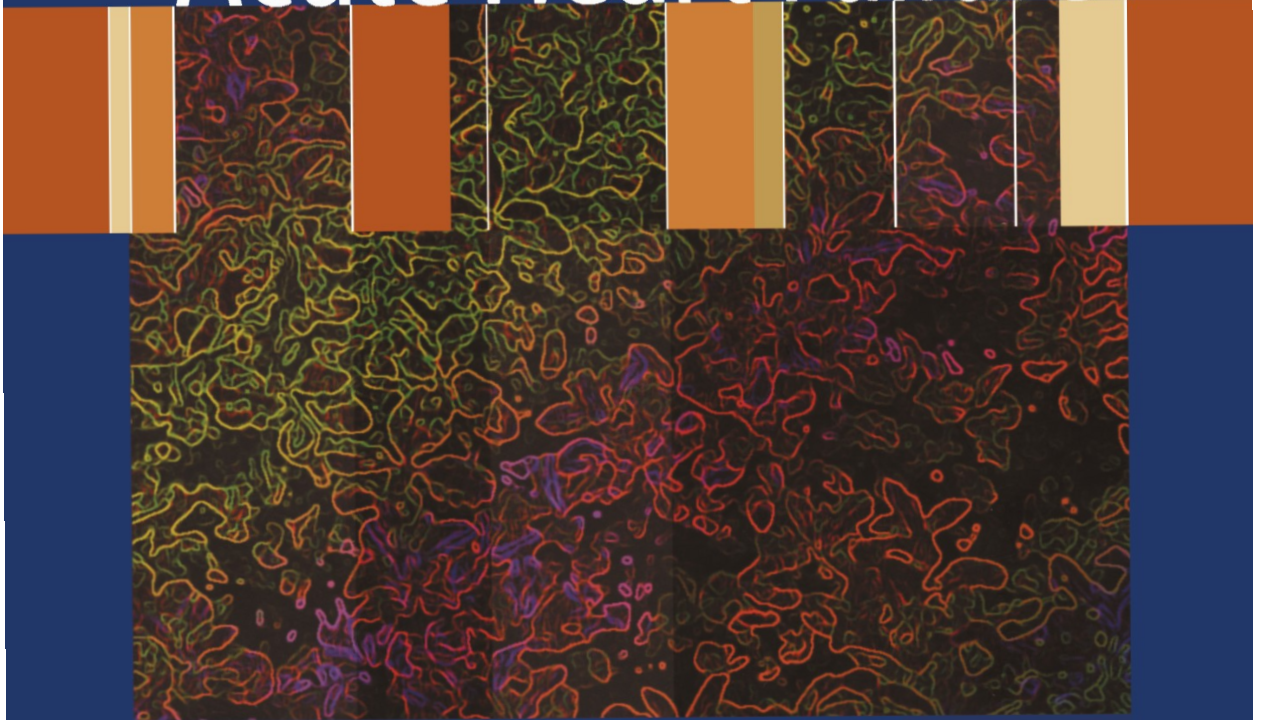


Alexandre Mebazaa
Mihai Gheorghiadu
Faiez M. Zannad
Joseph E. Parrillo *Editors*

Acute Heart Failure



 Springer

Ascendis EX1022
U.S. Patent No. 12,233,106

Acute Heart Failure

Alexandre Mebazaa, Mihai Gheorghiade,
Faiez M. Zannad, and Joseph E. Parrillo (Eds.)

Acute Heart Failure

Alexandre Mebazaa, MD, PhD
Professor of Medicine
Université Paris Diderot
Department of Anesthesiology and
Critical Care Medicine
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Paris, France

Mihai Gheorghiade, MD, FACC
Professor of Medicine and Surgery
Associate Chief, Division of
Cardiology
Chief, Cardiology Clinical Service
Northwestern University
Feinberg School of Medicine
Chicago, IL, USA

Faiez M. Zannad, MD, PhD, FESC
Professor of Medicine
University Henri Poincaré
Department of Cardiology
Centre d'Investigation Clinique (CIC)
INSERM U-684
Centre Hospitalier Universitaire
Nancy, France

Joseph E. Parrillo, MD
Professor of Medicine
Robert Wood Johnson Medical
School
University of Medicine and
Dentistry of New Jersey
Chief, Department of Medicine
Edward D. Viner MD Chair,
Department of Medicine
Director, Cooper Heart Institute
Cooper University Hospital
Camden, NJ, USA

Project Coordinator

Wendy A. Gattis Stough, PharmD
Department of Clinical Research
Campbell University School of
Pharmacy
Cary, NC, USA

British Library Cataloguing in Publication Data
Acute heart failure

1. Heart failure – Treatment 2. Heart failure

I. Mebazaa, Alexandre

616.1'2906

ISBN-13: 9781846287817

Library of Congress Control Number: 2007929111

ISBN: 978-1-84628-781-7 e-ISBN: 978-1-84628-782-4

© Springer-Verlag London Limited 2008

Apart from any fair dealing for the purposes of research or private study, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission in writing of the publishers, or in the case of reprographic reproduction in accordance with the terms of licences issued by the Copyright Licensing Agency. Enquiries concerning reproduction outside those terms should be sent to the publishers.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore free for general use.

Product liability: The publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check its accuracy by consulting other pharmaceutical literature.

9 8 7 6 5 4 3 2 1

Springer Science+Business Media
springer.com

Foreword

Acute heart failure is a leading cause of morbidity and mortality worldwide, and its incidence is increasing as the population ages. This represents a huge clinical and economic burden for all health care systems. With its high prevalence and associated morbidity and mortality, acute heart failure requires better therapies. Greater awareness of the disease process, better understanding of the underlying mechanisms, and improved management of patients with heart failure are urgently needed to ensure that the outcomes of patients with acute heart failure are optimized.

In recent years, the concept of acute heart failure as a single disease entity has changed, and the definition and classification of acute heart failure have gradually been modified with the increased realization that the term *acute heart failure* incorporates several acute heart failure syndromes, which differ in presentation, etiology, pathophysiology, and outcome. Clinicians and investigators around the world are now collaborating to establish more uniform definitions, collect relevant epidemiologic data, and develop more standardized guidelines and recommendations for the management of patients with acute heart failure. Recent epidemiologic studies have helped delineate key characteristics of patients with acute heart failure, highlight important risk factors, and identify national and international approaches to management.

This new book on acute heart failure is thus very timely, drawing together the most recent data and concepts in this field, and providing a fresh look at the complexities of acute heart failure. The editors, who are indeed authorities in the field, have succeeded in producing a truly complete review of this vast and important subject. The book is divided into two main parts, the first concentrating largely on epidemiology and pathophysiology, and the second focusing on diagnosis and management. In addition to the chapters covering the more traditional features of heart failure, other chapters address the nutritional, psychological, and ethical aspects. The text is supported throughout by ample and appropriate imaging and relevant references.

The 85 chapters are written by a broad cross-section of recognized experts from the different clinical arenas involved in the investigation and treatment of patients with acute heart failure, including cardiologists, cardiac and thoracic surgeons, intensivists, anesthesiologists, pharmacologists, nephrologists, and pulmonologists. The wide range of specialties represented by the

authors highlights the multidisciplinary nature of this disease process, which can affect almost all organ systems, creating a heterogeneous and complex entity. In addition, the international nature of the authors, including contributors from some 15 countries, helps make this text relevant for clinicians worldwide.

This highly comprehensive book is an important contribution to the literature in this field and will serve as a valuable text for all those involved in the care of patients with acute heart failure.

Jean-Louis Vincent
Head
Department of Intensive Care
Erasme Hospital
Free University of Brussels Belgium
Belgium

Preface

One challenge in editing a textbook is that by the time the the book is published, it is outdated. We believe that the present textbook on AHFS stands up to this challenge. AHFS is a new and rapidly evolving field. At present, we are just starting to learn about AHFS and to develop paradigms similar to those created in the early 1980s for chronic heart failure, one of the fastest changing areas in cardiovascular medicine during the last 20 years. Researchers have only started to measure how important a burden AHFS is on health care.

We are beginning to investigate some reasonable pathophysiological hypotheses. Only recently, the ESC and ACC/AHA issued the first set of guidelines. None of these guidelines is truly evidence based, as only a few clinical trials have investigated new treatments for AHFS and even fewer have yielded positive results. Therefore, the editors felt the need to assemble in a single compendium a baseline document that establishes the current knowledge of this syndrome. In so doing, we have also tried to highlight unmet needs and to delineate areas for future research. Finally, the editors addressed the large heterogeneity of this syndrome by inviting a variety of contributors with different backgrounds and from different continents to participate.

