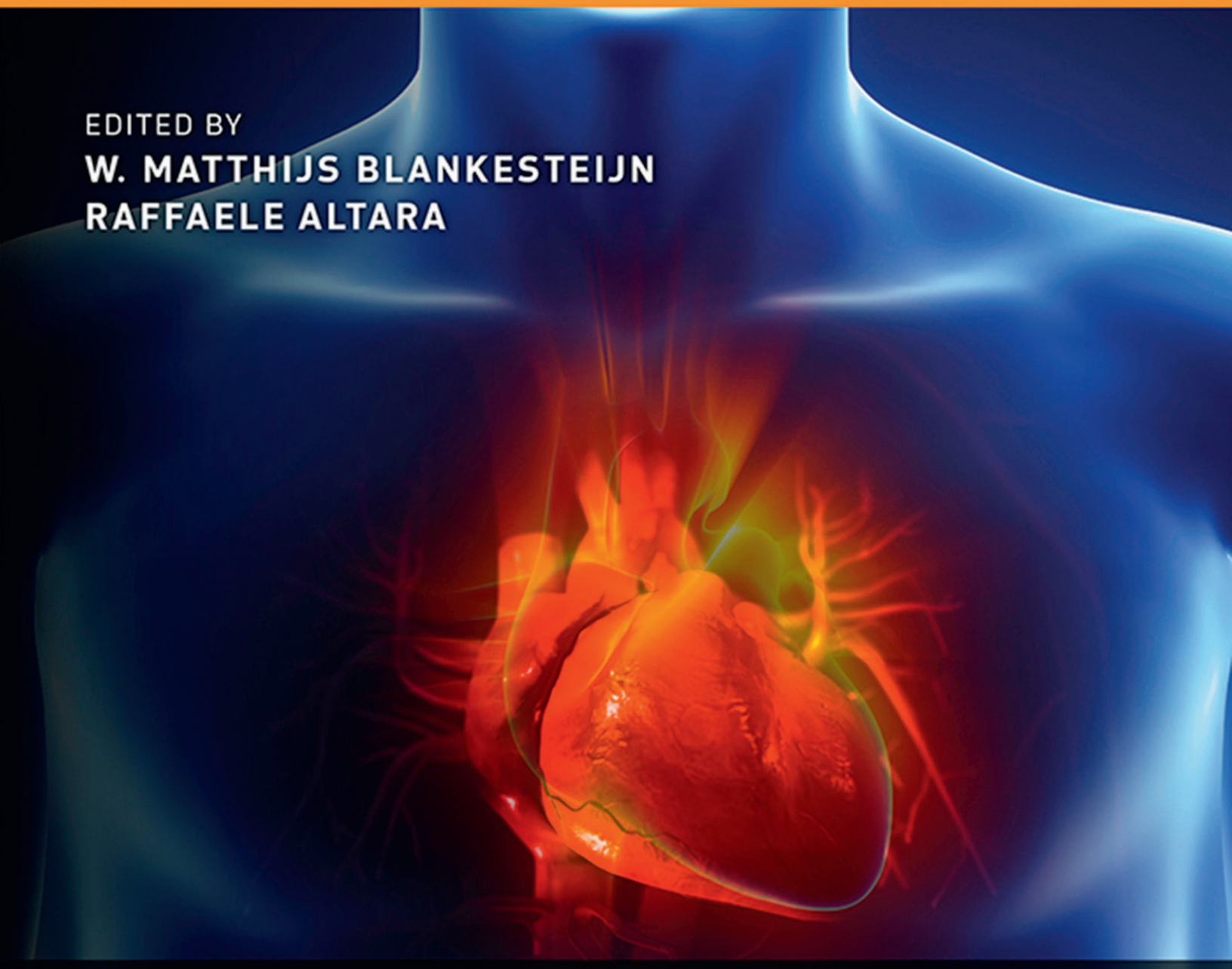

EDITED BY

W. MATTHIJS BLANKESTEIJN

RAFFAELE ALTARA

INFLAMMATION IN HEART FAILURE

INFLAMMATION IN HEART FAILURE

This page intentionally left blank

INFLAMMATION IN HEART FAILURE

Edited by

W. MATTHIJS BLANKESTEIJN
Department of Pharmacology,
Cardiovascular Research Institute Maastricht,
Maastricht University,
The Netherlands

