Advances in Biochemistry in Health and Disease

Devendra K. Agrawal
Ranko Škrbić
Miloš P. Stojiljković
Dragan M. Djuric *Editors*

Cardiovascular Toxicity

Incidence, Pathogenesis and Treatment Strategies

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Editors

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Preface

The physiological function of cardiovascular system in the body is the most critical pillar of human well-being. The heart and blood vessels play a major role in thermoregulation, transporting nutrients, gases, and waste products to body organs, maintain fluid balance within the body, and protect the body from infection and blood loss. Indeed, the cardiovascular diseases are the leading cause of morbidity and mortality. Pharmaceuticals, illicit drugs, toxins, poisons, and several environmental factors can induce toxic and adverse effects on the heart and blood vessels, leading to structural changes that impair the blood flow and circulation. Thus, the cardiovascular toxicity due to these factors is the culprit of the global surge in the rate and incidence of cardiovascular diseases and can significantly contribute to the overall burden of cardiovascular diseases. Co-morbidities, such as diabetes and obesity, epigenetic factors, and viral, bacterial, and parasite infections further enhance the cardiovascular toxicity. Thus, it is critical to recognize and understand the factors involved in the pathogenesis of cardiovascular toxicities and develop better therapeutic approaches.

The advent of new drugs and vaccines has been a boon in the treatment of various diseases. However, many drugs and vaccines can induce adverse effects, either directly or indirectly, by affecting the endothelium, coagulation factors, and platelet activation and thus inducing prothrombotic response, inducing oxidative stress and inflammation, interfering with the baroreceptors that regulate blood pressure and cardiovascular variability, altering the regulation of autonomic cardiovascular control, and disrupting electrophysiology and contractility. Unfortunately, this has been ignored for a long time and only lately realized with the attention and initiatives to expand and disseminate knowledge to general population and health practitioners, expand research activities to investigate the underlying cellular and molecular mechanisms, and develop better preventive and treatment strategies.

Cardiovascular adverse effects can be induced by many drug classes used in cancer treatment, such as kinase and proteasome inhibitors, as well as bacterial and viral infections, disorders of central nervous system and gastrointestinal system, and other inflammatory diseases. It is critical to understand the underlying mechanisms

of the cardiovascular toxicity and how to prevent it. What are the effects of different genetics, epigenetics, and chemical, physical, and biological influences in cardiovascular toxicity?

In this very timely topic, a comprehensive and up-to-date information in a critical manner is presented on relevant topics related to incidence, pathogenesis, and treatment strategies of cardiovascular toxicity. The major complications due to chemotherapeutic agents and drugs used in the treatment of allergy, diabetes, inflammatory bowel disease, psychiatric problems, viral infections, and others may encompass a large spectrum of disorders, including the trigger or the development of arrhythmia/QTc Prolongation, atrial flutter, atrial and ventricular fibrillation, atrioventricular block, heart failure, hypertension, myocardial infarction, myocarditis, toxic myocardial injury, pericardial disease, peripheral and cerebrovascular ischemia, sinus tachycardia, thromboembolic events leading to limb ischemia, transient ischemic attack, stroke, valvular heart disease, vasculitis, and venous injury. Distinguished scientists, physicians, and surgeons from all over the world with expertise in the fields of cardiovascular diseases, cancer, and other diseases contributed their knowledge and expertise. The biological system in health and disease is complex and dynamic. It is therefore critical to better understand the biological complexity, interactions between genetic–epigenetic–environmental factors, interconnecting genes, interplay of proteins in the cellular and molecular responses in the underlying pathophysiologic mechanisms, and biologic pathways in cardiovascular toxicity. This information is clinically relevant in the mitigation and management of cardiovascular complications for prediction, prevention, and treatment. The identified gaps in our knowledge provide future directions for further investigation.

This book presents a total of 40 chapters that are divided into sub-sections titled "Disease- and Drug-Induced Cardiovascular Toxicity: Incidence and Underlying Pathophysiological Mechanisms," "Toxins and Poison-induced Cardiovascular Toxicity," "Genetics, Epigenetics, Environmental Pollution and Nutritional Effects in the Pathogenesis of Cardiovascular Toxicity," and "Prevention, Management and Treatment of Cardiovascular Toxicity."

The presented information will be a key resource for knowledge and guidance to researchers in the fields of cardiovascular, cancer, and other diseases, as well as healthcare professionals, including physicians, physician-assistants, nurses, nurse practitioners, pharmacists, and academics interested in public health. This compilation will be ideal as a textbook in various undergraduate, graduate, and postgraduate courses in the public health program, cardiovascular diseases, chemotherapeutic agents and cardiovascular toxicity, cardiovascular toxicity in infectious disease, the pathogenesis of drug-induced cardiovascular toxicity, seminars on cardiovascular toxicity, and epigenetics and genetics in the effect of drugs on cardiovascular toxicity.