Alexandre Mebazaa
Mihai Gheorghiade
Faiez M. Zannad
Joseph E. Parrillo

Contents

Foreword by <i>Jean-Louis Vincent</i>	v
Preface	vii
Contributors	xvii
 Part 1 ACUTE HEART FAILURE SYNDROMES: FROM EPIDEMIOLOGY TO CLINICAL PRACTICE	
 Section 1.1 Epidemiology and Definitions	
1 Definitions of Acute Heart Failure Syndromes	5
<i>Alexandre Mebazaa, Mihai Gheorghiade, Faiez M. Zannad, and Joseph E. Parrillo</i>	
2 Risk Stratification Models and Predictors of Mortality in Acute Heart Failure Syndromes, Based on United States Registries	7
<i>Gregg C. Fonarow</i>	
3 Epidemiology and Management of Acute Heart Failure Syndromes in Europe	13
<i>François Alla and Faiez M. Zannad</i>	
4 Epidemiology and Management of Acute Decompensating Heart Failure in the Asia-Pacific Region	20
<i>Anthony S. McLean</i>	
5 Peculiarities of Acute Heart Failure Syndromes in Latin America and the Role of Chagas' Disease	30
<i>Fábio Vilas-Boas</i>	
 Section 1.2 Transition from Normal Physiology to Pathophysiology	
Section 1.2.1 Cardiac Level	
6 Normal Physiology and Pathophysiology of Left Ventricular Systole	43
<i>Marc A. Simon and Michael R. Pinsky</i>	

7	Normal Physiology and Pathophysiology of Left Ventricular Diastole	52
	<i>Gilles W. De Keulenaer and Dirk L. Brutsaert</i>	
8	Normal Physiology and Pathophysiology of the Right Ventricle	63
	<i>Etienne Gayat and Alexandre Mebazaa</i>	
9	Myocardial Protection from Ischemia and Reperfusion Injury	70
	<i>Stefan G. De Hert</i>	

Section 1.2.2 Cellular and Organ System Level

10	Receptor Signaling Pathways in Heart Failure: Transgenic Mouse Models	89
	<i>Juhsien Chen and Howard A. Rockman</i>	
11	Acute Heart Failure and Cardiac Remodeling	112
	<i>Jean-Jacques Mercadier</i>	
12	Reactive Oxygen Species in Heart Failure	118
	<i>Min Zhang and Ajay M. Shah</i>	
13	Mitochondrion: Key Factors in Acute Heart Failure	124
	<i>Christophe Rabuel</i>	
14	Immune System Alterations in Acute Heart Failure	134
	<i>Kirkwood F. Adams, Jr., and Tien M.H. Ng</i>	
15	Organ Perfusion in Acute Heart Failure Syndromes	148
	<i>Tal H. Kopel and Marie-Reine Losser</i>	

Section 1.3 Clinical Scenarios

Section 1.3.1 Acute Myocardial Dysfunction

16	Dyspnea: How to Differentiate Between Acute Heart Failure Syndrome and Other Diseases	161
	<i>Clément R. Picard and Abdellatif Tazi</i>	
17	Acute Heart Failure in the Setting of Acute Coronary Syndromes	168
	<i>Jose López-Sendón and Esteban López de Sá</i>	
18	Acute Heart Failure and Myocarditis	183
	<i>Fredric Ginsberg and Joseph E. Parrillo</i>	
19	Management of Severe Acute Heart Failure	200
	<i>Markku S. Nieminen</i>	

20	Cardiogenic Shock	207
	<i>Steven M. Hollenberg</i>	

21	Arrhythmia in Acute Heart Failure	221
	<i>Alexandru B. Chicos and Alan H. Kadish</i>	

Section 1.3.2 Right Ventricular Dysfunction

22	Right Ventricular Dysfunction in the Intensive Care Unit	237
	<i>Vincent Caille, Cyril Charron, François Jardin, and Antoine Vieillard-Baron</i>	

23	Acute Pericardial Disease	247
	<i>Gorazd Voga</i>	

24	Acute Pericardial Disease: Pericardiocentesis and Percutaneous Pericardiotomy	255
	<i>Hani Jneid, Andrew O. Maree, and Igor F. Palacios</i>	

Section 1.3.3 Acute Heart Failure Syndromes and Coexisting Disease

25	Severe Cardiac Disease in Pregnancy	269
	<i>Walther N.K.A. van Mook and Louis Peeters</i>	

26	Acute Heart Failure Syndromes and Endocrine Disorders	291
	<i>Ioannis Ilias, Ioanna Dimopoulou, and Stylianos Tsagarakis</i>	

27	Acute Heart Failure Syndromes in β -Thalassemia	297
	<i>Dimitrios Th. Kremastinos, John T. Parissis, and Gerasimos S. Filippatos</i>	

28	Acute Heart Failure and Systemic Diseases	306
	<i>Iris Cohen, Nadia Benyounes-Iglesias, Nadia Belmatoug, and Ariel A. Cohen</i>	

29	Acute Heart Failure in the Postoperative Period	323
	<i>Todd A. Watson and Lee A. Fleisher</i>	

30	Myocardial Dysfunction in Sepsis and Septic Shock	333
	<i>Anand Kumar, Aseem Kumar, and Joseph E. Parrillo</i>	

31	Acute Heart Failure Syndromes and Drug Intoxication	348
	<i>Bruno Mégarbane, Nicolas Deye, and Frédéric J. Baud</i>	

32	Sleep-Related Breathing Disorders and Acute Heart Failure Syndrome	359
	<i>Rami N. Khayat, Martin A. Valdivia-Arenas, and William T. Abraham</i>	

Section 1.3.4 Acute Heart Failure Syndromes in the Extreme Ages

33 Acute Heart Failure Syndromes in the Elderly 371
Michael W. Rich

34 Acute Heart Failure Syndromes in Neonatal and Pediatric Populations 378
Brian Feingold and Steven A. Webber

Part 2 DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF SEVERE ACUTE HEART FAILURE SYNDROMES

Section 2.1 Procedures and Technology

35 Esophageal Doppler: Noninvasive Estimation of Stroke Volume 391
Bernard P. Cholley

36 Minimally Invasive Cardiac Output Monitoring: Pulse Contour and Pulse Power Analysis 397
Andrew Tillyard and Andrew Rhodes

37 Oxygen Saturation Measurements in Acute Heart Failure Syndrome 406
Etienne Gayat, Alexandre Mebazaa, and Didier Payen de La Garanderie

38 Pulmonary Artery Catheter in the Intensive Care Unit 411
Xavier Monnet and Jean-Louise Teboul

39 Assessment of Critically Ill Patients with Acute Heart Failure Syndromes Using Echocardiography Doppler 424
Philippe Vignon

40 Portable Echocardiography and Acute Heart Failure Syndromes in the Emergency Room 446
Gerasimos S. Filippatos, Ioannis A. Paraskevaidis, and Dimitrios Th. Kremastinos

41 Coronary Angiography in Acute Heart Failure 451
Patrick Henry

42 Arterial Blood Gas Analysis in Acute Heart Failure Syndrome 455
Martin J. Cook and Andrew Rhodes

43 B-Type Natriuretic Peptide Testing in the Emergency Room and Intensive Care Unit for the Patient with Acute Heart Failure 468
Damien Logeart and Alain Cohen Solal

Section 2.2 Treatment of Acute Heart Failure Syndrome: Airway and Lung Management

- 44 Noninvasive Ventilation and Acute Heart Failure Syndrome ... 477
Laurent Ducros and Patrick I. Plaisance
- 45 Invasive Ventilation and Acute Heart Failure Syndrome 486
Jean-Damien Ricard and Damien Roux
- 46 Chest X-Ray in Acute Heart Failure 494
Laurence Monnier-Cholley

Section 2.3 Treatment of Acute Heart Failure Syndrome: Fluid Management

- 47 Management of Volume Overload in Acute Heart
Failure: Diuretics and Ultrafiltration 503
Maria Rosa Costanzo
- 48 Role of Anemia in Acute and Chronic Heart
Failure and the Role of Erythropoietin in Its Correction 519
*Donald S. Silverberg, Dov Wexler, Adrian Iaina,
and Doron Schwartz*

Section 2.4 Treatment of Acute Heart Failure Syndrome: Cardiovascular Management

Section 2.4.1 Vasodilators

- 49 Management of Chronic Heart Failure Therapy in
the Setting of Acute Heart Failure 533
Luigi Tavazzi, Aldo Pietro Maggioni, and Donata Lucci
- 50 Nitrates in Acute Decompensated Heart Failure 545
Jean-Michel Tarti re and Alain Cohen Solal
- 51 Use of Nesiritide in the Management Algorithm
of Acute Decompensated Heart Failure 551
Clyde W. Yancy

Section 2.4.2 Positive Inotropes and Vasopressors

- 52 Dobutamine in the Management of Acute Heart
Failure Syndrome 567
Rohit Mehta and Carl V. Leier
- 53 Therapeutic Role of Dopamine in Acute Heart
Failure Syndrome 577
*Vijay Karajala, Murugan Raghavan, Ramesh Venkataraman,
and John A. Kellum*

54	Vasopressors in Acute Severe Heart Failure	583
	<i>John H. Boyd and Keith R. Walley</i>	
 Section 2.4.3 Novel Cardiovascular Therapy for Acute Heart Failure Syndrome		
55	Calcium Sensitizer Levosimendan and Its Use in Acute Heart Failure and Related Conditions	595
	<i>Alexandre Mebazaa, John R. Teerlink, and Piero Pollesello</i>	
56	Natriuretic Peptides	608
	<i>Markus Meyer, Hartmut Lüß, Veselin Mitrovic, and Alexandre Mebazaa</i>	
57	Vasopressin Antagonists in Acute Heart Failure Syndromes ...	621
	<i>Cesare Orlandi, Filippo Brandimarte, and Mihai Gheorghiade</i>	
58	Endothelin Receptor Antagonists and Acute Heart Failure Syndromes	626
	<i>John R. Teerlink</i>	
59	Antiplatelets and Anticoagulation in the Setting of Acute Heart Failure Syndrome	639
	<i>Nathalie Dervaux, Gilles Montalescot, and Alexandre Mebazaa</i>	
 Section 2.5 Specific Intensive Care Unit Management of Acute Heart Failure Syndrome		
60	Successful Analgesia and Sedation for Patients with Acute Heart Failure Syndromes	655
	<i>Nuala J. Meyer and Jesse B. Hall</i>	
61	Intraaortic Balloon Pump in the Management of Acute Heart Failure Syndromes	671
	<i>Eleftheria P. Tsagalou, Stavros G. Drakos, Elias Tsolakis, and John N. Nanas</i>	
62	Cardiac Resynchronization Therapy in Acute and Chronic Heart Failure Syndromes	684
	<i>Paul Milliez, Abdeddayem Haggui, Fabrice Extramiana, Olivier Thomas, and Antoine Leenhardt</i>	
63	Acute Heart Failure Treatment and Brain Protection	692
	<i>Nicolas Deye, Bruno Mégarbane, and Frédéric J. Baud</i>	
64	End-of-Life Care for Critically Ill Patients with Heart Failure: A Multidisciplinary Viewpoint from the Intensive Care Unit	704
	<i>Thomas Fassier and Elie Azoulay</i>	