AND

RAFFAELE ALTARA
Department of Physiology and Biophysics,
University of Mississippi Medical Center,
Jackson, MS, USA

Department of Pharmacology,
Cardiovascular Research Institute Maastricht,
Maastricht University,
The Netherlands

ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
225 Wyman Street, Waltham, MA 02451, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-800039-7

Printed and bound in the United States
14 15 16 17 10 9 8 7 6 5 4 3 2 1

Contents

3 TARGETING OF THE INFLAMMATORY RESPONSE

Contributors

Raffaele Altara Department of Pharmacology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands, and Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Jonathan Beaudoin Massachusetts General Hospital, Boston, Massachusetts, USA

W. Matthijs Blankesteijn Department of Pharmacology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Hans-Peter Brunner-La Rocca Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands

Emmanuel Buys Massachusetts General Hospital, Boston, Massachusetts, USA

Federico Carbone Division of Cardiology, Department of Medical Specialties, Foundation for Medical Researches, University of Geneva, Geneva, Switzerland; Department of Internal Medicine, University of Genoa School of Medicine, and IRCCS Azienda Ospedaliera Universitaria San Martino–IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy

Arrigo F.G. Cicero Medical and Surgical Sciences Department, University of Bologna, Bologna, Italy

Evangelos P. Daskalopoulos Department of Pharmacology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Lisandra E. de Castro Brás San Antonio Cardiovascular Proteomics Center, and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Kristine Y. Deleon-Pennell San Antonio Cardiovascular Proteomics Center, and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Uli L.M. Eisel Department of Molecular Neurobiology, University of Groningen, and Department of Psychiatry, University Medical Centre Groningen, Groningen, The Netherlands

Elda Favari Pharmaceutical Sciences Department, University of Parma, Parma, Italy

Nikolaos G. Frangogiannis Department of Medicine (Cardiology), The Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, Bronx, New York, USA

Stefan Frantz Department of Internal Medicine I, University Hospital Würzburg, Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany

Olga Frunza Departm ent of Medicine (Cardiology), The Wilf Family Cardiovascular Research Institute, Albert Einstein College of Medicine, Bronx, New York, USA

Michael E. Hall San Antonio Cardiovascular Proteomics Center; Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, and Cardiology Division, University of Mississippi Medical Center, Jackson, MS, USA

Kevin C.M. Hermans Department of Pharmacology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Stephane Heymans Center for Heart Failure Research, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands

Rugmani Padmanabhan Iyer San Antonio Cardiovascular Proteomics Center, and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Dennis H.M. Kusters Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

Richard A. Lange San Antonio Cardiovascular Proteomics Center, Jackson, MS, and Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

Merry L. Lindsey San Antonio Cardiovascular Proteomics Center; Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, and Research Services, G.V. (Sonny) Montgomery Veterans Affairs Medical Center, Jackson, MS, USA

Yonggang Ma San Antonio Cardiovascular Proteomics Center, and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Douglas L. Mann Cardiovascular Division, Department of Medicine, Center for Cardiovascular Research, Washington University School of Medicine, St. Louis, MO, USA

Fabrizio Montecucco Department of Internal Medicine, University of Genoa School of Medicine; IRCCS Azienda Ospedaliera Universitaria San Martino–IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy, and Division of Laboratory Medicine, Department of Genetics and Laboratory Medicine, Geneva University Hospitals, Geneva, Switzerland

Anna Planavila Departament de Bioquímica i Biologia Molecular, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona and CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Barcelona, Spain

Chris P.M. Reutelingsperger Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

Nicoletta Ronda Pharmaceutical Sciences Department, University of Parma, Parma, Italy

Marielle Scherrer-Crosbie Massachusetts General Hospital, Boston, Massachusetts, USA

Regien G. Schoemaker Department of Cardiology, University Medical Centre Groningen, and Department of Molecular Neurobiology, University of Groningen, Groningen, The Netherlands

Blanche Schroen Center for Heart Failure Research, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands

