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The NO/ONOO(-) cycle is the central cause of heart failure, pulmonary hypertension and possibly other types of chronic cardiovascular disease

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The NO/ONOO(-) cycle is a primarily local biochemical vicious cycle mechanism which when localized to various regions of the body, may be the cause of various chronic inflammatory diseases characterized by oxidative stress and mitochondrial dysfunction. The author has published two cardiovascular disease papers, one arguing that pulmonary hypertension is probably caused by the cycle and the other providing a highly detailed case that the NO/ONOO(-) cycle is THE central cause of heart failure. My talk will focus mainly on heart failure. But first, we need to consider the cycle mechanism.

The NO/ONOO(-) cycle involves the elevation of 12 elements, each which interact with each other via 34 well-documented mechanisms, to form a redundant, complex and robust series of interacting vicious cycle mechanisms. The 12 elements are nitric oxide (NO), superoxide, peroxynitrite (ONOO-), oxidative stress, NF-kappaB, several inflammatory cytokines, iNOS, mitochondrial dysfunction, NMDA activity, intracellular calcium, tetrahydrobiopterin depletion and several of the TRP group of receptors.

In examining heart failure six types of evidence were examined, each of which provided a very different type of evidence for the NO/ONOO(-) cycle as the central cause of the disease. 19 initiating stressors were shown to each *raise two or more cycle elements in the context of heart failure initiation.* 11 of the 12 cycle elements are elevated in heart failure, the only possible exception being intracellular calcium. All 12 elements of the cycle have substantial roles in causing heart failure. Heart failure is clearly a primarily local mechanism, with many biochemical, physiological and histological changes localized to the myocardium; different types of heart failure can be best interpreted in terms of different localization within the myocardium, such as right vs left, with or without arrhythmia, varying valve impact. Heart failure is a disease of stunning complexity, with many changes involved in remodeling and additional changes in gene expression, in energy metabolism, in calcium control, activity of many specific enzymes and other biochemical and physiological changes. Each of these complex changes can be shown to be caused by NO/ONOO(-) cycle elements, with each cycle element having causal roles in several such *changes in the context of heart failure.* This pattern alone makes a very strong case that the NO/ONOO(-) cycle is the central cause of heart failure. Two causal factors of heart failure and pulmonary hypertension, RhoA and endothelin-1, both act as tissue limited NO/ONOO(-) cycle elements, a strong prediction of the cycle. Perhaps the most controversial part of the study is that heart failure is not a disease of "insufficient bioavailability of NO." It is the case that NO signaling via increased cGMP and G-kinase is protective, but its low effectiveness in heart failure is caused by the inhibition of this NO signaling pathway by peroxynitrite, a finding that has many implications.

A similar but less detailed case has been made that pulmonary hypertension is a NO/ONOO(-) cycle disease and it may be suggested that the cycle may also cause other types of chronic cardiovascular disease depending on its localization. Clearly the case for each disease must stand on its individual merits.

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