Section 2.6 Anesthesia and Surgical Management of Acute Heart Failure Syndrome

65	Anesthesia for Patients with Acute Heart Failure Syndromes	719
	<i>Dan Longrois and Paul Michel Mertes</i>	
66	Mechanical Circulatory Support for Management of Cardiogenic Shock Beyond Intraaortic Balloon Pump Support and Inotropes	730
	<i>Aly El-Banayosy, Reiner Koerfer, and Dagmar Cobaugh</i>	
67	Role of Left Ventricular Assist Devices in Acute Heart Failure Syndrome and the Future of the Replacement Heart	737
	<i>José A. Tallaj, Salpy V. Pamboukian, and Robert C. Bourge</i>	

Section 2.7 Management of Organ Dysfunction Associated with Acute Heart Failure Syndrome

68	Kidney in Acute Heart Failure	751
	<i>Guido Boerrigter, Fernando L. Martin, and John C. Burnett, Jr.</i>	
69	Acute Hypoxic Hepatitis and Hepatic Consequences of Acute Heart Failure Syndrome	763
	<i>Alain Cohen Solal and François Durand</i>	
70	Lactate and Acute Heart Failure Syndrome	768
	<i>Carole Ichai, Xavier Lerverve, and Jean-Christophe Orban</i>	
71	Glucose Disturbance and Acute Heart Failure Syndrome	781
	<i>Dirk Vlasselaers and Greet Van den Berghe</i>	
72	Hyponatremia in the Setting of Acute Heart Failure Syndrome	786
	<i>Carole Ichai and Diane Lena</i>	
73	Pulmonary Disease in the Setting of Acute Heart Failure Syndrome	797
	<i>Damien Roux and Jean-Damien Ricard</i>	

Section 2.8 Rescue Management in Acute Heart Failure Syndrome

74	Mechanical Devices to Improve Circulation During Cardiopulmonary Resuscitation	809
	<i>Keith G. Lurie, Anja K. Metzger, and Demetris Yannopoulos</i>	
75	Pharmacology in Cardiopulmonary Resuscitation	819
	<i>Patrick I. Plaisance, Claire Broche, and Karima Mezaïb</i>	

76	Role of Automated External Defibrillators in Acute Heart Failure Patients	827
	<i>Jane G. Wigginton, Paul E. Pepe, and Thomas R. Aversano</i>	
77	Post-Cardiopulmonary Resuscitation Management in the Intensive Care Unit	837
	<i>Christophe Adrie, Ivan Laurent, and Mehran Monchi</i>	
 Section 2.9 Acute Heart Failure Syndrome Management in Heart Failure Clinics		
78	Role of the Pharmacist in the Management of Acute Heart Failure Syndrome	847
	<i>Wendy A. Gattis Stough, J. Herbert Patterson, and Jo E. Rodgers</i>	
79	Role of Nursing in the Management of Acute Heart Failure Syndromes	857
	<i>Nancy M. Albert</i>	
80	Psychological Support in Acute Heart Failure Syndrome	867
	<i>Karen E. Joynt, Wei Jiang, and Christopher M. O'Connor</i>	
81	Nutrition in Acute Decompensation of Patients with Acute Heart Failure Syndrome	876
	<i>Roberto Aquilani, Cristina Opasich, Simona Viglio, Paolo Iadarola, and Evasio Pasini</i>	
 Section 2.10 Impact of Guidelines and Regulatory Views on Acute Heart Failure Syndrome Treatment		
82	Classification of the Level of Evidence in International Guidelines for Acute and Chronic Heart Failure	885
	<i>John G.F. Cleland</i>	
83	Drug Development for Acute Heart Failure Syndromes: European Regulatory View	892
	<i>Edmond Roland and Eric Abadie</i>	
84	Drug Approval Process for Acute Heart Failure Syndrome in the United States	899
	<i>Ileana L. Piña and Shari L. Targum</i>	
	Index	909

Contributors

Eric Abadie MD, MBA
French Health Products Safety Agency
(Agence Française de Sécurité Sanitaire
des Produits de Santé)
Saint-Denis, France

William T. Abraham, MD
Division of Cardiovascular Medicine
The Ohio State University
Columbus, OH, USA

Kirkwood F. Adams, Jr., MD
Heart Failure—Cardiology
University of North Carolina
Bolin Creek, NC, USA

Christophe Adrie, MD, PhD
General ICU
Delafontaine Hospital
Saint Denis, France

Nancy M. Albert, PhD
Nursing Research Innovation
Cleveland Clinic Foundation
Cleveland, OH, USA

François Alla, MD, PhD
Department of Epidemiology
University Hospital
Nancy, France

Roberto Aquilani, MD
Service of Metabolic-Nutritional
Patho Physiology
Scientific Institute of Montescano
(PV) “S.Maugeri”
Montescano, Pavia, Italy

Thomas R. Aversano, MD
Department of Medicine/Cardiology
Johns Hopkins Medical Institutions
Baltimore, MD, USA

Elie Azoulay, MD, PhD
Medical Intensive Care
Saint-Louis Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Frédéric J. Baud, MD
Department of Medical and Toxicological
Critical Care
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Nadia Belmatoug
Service de Medecine Interne
Hopital Beaujon
Assistance Publique Hôpitaux de Paris
Clichy, France

Nadia Benyounes-Iglesias, MD
Department of Cardiology-Internal
Medicine
Fondation Ophtalmologique de Rothschild
Paris, France

Guido Boerrigter, MD
Division of Cardiovascular Research
Mayo Clinic
Rochester, MN, USA

Robert C. Bourge, MD
 Division of Cardiovascular Disease
 University of Alabama at Birmingham
 Birmingham
 Jefferson, AL, USA

John H. Boyd, MD
 Division of Critical Care
 Department of Medicine
 The University of British Columbia
 St Paul's Hospital
 Vancouver, BC, Canada

Filippo Brandimarte
 Department of Cardiovascular,
 Respiratory and Morphological Sciences
 University of Rome "La Sapienza"
 Rome, Italy

Claire Broche, MD
 Department of Anesthesiology and Critical Care
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Dirk L. Brutsaert, MD, PhD
 Cardiology Department
 AZ Middelheim—University of Antwerp
 Antwerp, Belgium

John C. Burnett, Jr., MD
 Division of Cardiovascular Diseases
 Mayo Clinic
 Rochester, MN, USA

Vincent Caille, MD
 Intensive Care Unit
 Ambroise Pare Hospital
 Boulogne, France

Cyril Charron, MD
 Intensive Care Unit
 Ambroise Pare Hospital
 Boulogne, France

Juhsien Chen
 Department of Cardiovascular Medicine
 Duke University Medical Center
 Durham, NC, USA

Alexandru B. Chicos, MD
 Department of Cardiology
 Northwestern University
 Chicago, IL, USA

Bernard P. Cholley, MD, PhD
 Anesthesiology and Critical Care Medicine
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

John G.F. Cleland, MD
 Department of Cardiology
 University of Hull
 Kingston upon Hull
 East Yorkshire, UK

Dagmar Cobaugh, MD
 Department of Thoracic and Cardiovascular
 Surgery
 Heart and Diabetes Centre North-Rhine
 Westphalia
 Bad Oeymhausen, Germany

Ariel A. Cohen, MD, PhD, FESC, FACC
 Cardiology Department
 Assistance-Publique-Hôpitaux de Paris
 Saint-Antoine University and Medical School
 Assistance Publique-Hôpitaux de Paris
and
 Université Pierre et Marie Curie
 St-Antoine, Paris, France

Iris Cohen, MD
 The Non Invasive Echocardiography Laboratory
 The European Hospital Georges Pompidou
 Paris, France

Alain Cohen Solal, MD, PhD
 Department of Cardiology
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Martin J. Cook, MBChB, MRCP, FRCA
 St George's Hospital
 London, UK

Maria Rosa Costanzo, MD
Centre for Advanced Heart Failure
Edward Hospital—Midwest Heart Specialists
Naperville, IL, USA

Stefan G. De Hert, MD, PhD
Department of Anaesthesiology
University of Antwerp
Antwerp University Hospital
Edegem, Belgium

Nathalie Dervaux, MD
Centre de Médecine Préventive Cardiovasculaire
Centre Hospitalier Hôpital Européen Georges
Pompidou-Broussais
Assistance Publique-Hôpitaux de Paris
Paris, France

Nicolas Deye, MD
Department of Medical and Toxicological
Critical Care
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Ioanna Dimopoulou, MD
Department of Critical Care Medicine
Attikon University Hospital
Athens University, Medical School
Chaidari, Athens, Greece

Stavros G. Drakos, MD
Clinical Therapeutics
University of Athens
Athens, Attica, Greece

Laurent Ducros, MD
Department of Anaesthesiology and
Intensive Care
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

François Durand, MD
Hepatology Unit
Hospital Beaujon
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Clichy, France

Aly El-Banayosy, MD
Department of Thoracic and Cardiovascular
Surgery
Heart and Diabetes Centre North-Rhine
Westphalia
Bad Oeymhausen, Germany

Fabrice Extramiana, MD, PhD
Department of Cardiology
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Thomas Fassier, MD
Medical and Respiratory Intensive Care Unit
Croix Rousse Hospital
Lyon, France

Brian Feingold, MD
School of Medicine
Department of Paediatrics
Division of Cardiology
University of Pittsburgh
Children's Hospital Pittsburgh
Pittsburgh, PA, USA

Gerasimos S. Filippatos, MD
2nd University Department of Cardiology
University of Athens Hospital, Attikon
Athens, Greece

Lee A. Fleisher, MD, FACC
Department of Anaesthesiology and Critical
Care
University of Pennsylvania
Philadelphia, PA, USA