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Editors and Contributors

About the Editors

Devendra K. Agrawal holds multiple degrees, including MSc, PhD (Biochemistry), PhD (Medical Sciences), MBA, and MS (Information Technology and Management). He has served on several academic positions, including Clinical Biochemist, Professor, Founding Chairman of the Department of Clinical and Translational Science, Senior Associate Dean of Clinical and Translational Sciences, and Senior Vice President for Research and Biotechnology. Currently, Dr. Agrawal serves as Professor and Director, Department of Translational Research, Western University of Health Sciences, Pomona, CA, USA.

Dr. Agrawal is a member of the *Alpha Omega Alpha Honor Medical Society* and a Fellow of the AAAAI, AHA, APS, and IACS. He has been recognized with many awards, including the highest teaching award at Creighton University, Distinguished Research Career Award, Distinguished Professor Award, Distinguished Faculty Service Award, University Research Award, Distinguished Mentor Award, *Professor Bohuslav Ostadal Award* for Excellence in Cardiovascular Sciences, *Distinguished Leadership Award*, *Ricardo Gelpi Award, Andras Varro Award, Harpal Buttar Award for Excellence in Cardiovascular Sciences*, and *Cardiovascular Sciences Innovative Research Award.* Dr. Agrawal has been an invited speaker at many prestigious national and international scientific meetings. Dr. Agrawal is serving on the position of Secretary

General and Treasurer of the International Academy of Cardiovascular Sciences—North American section and the Director and Treasurer of the Academy of Cardiovascular Sciences Foundation USA, Inc.

Dr. Agrawal has served on many grant review panels, including the VA Merit Review, DoD, NIH-NIAID, NIH-NHLBI, MRC-UK, and US-Israel BSF Grant Review Committees, as well as the Science Foundation Ireland, Austrian Science Fund, British Lung Foundation, Swiss NSF, ViCi Netherlands, and the Asthma Research Foundation of Western Australia. Dr. Agrawal has served or is currently serving as an associate editor and on the editorial board of several prestigious journals. Dr. Agrawal contributed to science by publishing over 620 original research articles in peer-reviewed journals and book chapters. He has co-edited books on various topics, including allergy, asthma, and immunology, COVID-19 and stem cells, environmental factors in the pathogenesis of cardiovascular diseases, and flow cytometry. His major research areas include the cellular, molecular, and immunobiology of coronary and carotid artery disease, stem cell therapy, shoulder rotator cuff injuries, traumatic brain injury, diabetes and diabetic foot ulcers, renal diseases, and allergy and bronchial asthma. NIH funds his research educational programs and projects.

Dr. Agrawal has trained over 250 medical students, many of whom are now academic physician-scientists, and directly supervised and guided 73 graduate students to earn MD-PhD, MD-MS, MS, and PhD degrees, 74 postdoctoral fellows, and 15 assistant professors, many of whom are currently on high positions in academia and industries. Many clinical residents, fellows, and research investigators have received training under his direct supervision. He is passionate to train and mentor next generation of clinical and translational researchers.

Ranko Škrbić graduated in 1986 and received the MD degree from the Faculty of Medicine, University of Banja Luka, Bosnia and Herzegovina (ex-Yugoslavia), and MSc degree in 1991 from the Faculty of Natural Sciences, Zagreb University, Croatia. As a Japanese Government Research fellow, he spent 1 year at Shinshu University School of Medicine studying cardiovascular pharmacology. In 1994, he received his PhD degree from the Faculty of Medicine, Belgrade University, Serbia, and in the year 2000 the Clinical Pharmacology Specialist degree from the Faculty of Medicine, Novi Sad University, Serbia. He has also attended several short-term courses and trainings, including drug information training at Bristol Royal Infirmary, Bristol, UK in 1999; short-term course in pharmacoeconomics at the London School of Economics (LSE), London, UK; and a training in health management, the World Bank's Basic Health Project for Bosnia and Herzegovina, organized in collaboration with Imperial College London, UK, and Heidelberg University, Germany.

