Note from the Editor-in-Chief

All books in this series illustrate point-of-care testing and critically evaluate the potential of antioxidant supplementation in various medical disorders associated with oxidative stress. Future volumes will be updated as warranted by emerging new technology, or from studies reporting clinical trials.

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Editors

Studies on Cardiovascular Disorders

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Preface

The role of reactive oxygen species (ROS) in the cardiovascular system is Janus-faced. Whereas low concentrations of ROS are involved in variety of physiological signalling events, oxidative stress resulting from deregulated overproduction of ROS and/or impaired antioxidant defences contributes to cardiovascular disease. The actions of ROS in the cardiovascular system are a fascinating topic, not only for the basic science researcher but also for the clinician who is interested in seeking new therapies for his patients suffering from cardiovascular disease. The current book provides a comprehensive overview of the molecular mechanisms and pathophysiological settings in which chronic and detrimental oxidative stress arises within the heart and vasculature. The book also considers currently discussed strategies in avoiding chronic redox stress resulting from exposure to risk factors or various cardiovascular interventions.

The series starts with an overview by Denise de Castro Fernandes, Diego Bonatto and Francisco Laurindo of redox signaling models that could underlie the development of redox-associated cardiovascular disorders. The interactions of proteins within signalling cascades with ROS and the regulation of such interactions by the anti-oxidative capacity of the cell are discussed. Rebecca Charles, Joseph Burgoyne and Philip Eaton report on redox-mediated modifications of proteins under physiological and pathophysiological conditions and the variety of post-translational oxidative modifications that explain redox sensing and signal transduction by proteins at the molecular level.

ROS are generated during embryogenesis and may be involved in the proper development of the cardiovascular system. This is underscored by the increasing evidence that ROS regulate the cardiomyogenesis and vascular differentiation processes of stem cells, which mimic essential events occurring during normal embryogenesis of the cardiovascular system. Heinrich Sauer and Maria Wartenberg outline the signalling pathways in cardiovascular development during embryogenesis and their meaning in differentiation processes of resident cardiac stem cells and embryonic stem cells derived from the inner cell mass of blastocysts.

Sensory nerves act via perivascular neuronal networks to release potent vasoactive neuropeptides that work in combination with the autonomic nervous system to regulate both physiological vascular tone and pathophysiological disease processes. Sensory nerve endings can be in contact with vascular smooth muscle
cells and also in intimate contact with endothelial cells. In the article by Rabea Graepel, Jennifer Bodkin and Susan Brain, current knowledge of the sensory nervous system in terms of its influence on the cardiovascular system and the established and putative links between the sensory nervous system and ROS generation relevant to the cardiovascular system are outlined.

A major source of ROS is the mitochondrial respiratory chain where ROS are generated in the electron transport chain complexes I and III. Mitochondria-derived ROS are known to participate in cardiac reperfusion injury but paradoxically – as outlined in the article of Ariel Cardoso, Bruno Queliconi and Alicia Kowaltowski – also contribute to cardioprotection in myocardial pre- and postconditioning. Mitochondrial ROS generation is closely coupled to coenzyme Q9/Q10, which acts as an electron carrier between the nicotinamide adenine dinucleotide (NADH) and succinate dehydrogenases and the cytochrome system. The article by Samarjit Das, Somak Das and Dipak Das presents the intriguing hypothesis that increased ROS generation in mitochondria with abundance of CoQ could represent a novel mechanism of cardioprotection through the potentiation of redox signaling, thereby preventing oxidative damage and dysfunction of mitochondria under excess ROS-generating conditions. Furthermore, ROS derived from mitochondria are involved in homocysteine (HCY)-related cardiovascular diseases. As pointed out in the study of Karni Moshal and coworkers, HCY causes activation and the mitochondrial translocation of calpain-1 (calcium-dependent cysteine protease) thereby increasing intramitochondrial oxidative stress and leading to the induction of MMP-9. In their study, the authors summarize current knowledge on hydrogen sulphide in myocardial protection as well as the role that HCY-induced oxidative stress in the mitochondria plays during the regulation of myocyte contractility.

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are another important source of ROS in the cardiovascular system that have been shown to be involved in many human diseases, such as metabolic syndrome, hypertension, diabetes, left ventricular hypertrophy, heart failure, renal disease, atherosclerosis, and cerebrovascular disease. Tomasz Guzik reviews the important vascular roles of these complex enzymes in human circulation. Guillermo Zalba and Javier Diez summarize the experimental evidence supporting a pathophysiological role for polymorphisms in the p22phox gene (the CYBA gene), some of which are able to influence NADPH oxidase gene expression and activity in the context of cardiovascular diseases. The theme of genetic variation is also the subject of the article by Christian Delles and Anna Dominiczak, who report on strategies to unravel the genetics of redox-related cardiovascular diseases and describe the interactions of redox-regulated genes and the environment. Timo Kahles, Sabine Heumüller and Ralf Brandes focus their article on the role of NADPH oxidase in blood-brain barrier dysfunction, which occurs during ischemic stroke as well as during ischemia/reperfusion.