Gregg C. Fonarow, MD
UCLA Division of Cardiology
David Geffen School of Medicine at UCLA
Los Angeles, CA, USA

Etienne Gayat, MD
Department of Anesthesiology and
Critical Care
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Mihai Gheorghiade, MD, FACC
 Division of Cardiology
 Northwestern University
 Feinberg School of Medicine
 Chicago, IL, USA

Fredric Ginsberg, MD
 Department of Cardiovascular Disease and
 Critical Care Medicine
 Cooper University Hospital
 Camden, NJ, USA

Abdeddayem Haggui, MD
 Department of Cardiology
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Jesse B. Hall, MD, FCCP
 Department of Medicine
 University of Chicago
 Chicago, IL, USA

Patrick Henry, MD, PhD
 Department of Cardiology
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Steven M. Hollenberg, MD
 Coronary Care Unit
 Cooper University Hospital
 Camden, NJ, USA

Paolo Iadarola, PhD
 Department of Biochemistry
 University of Pavia
 Pavia, Italy

Adrian Iaina, MD
 Department of Nephrology
 A.P.C Health Specialists Clinic Ltd.
 Qiriat Ono, Israel

Carole Ichai, MD, PhD
 Department of Anesthesiology and
 Intensive Care Unit
 Hôpital Saint-Roch
 Nice, France

Ioannis Ilias, MD, PhD
 Department of Pharmacology
 Medical School
 University of Patras
 Rion, Achaia, Greece

François Jardin, MD
 Intensive Care Unit
 Ambroise Pare Hospital
 Boulogne, France

Wei Jiang, MD
 Psychiatric and Behavioural Sciences/Medicine
 Duke University Medical Center
 Durham, NC, USA

Hani Jneid, MD
 Division of Cardiology
 Massachusetts General Hospital
 and
 Harvard Medical School
 Boston, MA, USA

Karen E. Joynt, MD
 Internal Medicine
 Duke University Medical Centre
 Durham, NC, USA

Alan H. Kadish, MD
 Department of Cardiology
 Northwestern University
 Chicago, IL, USA

Vijay Karajala, MD
 Department of Critical Care Medicine
 University of Pittsburgh School of Medicine
 Pittsburgh, PA, USA

John A. Kellum, MD, FACP, FCCM, FCCP
 Department of Critical Care Medicine
 University of Pittsburgh School of Medicine
 Pittsburgh, PA, USA

Gilles W. De Keulenaer, MD, PhD
 Department of Cardiology
 AZ Middelheim
 Antwerp, Belgium

Rami N. Khayat, MD
 Department of Internal Medicine
 Ohio State University
 Columbus, OH, USA

Reiner Koerfer, MD

Department of Thoracic and Cardiovascular
Surgery

Heart and Diabetes Centre North-Rhine
Westphalia

Bad Oeymhausen, Germany

Tal H. Kopel, MD

Department of Internal Medicine

Jewish General Hospital, McGill University
Montreal, QC, Canada

Dimitrios Th. Kremastinos, MD, PhD

2nd Cardiology Department

University of Athens Medical School

University General Hospital “Attikon”
Athens, Greece

Anand Kumar, MD

Section of Critical Care Medicine

Health Sciences Centre

University of Manitoba

Winnipeg, MB, Canada

Aseem Kumar, BSc, MSc, PhD

Biomolecular Sciences Programme

Laurentian University

Sudbury, ON, Canada

Ivan Laurent, MD

Intensive Care Medicine

Institut Jacques Cartier

Massy, France

Antoine Leenhardt, MD

Department of Cardiology

Lariboisière University Hospital

Assistance Publique-Hôpitaux de Paris

Université Paris Diderot

Paris, France

Carl V. Leier, MD

Cardiovascular Division, Internal Medicine

Ohio State University

Columbus, OH, USA

Diane Lena, MD

Department of Anesthesiology and

Intensive Care Unit

Hôpital Saint-Roch

Nice, France

Xavier Leverve, MD, PhD

Department of Anesthesiology and
Intensive Care Unit

Hôpital Saint-Roch

Nice, France

Damien Logeart, MD, PhD

Department of Cardiology

Lariboisière Hospital

Paris, France

Dan Longrois, MD, PhD

Department of Anesthesiology
and Critical Care

Centre Hospitalier Universitaire de Nancy

Vandœuvre-les-Nancy, France

Esteban López de Sá

Coronary Care Unit

Hospital Universitario La Paz

Madrid, Spain

Jose López-Sendón, MD, PhD

Department of Cardiology

Hospital Universitario La Paz

Madrid, Spain

Marie-Reine Losser, MD, PhD

Anaesthesia and Critical Medicine

Lariboisière University Hospital

Assistance Publique-Hôpitaux de Paris

Université Paris Diderot

Paris, France

Donata Lucci, MS

ANMCO Research Centre

ANMCO (Italian Association of

Hospital Cardiologist)

Florence, Italy

Keith G. Lurie, MD

University of Minnesota

Department of Emergency Medicine

Hennepin County Medical Center

Eden Prairie, MN, USA

Hartmut Lüss, MD

Cardiopep Pharma GmbH

Hannover, Germany

Aldo Pietro Maggioni, MD
ANMCO Research Centre
ANMCO (Italian Association of
Hospital Cardiologist)
Florence, Italy

Andrew O. Maree, MSc, MB BCh
Division of Cardiology
Department of Medicine
Massachusetts General Hospital
and
Harvard Medical School
Boston, MA, USA

Fernando L. Martin, MD
Division of Cardiovascular Research
Mayo Clinic
Rochester, MN, USA

Anthony S. McLean, MB, ChB, BSc (Hons), FRACP
Department of Intensive Care Medicine
Nepean Hospital
Penrith, Sydney, Australia

Alexandre Mebazaa, MD, PhD
Department of Anesthesiology and
Critical Care Medicine
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France
and
School of Medicine of Tunis
Tunis, Tunisia

Bruno Mégarbane, MD, PhD
Department of Medical and Toxicological
Critical Care
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Rohit Mehta, MD
Cardiovascular Division, Internal Medicine
The Ohio State University
Columbus, OH, USA

Jean-Jaques Mercadier, MD, PhD
Department of Physiology
Groupe Hospitalier Bichat-Claude Bernard
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Paul Michel Mertes, PU-PH
Service d'Anesthésie Réanimation
Chirurgicale
Chu de Nancy—Hôpital Central
Nancy Cedex, France

Anja K. Metzger, PhD
University of Minnesota
Department of Emergency Medicine
Hennepin County Medical Center
Eden Prairie, MN, USA

Markus Meyer, MD, PhD
Cardiopep Pharma GmbH
Hannover, Germany

Nuala J. Meyer, MD
Section of Pulmonary and Critical Care
Department of Medicine
University of Chicago
Chicago, IL, USA

Karima Mezaïb, MD
Department of Emergency Medicine
Lariboisière University Hospital
Assistance-Publique Hôpitaux de Paris
Paris, France

Paul Milliez, MD, PhD
Department of Cardiology
Lariboisière University Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Veselin Mitrovic, MD
Department of Cardiology
Kerckhoff-Klinik GmbH
Bad Nauheim, Germany

Mehran Monchi, MD
Intensive Care Medicine
Intitut Jacques Cartier
Massy, France

Xavier Monnet, MD, PhD
Medical ICU
Bicêtre University Hospital
Assistance Publique-Hôpitaux de Paris
Le Kremlin-Bicêtre, France

Laurence Monnier-Cholley, MD
 Department of Radiology
 Hôpital Saint-Antoine
 Assistance Publique-Hôpitaux de Paris
 Paris, France

Gilles Montalescot, MD, PhD
 Institut de Cardiologie
 Groupe Hospitalier Pitié-Salpêtrière
 Assistance Publique-Hôpitaux de Paris
 Paris, France

John N. Nanas, MD, PhD
 Department of Clinical Therapeutics
 University of Athens School of Medicine
 Athens, Greece

Tien M.H. Ng, BSPharm, PharmD
 Pharmacy
 University of Southern California
 Los Angeles, USA

Markku S. Nieminen, MD, PhD
 Department of Medicine
 University Central Hospital
 Helsinki, Finland

Christopher M. O'Connor
 Duke University Medical Center
 Durham, NC, USA

Cristina Opasich, MD
 Cardiology Division
 Sc. Institute of Pavia
 S. Maugeri Foundation
 Pavia, Italy

Jean-Christophe Orban, MD
 Department of Anaesthesiology and
 Intensive Care Unit
 Hôpital Saint-Roch
 Nice, France

Cesare Orlandi, MD
 Otsuka Maryland Research Institute
 Rockville, MD, USA

Igor F. Palacios, MD
 Division of Cardiology
 Department of Medicine
 Massachusetts General Hospital
 and
 Harvard Medical School
 Boston, MA, USA

Salpy V. Pamboukian, MD, MSPH
 Division of Cardiovascular Disease
 University of Alabama at Birmingham
 Birmingham
 Jefferson, AL, USA

Ioannis A. Paraskevaïdis, MD
 Department of Cardiology
 Athens University Hospital Attikon
 Athens, Greece

John T. Parissis, MD
 Second Department of Cardiology and
 Heart Failure Unit
 University of Athens
 Athens, Greece

Joseph E. Parrillo, MD
 Robert Wood Johnson Medical School
 University of Medicine and Dentistry of
 New Jersey
 Chief, Department of Medicine
 Edward D. Viner MD Chair, Department
 of Medicine
 Director, Cooper Heart Institute
 Cooper University Hospital
 Camden, NJ, USA

Evasio Pasini, MD
 Cardiology Division
 Sc. Institute of Gussago
 S. Maugeri Foundation
 Gussago (BS), Italy