Dr. Škrbić is a Full Professor of Pharmacology, Toxicology, and Clinical Pharmacology since 2009. Notably, his professional career includes the following positions: Head of the Department of Pharmacology, Faculty of Medicine, University of Banja Luka (2002–2009); Head of the National Drug Information Centre, established in collaboration with WHO and EU-ECHO (1998–2006); Chairman of the Drug Registration Committee of the Republic of Srpska, Bosnia and Herzegovina (1999–2002); EU PHARE Regional Coordinator for Pharmaceutical Sector Development in Bosnia and Herzegovina (1998–1999); UNICEF Regional Coordinator for Essential Drugs and Rational Drug Use in the Republic of Srpska, Bosnia and Herzegovina (1999–2000); EU-CARDS Regional Coordinator for Health Care Reform in Bosnia and Herzegovina (2000–2002); Short-term consultant for the Development of Accreditation Standards and Clinical Guidelines, EPSILON Research, Development and Consulting, doo, Banja Luka (Basic Health Project of the World Bank; Accreditation and Quality Assurance) (2001–2003); Minister of Health and Social Welfare, Government of the Republic of Srpska, Bosnia and Herzegovina (2005–2013); Ambassador of Bosnia and

Herzegovina in Serbia (2013–2015); and Dean of the Faculty of Medicine, University of Banja Luka (2016–now).

Dr. Škrbić was the Founder and Chair of the PhD Program in Biomedical Sciences at the Faculty of Medicine, University of Banja Luka (2015); Visiting Professor, Faculty of Medicine, Belgrade University, Serbia (since 2019); and Visiting Professor at the First Moscow State Medical University, Moscow, Russia (2024). Dr. Škrbić has organized and chaired several international conferences, including *The 6th Xenobiotic Metabolism and Toxicity Workshop of Balkan Countries*, Banja Luka, Bosnia and Herzegovina, June 16–20, 2004; *The Third Health Ministers' Forum*: *Health in All Policies in South-eastern Europe—A Shared Goal and Responsibility*, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina, October 13–14, 2011; *The International Conference on Medical and Biological Engineering 2019* (*CMBEBIH 2019*), Banja Luka, the Republic of Srpska, Bosnia and Herzegovina May 16–19, 2019*;* and *The 7th Meeting of the European Section and 8th Meeting of North American Section of the International Academy of Cardiovascular Sciences* (*IACS*), Banja Luka, the Republic of Srpska, Bosnia and Herzegovina, September 20–23, 2021

Dr. Škrbić is a member of several professional societies, including the Serbian Pharmacological Society, the Section for toxicology of the Serbian Medical Association, and the Association of Clinical Pharmacological Societies with Sections of Clinical Pharmacists and Pharmacoinformatics of Bosnia and Herzegovina. He is also an Honorary Member of the Cardiology Society of Serbia. Additionally, he serves as the President of the Association for Atherosclerosis and Cardiovascular Research, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina. He is a Fellow of the International Academy of Cardiovascular Sciences (FIACS) and a Member of the Executive Council of the International Academy of Cardiovascular Sciences, European Section (IACS-ES). He is also a member of the Academy of Science and Arts of the Republic of Srpska. He has served as the associate editor or the member of editorial board of the several prestigious international journals.

Dr. Škrbić is the founder and head of the Centre for Biomedical Research, established in 2018 within the Faculty of Medicine, Banja Luka University. His research has been recognized mostly in the areas of cardiovascular pharmacology, pharmacoepidemiology, inflammation, ischemia-reperfusion injury, cardioprotection, and pharmacogenetics. Over the past 10 years, Dr. Škrbić's Centre has made significant contributions to the field by studying various well-established experimental methods and translating them into clinical practice. He has published more than 120 publications in peer-reviewed international journals, authored 4 chapters in international textbooks/monographs, and edited/co-edited 15 monographs/books.

Dr. Škrbić is a recipient of several awards and honors, including a Fellowship of the International Academy of Cardiovascular Sciences (IACS), the IACS Lifetime Achievement Award in Cardiovascular Science, Medicine and Surgery (2021), the Gold Medal for outstanding leadership in cardiovascular sciences (2022), a special award from the Ministry of Foreign Affairs of Japan (2021), and the Ricardo Gelpi Award for Excellence in Cardiovascular Sciences (2024).

Miloš P. Stojiljković, MD, PhD, FIACS holds MSc and PhD degrees. He is an experienced biomedical researcher who discharged numerous research, teaching, and managerial duties, including clinical pharmacologist, assistant professor, associate professor, and full professor of pharmacology, toxicology, and clinical pharmacology, as well as Vice-Dean for Scientific Research. Currently, Dr. Stojiljković is the Professor and Director, PhD Programme, Faculty of Medicine, University of Banja Luka.

