CRITICAL REVIEW OF CLINICAL STUDIES OF ANTIOXIDANT COMPOUNDS AS A THERAPEUTIC STRATEGY

Francisco R. M. Laurindo, Célio X.C. Santos, Marcel Liberman, Estêvão Bassi, Marina K. Martinatti

Heart Institute (InCor), Univ. São Paulo School of Medicine, São Paulo, Brazil.

The ubiquity and strength of biological effects of redox processes indicate that redox-centered therapeutic interventions can potentially be quite effective in several diseases. However, recent evidences of increasing chemical/biological complexity of redox processes poses significant challenges for design of antioxidant interventions. The simple model of ROS as accidental exogenous toxicants has evolved to a much more complex picture in which ROS can generally exert a varied signaling role in pathophysiological cellular events. Also, redox signaling can occur in the absence of overall changes in redox status of major intracellular reductants glutathione or thioredoxin, forcing redefinition of oxidative stress as a disruption of redox signaling rather than solely pro-/anti-oxidant imbalance. This raises issues regarding redox subcellular compartmentation and questions about the structure of intermediates, e.g., of thiol oxidation. In addition, while ROS generation is mainly enzymatic, even under exogenous oxidant exposure, little is known about regulation of such sources. Therefore, even the definition of an expected antioxidant strategy must be considerably expanded. Accordingly, it is not unexpected that results of clinical trials with traditional antioxidants have yielded conflicting or negative results, with positive results still viewed as sporadic -although encouraging- exceptions. Those considerations are discussed in perspective with recently studies showing a complex regulation of NADPH oxidase, a major enzyme source of ROS. Also, we developed a model of aortic valve stenosis in the rabbit, in which the antioxidant tempol, contrarily to lipoic acid, induced an increase is vascular/valve calcification, thus exemplifying the complexity of redox interventions.