J. Herbert Patterson, PharmD
 School of Pharmacy
 University of North Carolina
 Chapel Hill, NC, USA

Didier Payen de La Garanderie, MD, PhD
 Department of Anesthesiology and Critical Care
 Medicine
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Louis Peeters, MD, PhD
 Ob-Gyn Department
 University Hospital Maastricht
 Maastricht, The Netherlands

Paul E. Pepe, MD, MPH
 Department of Surgery
 UT Southwestern Medical Center at Dallas
 Dallas, TX, USA

Clément R. Picard, MD
 Department of Respiratory Disease
 Saint-Louise Teaching Hospital
 Paris, France

Ileana L. Piña, MD
 Department of Medicine
 Case Western Reserve University
 Cleveland, OH, USA

Michael R. Pinsky, MD, CM, Dr, hc
 Department of Critical Care Medicine
 University of Pittsburgh
 Pittsburgh, PA, USA

Patrick I. Plaisance, MD, PhD
 Department of Emergency Medicine
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Piero Pollesello, PhD
 Department of Cardiology and Critical Care
 Orion Pharma
 Espoo, Finland

Christophe Rabuel, MD
 Department of Anaesthesiology and
 Critical Care Medicine
 Lariboisière University Hospital
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Paris, France

Murugan Raghavan, MD, MRCP
 Department of Critical Care Medicine
 University of Pittsburgh School of Medicine
 Pittsburgh, PA, USA

Andrew Rhodes, MRCP, FRCA
 St George's Hospital
 London, UK

Jean-Damien Ricard, MD, PhD
 Service de Réanimation Médicale
 Hôpital Louis Mourier
 Assistance Publique-Hôpitaux de Paris
 Université Paris Diderot
 Colombes, France

Michael W. Rich, MD
 Cardiovascular Division
 Department of Medicine
 Washington University, School of Medicine
 St. Louis, MO, USA

Howard A. Rockman, MD
 Department of Cardiovascular Medicine
 Duke University Center
 Durham, NC, USA

Jo E. Rodgers, PharmD
 School of Pharmacy
 University of North Carolina
 Chapel Hill, NC, USA

Edmond Roland, MD, FAHA
 French Health Products Safety Agency
 (Agence Française de Sécurité Sanitaire
 des Produits de Santé)
 Saint-Denis Cedex, France

Damien Roux, MD, MSc
 INSERM U722
 Université Paris Diderot
 Paris, France

Doron Schwartz, MD
 Department of Nephrology
 Tel Aviv Sourasky Medical Centre
 Tel Aviv, Israel

Ajay M. Shah, MD, FRCP, FMedSci
 Department of Cardiology, Cardiovascular
 Division
 King's College London School of Medicine
 London, UK

Donald S. Silverberg, MD, FRCPC
 Department of Nephrology
 Tel Aviv Medical Centre
 Tel Aviv, Israel

Marc A. Simon, MD
Department of Medicine
University of Pittsburgh
Pittsburgh, PA, USA

Wendy A. Gattis Stough, PharmD
Department of Clinical Research
Campbell University School of Pharmacy
Cary, NC, USA

José A. Tallaj, MD
Division of Cardiovascular Disease
University of Alabama at Birmingham
Birmingham
Jefferson, AL, USA

Shari L. Targum, MD
Division of Cardio-Renal Products
Center for Drug Evaluation and Research,
Food and Drug Administration
Silver Springer London Ltd.
Silver Spring, MD, USA

Jean-Michel Tartière, MD
Lariboisière Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Luigi Tavazzi, MD
Department of Cardiology
Istituti di Ricovero e Cura a
Carattere Scientifico
Policlinico S Matteo
University Hospital
Pavia, Italy

Abdellatif Tazi, MD, PhD
Department of Respiratory Disease
Saint-Louis Teaching Hospital
Assistance Publique-Hôpitaux de Paris
Université Paris Diderot
Paris, France

Jean-Louise Teboul, MD, PhD
Medical ICU
Bicetre University Hospital
Assistance Publique-Hôpitaux de Paris
Le Kremlin-Bicêtre, France

John R. Teerlink, MD, FACC, FAHA, FESC
Section of Cardiology
San Francisco Veterans Affairs Medical Center
University of California
San Francisco, CA, USA

Olivier Thomas, MD
Cardiology Department
Ambroise Pare Clinic
Neuilly Sur Seine, France

Andrew Tillyard, B.Apple.Sc, FRCA
St George's Hospital
London, UK

Eleftheria P. Tsagalou, MD
Department of Clinical Therapeutics
University of Athens
Athens, Attica, Greece

Stylios Tsagarakis, MD, PhD
Department of Endocrinology
Athens Polyclinic
Athens, Greece

Elias Tsolakis, MD
Department of Clinical Therapeutics
University of Athens
Athens, Attica, Greece

Martin A. Valdivia-Arenas, MD
Internal Medicine, Division of Pulmonary,
Critical Care, Allergy and Sleep Medicine
The Ohio State University
Columbus
Franklin, OH, USA

Greet Van den Berghe, MD, PhD
Intensive Care Unit
Catholic University of Leuven
Leuven, Belgium

Walther N.K.A. van Mook, MD
Intensive Care
University Hospital Maastricht
Maastricht, The Netherlands

Ramesh Venkataraman, MD
Department of Critical Care Medicine
University of Pittsburgh School of Medicine
Pittsburgh, PA, USA

Antoine Vieillard-Baron, MD, PhD
 Medical Intensive Care Unit
 Hopital Ambroise Pare
 Assistance Publique-Hôpitaux de Paris
 Boulogne, France

Simona Viglio, PhD
 Department of Biochemistry
 University of Pavia
 Pavia, Italy

Philippe Vignon, MD, PhD
 Medical Surgical Intensive Care Unit
 Dupuytren Teaching Hospital
 Limoges, France

Fábio Vilas-Boas, MD, PhD
 Department of Cardiology
 Hospital Espanhol
 Salvador, Bahia, Brazil

Dirk Vlasselaers, MD
 Intensive Care Unit
 Catholic University of Leuven
 Leuven, Belgium

Gorazd Voga, MD, PhD
 Department for Intensive Internal Medicine
 General and Teaching Hospital
 Celje, Slovenia

Keith R. Walley, MD
 Division of Critical Care
 Department of Medicine
 The University of British Columbia
 St Paul's Hospital
 Vancouver, BC, Canada

Todd A. Watson, MD
 Department of Anesthesiology
 and Critical Care
 University of Pennsylvania
 Philadelphia, PA, USA

Steven A. Webber, MBChB, MRCP
 School of Medicine
 Department of Paediatrics
 Division of Cardiology
 University of Pittsburgh
 Children's Hospital Pittsburgh
 Pittsburgh, PA, USA

Dov Wexler, MD
 Department of Cardiology
 Tel Aviv Sourasky Medical Centre
 Tel Aviv, Israel

Jane G. Wiggington, MD
 Department of Surgery
 UT Southwestern Medical Center at Dallas
 Dallas, TX, USA

Clyde W. Yancy, MD, FACC, FAHA, FACP
 Baylor Heart and Vascular Institute
 Baylor University Medical Center
 Dallas, TX, USA

Demetris Yannopoulos, MD
 Department of Cardiology
 University of Minnesota
 Minneapolis, MN, USA

Faiez M. Zannad, MD, PhD, FESC
 Heart Failure and Hypertension Unit
 Department of Cardiology
 Centre d'Investigation Clinique (CIC)
 INSERM U-684
 Centre Hospitalier Universitaire
 University Henri Poincaré
 Nancy, France
and
 School of Medicine of Tunis
 Tunis, Tunisia

Min Zhang, MD, PhD
 Department of Cardiology
 Cardiovascular Division
 London, UK

56

Natriuretic Peptides

Markus Meyer, Hartmut Lüss, Veselin Mitrovic, and Alexandre Mebazaa

Peptide hormones belonging to the natriuretic peptide (NP) family play an important role in maintaining cardiac and renal function by regulating fluid volume, pressure, and sodium concentration. The principal members of this family are atrial natriuretic peptide (ANP); urodilatin (URO); brain natriuretic peptide (BNP); and C-type natriuretic peptide (CNP). The physiologic effects of these molecules generally lead to vasodilation, natriuresis, and diuresis, and regulate sodium and water homeostasis, rendering them promising candidates for potential therapeutic use in cardiovascular and renal dysfunction. This chapter reviews the biochemistry, physiology, and pharmacologic potential of the major natriuretic peptides, with particular emphasis on their clinical importance in the treatment of acute heart failure syndrome (AHFS).

Biochemistry

Structure and Synthesis

The natriuretic peptides are characterized by a highly conserved 17-amino-acid ring structure that varies little even among different species. Whereas the amino- and carboxy-terminal amino acid sequences vary markedly, the ring structure differs in only five positions between ANP/URO, BNP, and CNP (Fig. 56.1). The biologically active forms of these molecules are processed from precursor proteins encoded by two genes on chromosome 1 (ANP/URO and BNP) and a third gene on chromosome 2 (CNP). Atrial natriuretic peptide and URO share the same amino acid sequence

from position 99 to 126 of the ANP-prohormone; however, URO has an additional N-terminal extension of 4 amino acids.