Leon J. Schurgers Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

Jan Tegtmeier Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

Robrecht Thoonen Massachusetts General Hospital, Boston, Massachusetts, USA

Hiroe Toba San Antonio Cardiovascular Proteomics Center, Jackson; Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA, and Department of Clinical Pharmacology, Division of Pathological Sciences, Kyoto Pharmaceutical University, Kyoto, Japan

Marc van Bilsen Department of Physiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

Lieke van Delft Department of Pharmacology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

Vanessa van Empel Department of Cardiology, Maastricht University Medical Centre, Maastricht, The Netherlands

Sara Vandenwijngaert Massachusetts General Hospital, Boston, Massachusetts, USA

Johannes Weirather Department of Internal Medicine I, University Hospital Würzburg, Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany

Andriy Yabluchanskiy San Antonio Cardiovascular Proteomics Center, Jackson, and Mississippi Center for Heart Research, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

Francesca Zimetti Pharmaceutical Sciences Department, University of Parma, Parma, Italy

Preface

Heart failure is a progressive condition that affects an increasing number of patient worldwide and severely impairs their physical capabilities and quality of life. Despite large scientific efforts, the molecular mechanisms that lead to heart failure are still far from elucidated. Therefore, diagnosis of this condition is difficult unless the patient has reached a progressed state, accompanied with clinical symptoms. A better understanding of the molecular mechanisms contributing to the earlier phases of heart failure development would therefore help to improve the diagnosis and therapy. The drugs that are currently used can slow down heart failure progression but cannot cure the patient; moreover, the effectiveness of these interventions may very much depend on the subtype of heart failure, as many patients suffering from heart failure with preserved ejection fraction show little benefit from therapies with proven efficacy in heart failure with reduced ejection fraction.

An example of a molecular mechanism that is involved in the development and progression of heart failure is inflammation. It was originally observed in the wound-healing response that takes place in the area of injury after myocardial infarction. There, the inflammatory response is crucial for the removal of the necrotic debris from the area of injury and helps to attract the cells involved in the formation of a scar. In the meantime, inflammation has been described in cardiac remodeling due to other causes, for example, hypertension, and is already activated early on in its development. This highlights the importance of inflammation as a common molecular pathway of heart failure, providing potentially interesting options for diagnosis and therapy. However, the clinical results of interventions in inflammatory pathways have been disappointing so far, underscoring the complexity of the inflammatory response and the need for a better understanding of its molecular mechanisms. Therapeutic targeting of inflammation will therefore likely require careful patient selection and precise timing of the intervention to become successful.

The purpose of this book is to provide the latest information on the role of inflammation in heart failure to researchers and advanced students in the cardiovascular diseases. To this end, we have invited experts in the field to provide a comprehensive and timely overview of their research areas. The book is structured into three sections, providing the reader with easy access to the information. In Section 1, which focuses on the *pathophysiology of the inflammatory response in heart failure*, an overview is provided of the extensive literature on the role of inflammation in heart failure, with a distinction between ischemia-induced heart failure and heart failure due to other causes. Specific emphasis is put on the role of the innate immune system and the interaction between the extracellular matrix and the inflammatory mediators. The cross talk between the inflammatory response in the heart and the brain is highlighted and the section is finalized with an overview of different animal models of heart failure and their advantages and restrictions for the study of this condition.

In Section 2, the focus is on *inflammatory biomarkers*. The section starts with an overview of multiple inflammatory mediators as biomarkers for adverse remodeling and heart failure. Next, the pros and cons of different analytical techniques for measuring panels of inflammatory biomarkers in a single sample are discussed. In the last chapter of this section, an overview of imaging modalities to visualize the inflammatory response is provided.

Targeting of the inflammatory response is the subject of the third section of this book. Here, we focus on the experimental and clinical evidence for the beneficial effects of interventions on mineralocorticoid receptor and peroxisome proliferator-activated receptors. The modulating effects of statins and the involvement of miRNAs in the control of the inflammatory response and their therapeutic potential are discussed. Finally, the results of clinical trials with anti-inflammatory agents are presented and interpreted in light of our current understanding of the inflammatory response in heart failure.

W. Matthijs Blankesteijn
Raffaele Altara

This page intentionally left blank

SECTION 1

PATHOPHYSIOLOGY OF THE INFLAMMATORY RESPONSE IN HEART FAILURE

This page intentionally left blank