneficial effect for treatment heart failure with non-obstructive coronary artery disease. Accordingly, we propose that the coronary hyperemia, produced by Chromonar, will be effective in facilitating recovery of the heart from DiC. C56Bl/6J mice (N=10) were used for each group. Group 1 received doxorubicin and Chromonar same time, Group 2 received Doxorubicin for 6 weeks with Chromonar treatment to follow. Relationship between myocardial blood flow (MBF) and cardiac work in wild type WT+DOX and WT+DOX+ Chromonar for 6 weeks was observed. The MBF was significantly lower in DOX-treated mice and had a blunted response (vs WT) at any given increment of cardiac work. Ejection fraction (%EF) of the heart also decreased after DOX and Chromonar treatment. Based on these findings, we speculate that the cause of doxorubicin induced cardiomyopathy is inadequate myocardial blood flow to the heart. Pharmacological coronary vasodilation with Chromonar to increase myocardial blood flow stops and reverses the functional decline and improves cardiac function.