Atrial Natriuretic Peptide

Human ANP is a 28-amino-acid peptide synthesized in the myoendocrine cells of the heart atria, derived from a 151-amino-acid prehormone through a series of proteolytic processing steps. An N-terminal, 126-amino-acid precursor, pro-ANP (ANP₁₋₁₂₆), is first derived from the prehormone and stored in atrial myocyte granules. Pro-ANP is then cleaved into a 98-amino-acid N-terminal fragment and the biologically active, 28-amino-acid C-terminal atrial natriuretic peptide (ANP₉₉₋₁₂₆); both are released by exocytosis into the circulation.^{1,2} Under normal conditions, ANP gene expression in the ventricles is seen only at very low levels (about 7% that in the atria), but increased ANP messenger RNA (mRNA) production may occur in pathologic conditions such as heart failure and left ventricular (LV) hypertrophy.³ Atrial natriuretic peptide release is induced by elevations in cardiac-wall tension,⁴ which may be due to physical exercise, neurohumoral stimuli, and other physiologic factors.¹

Urodilatin

Urodilatin (URO/ANP₉₅₋₁₂₆) is a 32-amino-acid peptide that is produced by differential processing of the pro-ANP precursor peptide in distal renal tubule cells; therefore, it is identical to ANP except for the presence of four additional N-terminal amino acids. Urodilatin is found in urine

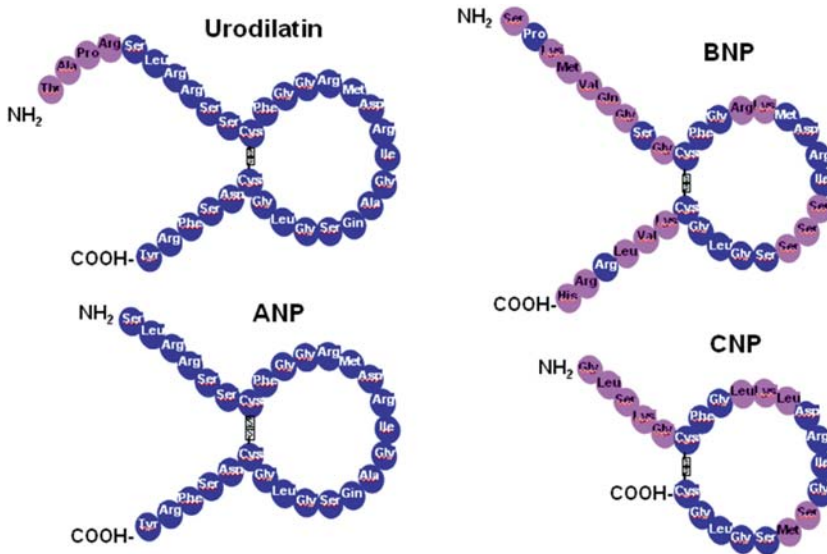


FIGURE 56.1. Structure of the natriuretic peptides ANP_{99–126}, urodilatin/ANP_{95–126}, BNP_{77–108}, and CNP_{105–126} showing the conserved 17-amino-acid ring configuration. Nonconserved residues are indicated in pink.

and has not been detected and isolated from plasma. It is secreted into the tubular lumen and acts as a paracrine hormone, binding further downstream to receptors in the inner medullary collecting duct and inhibiting sodium reabsorption.^{5,6} Urodilatin release occurs in response to acute volume load and selective increases in sodium concentration and dietary sodium intake,^{7,8} and is closely correlated with the circadian rhythm of urinary sodium excretion.⁹ In congestive heart failure (CHF), urinary urodilatin excretion was found to be increased, apparently to counteract antinatriuresis and fluid retention.¹⁰

Brain Natriuretic Peptide

Brain natriuretic peptide was originally isolated from porcine brain extracts and later identified from human cardiac tissue. It consists of 32 amino acids (BNP_{77–108}) derived from a 108-amino-acid pro-BNP precursor that is found, in humans, predominantly in the ventricles of the heart and in much smaller amounts in the atria, brain, and amniotic tissue.^{11,12} N-terminal pro-BNP and mature BNP molecules are released from ventricular myocytes at a 1:1 molar ratio and circulate in plasma. Unlike ANP, which is stored in the form of the 126-amino-acid precursor pro-ANP, BNP is stored mainly as the mature peptide.^{4,13} Whereas

there is a threefold greater concentration of BNP mRNA in the ventricles than in the atria, the ventricles have only 1% of the amount of mature BNP that is in the atria.¹⁴ Brain natriuretic peptide mRNA is transcribed in response to stretching of ventricle and atrial walls from increased blood pressure or elevated venous volume.^{12,15–17}

C-Type Natriuretic Peptide

Processing of CNP starts with the removal of a 23-amino-acid signal peptide from the 126-amino acid preprohormone (prepro-CNP), converting it into pro-CNP (CNP_{24–126}). Pro-CNP is then cleaved to produce a 53-amino-acid intermediate peptide, CNP-53 (CNP_{74–126}); further cleavage of CNP-53 produces biologically active CNP-22 (CNP_{105–126}).¹⁸ CNP-22 is produced in brain and endothelial cells and acts primarily as an autocrine or paracrine hormone that regulates vascular tone and blood pressure.^{4,19} It is found in much lower concentrations than either ANP or BNP in the heart or in plasma. Like ANP, CNP is stored mainly in the 104-amino-acid propeptide (pro-CNP) form.¹⁸

Atrial natriuretic peptide and BNP secretion is regulated mainly by the degree of atrial and ventricular wall stress that results from volume or pressure overload and by several endogenous

hormones, neurotransmitters, proinflammatory cytokines, and vasoactive factors. Both CNP production and secretion *in vitro* are stimulated by ANP, 20-fold more potently by BNP, and by several cytokines and growth factors, including transforming growth factor- β (TGF- β), tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), and lipopolysaccharide (LPS), although no relation has been established between CNP and any pathologic effects caused by these cytokines.²

Natriuretic Peptide Receptors and Metabolism

The three types of natriuretic peptide receptors (NPRs) are NPR-A, NPR-B, and NPR-C. NPR-A and NPR-B are expressed at high levels in the atria, ventricles, aorta, peripheral blood vessels, platelets, lungs, skin, tubules, smooth muscles of the kidney, and presynaptic sympathetic nerve fibers. Both are highly homologous transmembrane proteins composed of an extracellular binding domain (~440 amino acids), a transmembrane domain (37 amino acids), and intracellular domains with kinase (~280 amino acids) and guanylyl cyclase (~250 amino acids) activity. The guanylyl cyclase domain catalyzes the generation of cyclic guanosine monophosphate (cGMP), which mediates most of the physiologic effects of natriuretic peptides.⁴ Atrial natriuretic peptide, BNP, and urodilatin all bind predominantly to NPR-A; ANP is the natural ligand for NPR-A and binds to it with a 10-fold higher affinity than BNP. C-type natriuretic peptide binds most strongly to NPR-B.^{2,14}

Natriuretic peptide receptor C is expressed in cells of the kidney, adrenal gland, brain, lungs, and blood vessel walls. It is more abundantly expressed than any other NP receptor type, constituting 90% of all NP receptors in target tissues.⁴ It has an extracellular binding domain that is approximately 30% homologous to its NPR-A and NPR-B counterparts and a short, noncatalytic 37-amino-acid intracellular domain that shares no homology with the corresponding domains of the other two receptor types. Natriuretic peptide receptor C is considered a “clearance” receptor whose action is geared toward internalization of receptor-ligand complexes and subsequent lysosomal degradation of the ligand.^{20,21} One function

of NPR-C may be the removal of excess natriuretic peptides in the circulation, although it may achieve other effects through signaling pathways involving other second messengers such as cyclic adenosine monophosphate (cAMP) or by coupling with G proteins. All natriuretic peptides bind avidly to NPR-C, although ANP and CNP bind with a somewhat higher affinity than BNP.^{4,22,23}

Natriuretic peptide binding to NP receptors stimulates cGMP production and elevation of intracellular cGMP levels. Cellular responses depend on downstream cGMP signal transduction, mediated by cGMP-dependent protein kinases (PKGs) that catalyze phosphorylation of target proteins (reviewed by D’Souza et al.⁴). Two protein kinases, PKG-I and PKG-II, appear to be involved in this signaling pathway. PKG-I is a soluble cytoplasmic enzyme that modulates intracellular calcium levels and is present in cardiac myocytes, vasculature, lung, cerebellum, kidney, adrenal glands, and uterus. PKG-II regulates fluid homeostasis at the cell membrane and is found in brain, intestine, lung, kidney, and bone but is absent from the heart and vascular tissue. Cyclic GMP may also activate cAMP-dependent protein kinase A (PKA) or cGMP-regulated phosphodiesterases (PDEs) in certain tissues such as the heart, lung, liver, adrenals, brain, platelets, and smooth muscle.

Natriuretic peptides are cleared from the circulation by NPR-C uptake and the enzymatic action of neutral endopeptidase (NEP), a zinc metallo-peptidase enzyme present in high concentrations in the brush border of renal proximal tubular cells and also in the vascular endothelium. Neutral endopeptidase digests other vasodilators such as bradykinin, substance P, and adrenomedullin, and vasoconstrictors such as angiotensin II and endothelin 1 (ET-1) (reviewed in Schmitt et al.¹⁴).

Physiology and Pharmacology

Atrial Natriuretic Peptide and Brain Natriuretic Peptide

Atrial natriuretic peptide and lower levels of BNP are produced in the atria and ventricles in response to changes in transmural atrial pressure or stretch

as a consequence of pressure or volume expansion. Neurohumoral stimuli such as vasopressin, angiotensin II, endothelin (ET), enkephalin, morphine, and TNF- α also induce ANP release.²⁴⁻²⁸

The effects of ANP and BNP on the cardiovascular and renal systems are well documented.^{17,29-36} Under physiologic conditions, ANP and BNP have similar physiologic effects, including vasodilation; suppression of the renin-angiotensin-aldosterone system (RAAS), endothelin, and sympathoadrenergic systems; reduced blood pressure and peripheral vascular resistance; and enhanced diuresis, natriuresis, and kaliuresis.^{29,30,36} In canine models and isolated arterial strips, ANP relaxes coronary arteries³⁷ and appears to be more selective for the renal arteries when compared to others (vertebral, femoral, and common carotid).³⁸ In humans, however, results of studies on the effects of BNP on coronary arteries and coronary flow rate have been equivocal.^{39,40}

As natural antagonists of the RAAS, ANP and BNP inhibit Na⁺ reabsorption in the inner medullary collecting duct and also modify the renal hemodynamics by increasing preglomerular vasodilation and postglomerular vasoconstriction, thereby increasing the glomerular filtration rate (GFR). All these actions have the end effect of enhancing natriuresis and diuresis. The pro-ANP fragment ANP₃₁₋₆₇ also stimulates the release of prostaglandins, which induce natriuresis indirectly by blocking adenosine triphosphatase (ATPase)-dependent sodium exchange in the inner medullary collecting duct of the kidney.

