DYSFUNCTIONAL IRON HOMEOSTASIS IN MITOCHONDRIA FROM LEFT VENTRICULAR MYOCARDIUM OF DOGS WITH ADVANCED HEART FAILURE

Poster Contributions
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Background: Iron is an essential molecule for cellular function but when present in excess, it increases formation of reactive oxygen species (ROS). Mitochondria (MITO) are key regulators of iron homeostasis. Because MITO function is impaired in the failing heart of both patients and animals with experimental heart failure (HF), and because iron accumulation can lead to ROS formation, we hypothesized that iron regulation may be impaired in MITO of the failing heart. Iron homeostasis within MITO is regulated by MITO ferritin iron-binding protein (mtFt) containing ferroxidase (FeOX). FeOX rapidly catalyzes ferrous (Fe2+) to ferric (Fe3+) thus limiting excessive ROS formation. This study examined changes in Fe2+, Fe3+ and FeOX activity in MITO isolated from LV myocardium of dogs with microembolization-induced HF (LV ejection fraction ~30%).

Methods: LV tissue was obtained from 6 normal (NL) and 7 HF dogs and used to isolate MITO fractions. Fe2+ and Fe3+ levels were determined using a commercially available kit (Sigma) and expressed as nmols/mg protein. FeOX activity was measured using Fe2+ as substrate and the non-oxidized form was measured with a Ferene S compound to produce a colored complex. The difference in the Fe2+ ion concentration before and after the reaction corresponded to the amount of Fe2+ oxidized to Fe3+ and directly attributed to the total FeOX activity expressed as nmol/min/mg protein.

Results: Fe2+ levels were significantly higher in HF compared to NL MITO fractions (9.69 ± 0.82 vs. 5.04 ± 0.40 nmols/mg, p<0.05). Fe3+ levels were lower in HF compared to NL but the change was not statistically different (14.86 ± 1.75 vs. 19.83 ±+ 1.07 nmols/mg). FeOX activity was significantly reduced in HF dogs compared to NL (21.9 ± 3.5 vs. 40.2 ± 3.5 nmols/min/mg, p<0.05).

Conclusion: Fe2+ levels are increased in MITO fraction from LV of HF dogs due to reduced FeOX activity suggesting that an abnormality of iron metabolism may exist in MITO of the failing heart. Increased Fe2+ ions are reactive and can accelerate ROS formation. The latter can MITO injury with subsequent worsening of oxidative phosphorylation.