The likelihood of adverse cardiovascular events has been associated with risk factors related to a “typical western lifestyle” such as physical inactivity, obesity and smoking, which all appear to be associated with oxidative stress. The link between smoking and increased oxidative stress is reviewed by David Bernhard.
Elevated levels of ROS have also been linked with increasing age and vascular aging (reviewed by Anna Csiszar and Zoltan Ungvari), heart failure, diabetes mellitus (reviewed by Divya Gupta, Kathy Griendling and Robert Taylor), coronary artery disease, hypertension (reviewed by Rhian Touyz, Andrea Chignalia, and Mona Sedeek), as well as with relatively rare cardiac diseases such as peripartum cardiomyopathy, which has been associated with increased oxidative stress during pregnancy (reviewed by Denise Hilfiker-Kleiner, Arash Haghiokia and Andres Hilfiker). However, oxidative stress not only arises in the sequence of cardiovascular diseases but also in response to cardiovascular interventions such as coronary angiography (reviewed by Raymond Farah) or during cardiac transplantation (reviewed by Galen Pieper and Ashwani Khanna). Interestingly, conditions of chronically elevated ROS within the heart are associated with atrial fibrillation, which among other problems may cause stroke and peripheral embolization (reviewed by Ali Sovari and Samuel Dudley).

Acute myocardial infarction due to atherosclerotic coronary artery disease often results in remodeling responses of the myocardium that may culminate in congestive heart failure. Yao Sun describes the current knowledge on oxidative stress arising during cardiac infarction and its role in influencing the severity of cellular apoptosis, the inflammation process and development of hypertrophy. Min Zhang, Alex Sirker and Ajay Shah report on the process of cardiac remodelling with an emphasis on cardiomyocyte hypertrophy, apoptosis, interstitial fibrosis, contractile dysfunction and chamber dilatation through specific modulation of redox-sensitive signalling pathways that alter gene and protein expression and function. A deepened insight into cardiovascular fibrosis is provided by the article by Subramaniam Pennathur, Louise Hecker and Victor Thanickal, who describe the role of NADPH oxidases in the initiation of fibrotic processes and outline therapeutic strategies to inhibit oxidative stress in cardiovascular fibrosis.

Cardiovascular disease is not uniformly distributed between the sexes. Risk factors specific to women include parity, oophorectomy, pre-eclampsia and menopause. In the article by Manuela Gago-Dominguez, Xuejuan Jiang, and Jose Esteban Castelao, the oxidation hypothesis of reproductive factor-cardiovascular disease association is developed, which is based on the observation that pregnant, oophorectomized, and postmenopausal women exhibit higher levels of lipid peroxidation than nonpregnant, nonoophorectomized and premenopausal women, respectively. The authors propose that the increased levels of lipid peroxidation during these states are responsible, at least in part, for the increased risk of cardiovascular disease in women.

The well-established connection between cardiovascular disease and oxidative stress has led to the investigation of various antioxidative strategies for patient treatment. The most natural way to cope with cardiovascular disease is perhaps by prevention. Alfonso Giovanni, and Claudio Napoli report on the French paradox of cardiovascular disease and consider the potential beneficial effects of the Mediterranean diet, which could be related to antioxidants contained in red wine or vegetable, fruit and olive oil. During recent years, novel synthetic antioxidants such as hybrid compounds designed to improve the efficacy of natural
antioxidants have been developed. *Gloria López* and *Homero Rubbo* describe novel hybrid antioxidants (tocopherol analogs-nitric oxide donors) that share nitric oxide-releasing properties and LDL incorporation capacity, demonstrating the importance of this site-specific release of nitric oxide in the cascade of events involved in the inhibition of LDL oxidation. This may offer novel approaches for the prevention of atherosclerosis and related disorders that involve reactive oxygen and nitrogen species, although this remains to be demonstrated in clinical trials. Alternative approaches could utilize the antioxidative capacity of the cell, e.g. thioredoxin (TRX), which catalyzes the conversion of disulfide oxidized proteins to their thiol-reduced forms, and has been shown to exert protective effects when intravenously administered in laboratory animals (reviewed by *Bradford Berk*). A further substance produced naturally in the body is the pineal gland hormone melatonin, which besides regulating circadian rhythms is a strong antioxidant and – as elaborated on by *Amanda Lochner* – ameliorates tissue damage in ischaemia/reperfusion in a number of organs. A wealth of recent studies demonstrate that the physiological stimulus of endurance exercise is overwhelmingly cardioprotective. In their article, *Karyn Hamilton* and *John Quindry* focus their discussion on the role of endogenous antioxidants in mediating protection and secondarily on the protective mechanisms peripheral to redox control. The overall benefits observed with the lipid-lowering HMG CoA reductase inhibitors (statins) appear to be greater than might be expected from changes in lipid levels alone. *Oliver Adam* and *Ulrich Laufs* review the current knowledge on the action of statins regarding endothelial NO synthase (eNOS), endothelin, free oxygen radicals, MHC-II, the protein kinase Akt and metalloproteinases.

The present series of articles on oxidative stress in clinical practice summarizes the current knowledge in a rapidly evolving field. Its intention is both to provide a mechanistic overview of the ways in which oxidative stress impacts cardiovascular disease and to consider potential therapeutic options to target such pathways. Although large clinical trials of “simple” antioxidant approaches, such as vitamin C and E, have not demonstrated significant benefit for cardiovascular end points, the data discussed in this book should make quite clear that such an approach is too simplistic. Understanding the complexity of the cellular redox system may in the future allow the development of better-targeted interventions to facilitate the path of patients from disease back to health.
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