Atrial natriuretic peptide or BNP infusions in healthy subjects increase urinary flow rate and Na⁺ excretion in a dose-dependent manner and inhibit plasma renin secretion.^{34,41} Brain natriuretic peptide also has predominantly central hemodynamic effects, such as decreased stroke volume and mean arterial pressure and increased heart rate, but it does not seem to affect the peripheral microcirculation in the skin and conjunctiva, capillary density, or skin oxygen capacity.³⁶

Atrial natriuretic peptide also appears to play an important role in organogenesis and embryogenesis by regulating the differentiation and regulation of multiple organ systems, including the skeletal system, immune response, natural killer cell activation, histamine release, reproductive system, and central nervous system (reviewed

in Schmitt et al.¹⁴). Additionally, other studies emphasize the potential role of ANP and BNP as important factors in cardiovascular remodeling as a result of their antiproliferative activity.⁴ The mechanism by which these NPs modulate proliferation, cell growth, and apoptosis in cardiac myocytes, smooth muscle cells, and fibroblasts, as well as extracellular matrix production, is currently the subject of intensive research.

The biological half-life of ANP is approximately 3.5 minutes, whereas that of BNP is nearly seven times longer at 22.6 minutes as a result of its slower degradation by NEP and lower affinity for the NPR-C.²

Urodilatin

Because they are highly homologous to each other and are derived from the same precursor, the biologic actions of urodilatin and ANP are similar; however, the effects of urodilatin on renal sodium excretion are more critical than those of ANP. Urodilatin infusion in animal models results in a much stronger natriuretic and diuretic effect than that produced by an equimolar ANP infusion.^{42,43} This is most likely due to the lesser susceptibility of urodilatin to degradation by the neutral endopeptidase as it passes the proximal tubules in the kidney.⁴⁴

Urodilatin causes dilation of preglomerular and constriction of postglomerular vessels⁴⁵ and also increases GFR in animal models of acute renal failure.⁴⁶ In healthy human volunteers, urinary excretion of urodilatin is directly correlated to increased sodium intake and renal sodium excretion.⁷ After prolonged diets with varying sodium doses, infused urodilatin at 20 ng/kg/min for 60 minutes increased diuresis and natriuresis in proportion to the amount of sodium in the diet, further suggesting an important role for endogenous urodilatin in sodium homeostasis.³⁵ The renal response to urodilatin appears to be exerted at the collecting duct where sodium reabsorption is inhibited. Even lower doses (5 and 10 ng/kg/min) of intravenously administered urodilatin to healthy subjects with normal LV function have significant systemic effects on the cardiovascular, endocrine, and renal systems. In contrast to the response in heart failure patients, in healthy volunteers these low doses led to a reduction in the

cardiac output by 7% and 16%; in stroke volume by 10% and 20%, respectively, most likely due to venodilation; and in renal blood flow (hippurate clearance) by 13% to 37%, with no changes in arterial pressure or GFR.⁴⁷

In addition to its effects on the kidney, in healthy volunteers, urodilatin at ≤ 20 ng/kg/min inhibits the neurohumoral axis, resulting in decreased secretion of renin, angiotensin II, aldosterone, vasopressin, and BNP into the plasma. At higher dosages, plasma renin, angiotensin II, aldosterone, and vasopressin levels actually increase in a compensatory fashion because of the decrease in blood pressure.^{5,47,48}

In a randomized, placebo-controlled phase II study of subjects with bronchial asthma, urodilatin at various doses, alone or in combination with albuterol, improved bronchodilation parameters, including forced expiratory volume (FEV), maximum expiratory flow (MEF), and peak expiratory flow (PEF), and showed potential as an adjunct to β_2 -adrenergic agonists for asthma management.⁴⁹

Unlike ANP, urodilatin is more resistant to NEP degradation, probably because of the four additional amino acids at its N-terminal tail, and it seems to be cleared from circulation also by binding to NPR-C.⁵⁰ Infused urodilatin has a plasma half-life of approximately 5 to 24 minutes; with bolus injections, however, the half-life is shortened to 2 to 3 minutes.⁴⁸

C-Type Natriuretic Peptide

C-type natriuretic peptide is produced in endothelial cells, acts in a paracrine/autocrine manner, and is rapidly inactivated so that plasma measurements do not always reflect changes in CNP levels. C-type natriuretic peptide has been shown to regulate vascular tone and induce arterial vasodilation and relaxation. Its potency varies with the size of the blood vessel and the type of NP receptor expressed on the vessel. It is more potent than ANP in relaxing smooth muscle and likely plays a more important role in dilating blood vessel walls than in inducing diuresis or natriuresis.¹⁹

Infused CNP has been shown to lower blood pressure in animal models as well as in healthy human volunteers.¹⁸ C-type natriuretic peptide knockout mice, however, appear to compensate

with increased ANP production so that they are not hypertensive as expected; rather, they are mildly hypotensive. C-type natriuretic peptide also suppresses adrenocorticotrophic hormone (ACTH), vasopressin, and aldosterone synthesis.

C-type natriuretic peptide plays an important role in modulating vascular inflammation and in other vascular protective mechanisms (reviewed in Scotland et al.¹⁸). C-type natriuretic peptide production is stimulated by inflammatory cytokines such as IL-1 and TNF and by LPS; septic shock patients actually have significantly higher levels of circulating CNP. The antiinflammatory effect of CNP includes suppression of proinflammatory prostaglandin E₂ (PGE₂) production in isolated cells, reduced expression of vascular adhesion molecules, and inhibition of leukocyte migration, or “rolling.” Vascular protection by CNP may also involve its beneficial effects on the vascular endothelium and smooth muscle and inhibition of coagulation and thrombus formation.

Clinical Significance

Studies of NPs have significantly expanded our understanding of homeostatic mechanisms underlying fluid volume and pressure regulation. Alterations in circulating levels of the cardiac NPs have been used as diagnostic and prognostic markers in various cardiovascular conditions, such as CHF, hypertension, LV dysfunction, acute coronary syndromes, and aortic valve diseases^{2,51–53} (reviewed in D’Souza et al.⁴).

Natriuretic Peptides as Disease Indicators

Congestive Heart Failure

Increased mechanical strain in the atria and ventricles is a major stimulus for the synthesis and release of both ANP and BNP, resulting in a marked increase in ANP and BNP levels in circulation during the development of heart failure. Plasma ANP and BNP are negatively correlated with left ventricular ejection fraction (LVEF). Several studies have shown that plasma BNP, as well as the N-terminal pro-BNP fragment (NT-pro-BNP), may be a more powerful prognostic

indicator of development of LV systolic or diastolic dysfunction and LV hypertrophy than is ANP.^{2,17,51,52,54}

Rapid (15-minute) BNP immunofluorescence assays (Biosite Diagnostics, San Diego, CA, and Bayer Diagnostics, Tarrytown, NY) are currently approved as a tool for the diagnosis and prognosis of patients with acute coronary syndromes, including acute decompensated heart failure. There is also an 18-minute electrochemiluminescence assay for NT-pro-BNP (Roche Diagnostics, GmbH, Basel, Switzerland). Although BNP testing does not replace echocardiography and a full cardiologic assessment and should be used only within the clinical context, heart failure appears more likely with plasma BNP concentrations above 100 pg/mL.^{51,52} At or above this level (100 pg/mL), BNP was more accurate than the National Health and Nutrition Examination Survey (NHANES) and Framingham criteria in diagnosing heart failure.⁵⁴ The ratio of plasma ANP to plasma BNP is significantly higher in patients with obstructive airway disease than in those who have heart failure, perhaps because of increased right atrial pressures secondary to severe primary lung disease.^{4,55}

Serum BNP levels are useful guides for risk stratification for predicting mortality and for designing heart failure treatment regimens by titrating doses of standard medications to a desired BNP level.⁵⁶ The BNP levels rise in direct proportion to the severity of symptoms and cardiac damage, and BNP is an independent predictor of mortality in CHF patients. A pilot study of patients with decompensated heart failure has suggested that BNP concentration measured before discharge may help determine the risk of readmission within the month following discharge.⁵⁷

Because BNP concentration is a good indicator of elevated end-diastolic pressure and LV wall tension, which in turn closely correlates with dyspnea, it also correlates well with the New York Heart Association (NYHA) classification scheme. However, tests are currently in progress to evaluate the prognostic and diagnostic value of NT-pro-BNP, which may be a better indicator of abnormal cardiac function than BNP itself in NYHA class I and II patients. In NYHA class III and IV patients, sensitivity and specificity are

comparable. The NT-pro-BNP levels may also be more tightly linked to renal function, and negative predictive values for NT-pro-BNP are >95%.⁵⁴ The diagnostic value of NT-pro-BNP, however, depends on the patient's age, because NT-pro-BNP levels change with age and declining GFR (the cutoff for detecting CHF rises sharply from 125 pg/mL to 450 pg/mL after age 75), and there is a gray period coinciding with the peak incidence of CHF between 65 and 85 years of age when NT-pro-BNP is of little use to the clinician. Clearly, further research is required to determine how NT-pro-BNP measurements can be best applied in cardiovascular and cardiorenal management.

Acute Myocardial Infarction

Acute myocardial infarction is associated with compensatory activation of the RAAS and sympathetic nervous system, a low to moderate rise in ANP, and a 100-fold increase in plasma BNP via rapid synthesis in infarcted and periinfarcted areas. The ANP and BNP levels correlate with pulmonary capillary wedge pressure (PCWP), but BNP levels at 72 hours correlate inversely with the cardiac index (CI) and LVEF at day 5 and month 3 post-MI.⁴ Although BNP gene expression and de novo synthesis occur rapidly in both ventricles, ANP is secreted from storage in the atrium, further indicating distinct pathologic roles for ANP and BNP in AMI.