Dr. Stojiljković was a Postdoctoral Fellow at the Medical University of South Carolina. He is a Fellow of the International Academy of Cardiovascular Sciences (IACS) and member of several distinguished scientific societies, such a German Society for Experimental and Clinical Pharmacology and Toxicology, British Pharmacological Society. He has been recognized with many awards, including several publication rewards from the Faculty of Medicine,

University of Banja Luka and *Distinguished Leadership Award* and *Vincenzo Panagia Distinguished Lecture Award* from the IACS. Dr. Stojiljković has been an invited speaker at many prestigious national and international scientific meetings. Dr. Stojiljković is currently a member of the Council of the IACS-European section.

Dr. Stojiljković has been serving as Editor-in-Chief of the biomedical journal *Scripta Medica* and as Associate Editor of the renowned international journals *Drug and Chemical Toxicology* and *Molecular and Cellular Biochemistry*. Dr. Stojiljković contributed to science by publishing over 200 original research articles in peer-reviewed journals and book chapters. His major research areas include the toxicology of carbamate and organophosphate acetylcholinesterase inhibitors, the influence of lipids on blood pressure, and the use of various chemical substances in cardioprotection.

Dr. Stojiljković has been an experienced teacher for 37 years and is dedicated to training and mentoring younger researchers.

Dragan M. Djuric earned his MD degree in 1987, an MS degree in 1991, a PhD degree in 1993, and a Clinical Physiologist degree in 2007, all from the Faculty of Medicine, University of Belgrade (Belgrade, Serbia). He finished his postdoctoral training in Germany at the Max Planck Institute for Physiological and Clinical Research and Kerckhoff Klinik GmbH, Bad Nauheim (1998 and 2001–2002) and in the USA at the Department of Physiology, College of Medicine, University of South Alabama, Mobile (2000). After serving in several academic positions, including Director and Chair, Institute of Medical Physiology, Faculty of Medicine, University of Belgrade (2006–2012), Founder and Chair, PhD Program in Physiological Sciences (2009–2024), leadership positions in Serbian Physiological Society (2003–2021), the FEPS Task Force Group on Education in Physiology (2007–2008), and national atherosclerosis societies (since 1998), he is currently a Professor of Medical Physiology, Faculty of Medicine, University of Belgrade (Belgrade, Serbia), and a Visiting Professor, Faculty of Medicine, University of Banja Luka (Bosnia and Herzegovina) (since 2019). Dr. Djuric is a Fellow of IACS and IUPS Academy of Physiology. He has been recognized with many awards, including

the Naranjan Dhalla Award for Innovative Investigators in Cardiovascular Sciences (2024), the Oration Award from Prof. Harpal Buttar (2024), the Howard Morgan Award for Distinguished Achievements in Cardiovascular Research (2022), the James Willerson Award for Excellence in Cardiovascular Sciences (2021), the Distinguished Leadership Award in Cardiovascular Sciences (2019), the Andras Varro Award for Excellence in Cardiovascular Sciences (2018), and the Lifetime Achievement Award in Cardiovascular Science, Medicine and Surgery (2015), all from the International Academy of Cardiovascular Sciences (IACS), including European, North American, and Indian sections. Additionally, he has been honored with the Serbian Physiological Society Award for Lifetime Achievement in Physiological Sciences (2016); the Samuel Racz Medal and Honorary Membership for his contributions to physiology from the Hungarian Physiological Society (2010); Honorary Membership, Bulgarian Society for Cell Biology (2009); Honorary Membership, Romanian Society for Laboratory Medicine (2008); the Medal of the Yugoslav Society of Cardiology (2002); and the Belgrade City October Award (1987). Dr. Djuric has served on the editorial boards of several prestigious journals and in a few grants review panels. He was a reviewer in many journals, books, and meeting abstracts. Dr. Djuric contributed to science by publishing over 300 original research, review and editorial articles in peer-reviewed journals and book chapters. He has edited/co-edited 6 books on medical physiology, 7 monographs on endothelium, vascular biology, atherosclerosis, and nutrition, including Springer Nature book entitled *Environmental Factors in the Pathogenesis of Cardiovascular Diseases* (2024), 15 abstracts from scientific meetings which he organized/co-organized, and served as guest editor for 13 special or topic issues of prestigious international journals. He has been an invited speaker at many prestigious national and international scientific meetings and academic institutions. Dr. Djuric has trained over 30 medical students in research work and has directly supervised and guided 20 graduate students in earning their MD-MS and MD-PhD degrees. The National Ministry of Education, Science and Technological Development and EU COST funded his research projects. His major research areas

include cardiovascular research, cardioprotection, experimental cardiometabolic models, endothelial dysfunction, experimental vascular models, gasotransmitters and oxidative stress, homocysteine and related vitamins, nutraceuticals, micronutrients and cardiovascular health, risk factors and cardiovascular health, vascular reactivity, mediators of inflammation, atherosclerosis, and environmental factors in the pathogenesis of cardiovascular diseases.

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