Myocardial Ischemia and Coronary Artery Disease

In vivo models of experimental ischemia have shown that even brief periods of hypoxia generated by coronary artery occlusion trigger the rapid release of both ANP and BNP without any correlation to myocardial wall stress. In patients undergoing percutaneous transluminal coronary angioplasty (PTCA), inflation of the PTCA balloon induces transient myocardial ischemia, followed immediately by a rapid and transient increase in plasma BNP levels. However, no correlation was found between the magnitude of increase in BNP levels and the duration of myocardial ischemia from this procedure. The ANP levels also increased slightly after balloon inflation. Plasma BNP and pro-BNP levels are also elevated in patients with

chronic coronary artery disease CAD without LV dysfunction.⁵⁸

Natriuretic Peptides as Therapeutic Agents in Acute Heart Failure Syndrome

Acute heart failure syndrome (AHFS) comprises a set of severe, life-threatening symptoms resulting from congestion or fluid retention in the lungs and inadequate perfusion of tissues and organs.⁵⁹ Specific signs and symptoms of AHFS include dyspnea or orthopnea, fatigue, pulmonary congestion, rales, coughing, cachexia, peripheral edema, hypoperfusion, and jugular vein distention. Patients with AHFS may not have any previously known cardiac dysfunction but may suffer from symptoms following an acute coronary event such as a myocardial infarction (new-onset AHFS), or they may experience acute decompensation of chronic heart failure.⁶⁰

Current Therapy of Acute Heart Failure Syndrome

The goals of AHFS therapy are (1) to improve clinical symptoms and hemodynamics without increasing the risk of short- and long-term mortality, (2) to preserve or improve renal function, and (3) to minimize myocardial damage. Current treatment strategies focus on rapidly improving hemodynamics and relieving congestion by reducing fluid volume with diuretics; increasing contractility and cardiac output with digoxin and inodilators such as dobutamine, dopamine, and milrinone; and enhancing pulmonary and peripheral circulation with vasodilators such as nitroglycerin and angiotensin-converting enzyme (ACE) inhibitors such as lisinopril and enalapril.

Current therapies have limitations, however. Controlled clinical trials have shown that hemodynamic improvements observed with AHFS interventions do not translate into long-term patient benefit, with most resulting in minimal or no benefit, some deleterious effects, or high mortality rates. For instance, vasodilators generally used when hypoperfusion is accompanied by con-

gestion, normal or high blood pressure, and insufficient response to diuretics alone can also cause hypotension and induce tolerance with prolonged use. High-dose diuretics are associated with increased risk of renal deterioration and neurohormonal activation of the angiotensin-aldosterone and sympathetic nervous systems, perhaps affecting long-term outcomes such as mortality.⁶¹ Some inodilators such as dobutamine and milrinone may increase the risk of ventricular arrhythmias, postdischarge morbidity, and mortality.^{61,62} Digoxin increases cardiac contractility and improves symptoms with possible a reduction in the number of hospitalizations, but its long-term clinical outcomes are neutral at best.⁶³ Therefore, new therapeutic approaches that improve short-term outcomes without negatively affecting renal and cardiac function and long-term survival are desired.

Newer therapies include levosimendan, an inotropic, Ca^{2+} -sensitizing, K^+ channel opener with antiischemic and anti-stunning effects that increases myocardial contraction without increasing myocardial oxygen consumption, and tolvaptan, a vasopressin V2-receptor antagonist that increases urine volume and serum sodium with little or no sodium loss (reviewed in Gheorghiade et al.⁶⁴). Levosimendan is well tolerated. Most common adverse effects include headache, hypotension, nausea, and dizziness believed to be secondary to its vasodilatory effects and slight reductions in red blood cell count, hemoglobin, and serum potassium, but no proarrhythmic effects.^{65,66} However, a multicenter randomized trial (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support [SURVIVE]) evaluating its efficacy in improving survival in AHFS patients showed no significant reduction in mortality when compared with dobutamine.⁶⁷

Natriuretic Peptide Therapy for Acute Heart Failure Syndrome

Three natriuretic peptide agents are currently approved or undergoing development for the management of acute heart failure (Table 56.1). Carperitide and ularitide are synthetic analogues of ANP and urodilatin, respectively, and nesiritide is a recombinant form of human BNP. All three

TABLE 56.1. Characteristics of therapeutic natriuretic peptides

	Carperitide	Nesiritide	Ularitide
Peptide analogue	ANP _{99–126}	BNP _{77–108}	Urodilatin (ANP _{95–126})
Source	Synthetic	Recombinant	Synthetic
Development phase	Approved in Japan for acute heart failure	Approved in the U.S. for ADHF	Phase II–III
Secreted by	Atrial and ventricular myocytes	Ventricular myocytes	Renal tubular cells
Stimulus for secretion	↑ Blood pressure, venous volume; atrial wall stretching	↑ Blood pressure, venous volume; ventricular wall stretching	↑ Plasma Na ⁺ ; ↑ blood pressure
Receptor	NPR-A, NPR-C	NPR-A, NPR-C	NPR-A, NPR-C
Plasma half-life	2–5 min	18–23 min	2–24 min
Sensitivity to NEP	Yes	Yes	Yes, but less than ANP
Physiologic targets	Vascular wall endothelium and smooth muscle	Vascular-wall endothelium and smooth muscle	Collecting ducts
Pharmacologic effects: mechanism of action	↓ Na ⁺ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; predominantly venous vasodilation; bronchodilation	↓ Na ⁺ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; vasodilation; bronchodilation	↓ Na ⁺ reabsorption, ↓ renal perfusion rate; ↑ GFR; ↓ RAAS; vasodilation; bronchodilation
Clinical effects in ADHF patients	↓ PCWP, LVFP; ↑ CI	↓ PCWP and systemic arterial pressure; relief from dyspnea	↓ PCWP, PAP, and SVR; ↑ CI; ↑ relief from dyspnea
Adverse effects	Hypotension; renal dysfunction	Hypotension; renal dysfunction (azotemia, ↑ serum creatinine); potential ↑ mortality	Sweating; hypotension; nausea; dizziness; bradycardia

ADHF, acute decompensated heart failure; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; LVFP, left ventricular filling pressure; NPR-A and NPR-C, natriuretic peptide receptor-A and -C; CI, cardiac index; RAAS, renin-angiotensin-aldosterone system; GFR, glomerular filtration rate; NEP, neutral endopeptidase; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

restore hemodynamic balance and improve cardiac or renal function in patients experiencing AHFS.

Carperitide (Synthetic Atrial Natriuretic Peptide)

Carperitide is a synthetic form of human ANP that was approved for use in Japan in 1995 for the management of acute heart failure (AHF). In a 6-year open-label study of 3777 patients with AHF treated with 0.085 µg/kg/min carperitide for 65 hours, 82% of patients experienced clinical improvement in terms of severity of Killip classification and renal dysfunction.⁶⁸ A much smaller, earlier study in patients who had severe heart failure with AMI also demonstrated a decrease in PCWP by almost 50% (21 to 11 mm Hg) and plasma aldosterone from 148 to 56 pg/mL after carperitide infusion (0.05 to 1.0 µg/kg/min) without altering heart rate and systemic blood pressure.⁶⁹

Studies on the effect of ANP infusion in CHF patients vary widely in design, patient population, and type of ANP analogue used, making interpretation difficult.¹⁴ They all show an invariable reduction in cardiac filling pressure, however,

that occurs too early to be due to a fluid shift or changes in diuresis and pulmonary or peripheral vascular resistance and has been attributed to ANP-induced venous vasodilation. This reinforces the concept of ANP as a vasodilator on veins rather than arteries in patients with high PCWP and plasma noradrenaline.⁷⁰

Nesiritide (Recombinant Brain Natriuretic Peptide)

Nesiritide (Natrecor®) is a recombinant human B-type natriuretic peptide (hBNP) that was approved in the United States in 2001 for the treatment of AHFS patients with dyspnea at rest or minimal activity. The recommended dose is an intravenous bolus of 2 µg/kg followed by a continuous infusion of 0.01 µg/kg/min. Nesiritide improves short-term dyspnea and produces dose-dependent reductions in PCWP and systemic arterial pressure in patients with heart failure.⁷¹ In clinical trials, the decrease in PCWP was observed within 15 minutes of the start of administration, and most of the effect was achieved at 60 minutes of the infusion.

Unlike dobutamine, nesiritide did not cause ventricular or supraventricular arrhythmias in patients with decompensated heart failure, and it actually reduced ventricular ectopy or had a neutral effect (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natreacor Therapy [PRECEDENT] study).⁷² Urine output (mean change in volume status) during the first 24 hours of nesiritide infusion did not differ from that obtained with nitroglycerin treatment. Nesiritide may also cause hypotension (Vasodilation in the Management of Acute Congestive Heart Failure [VMAC] study).⁷³ The VMAC study also showed that relief from dyspnea was indeed reduced by nesiritide treatment but at levels not significantly different from the reduction caused by the relatively low dose of nitroglycerin used for comparison.

Controversy remains, however, as to whether nesiritide is associated with a significantly increased risk of worsening renal function and death after treatment.^{74,75} This finding was based on meta-analyses of all available randomized clinical trials evaluating nesiritide in acute decompensated heart failure. Its use has not translated into long-term improvement in clinical outcome.⁷³

Ularitide

Ularitide is a synthetic version of urodilatin that is currently under clinical development for the treatment of AHFS. Ularitide has the same ANP₉₅₋₁₂₆ amino acid sequence as urodilatin. Like urodilatin, the synthetic version ularitide also binds to NPR-A receptors. Maximum concentration is reached 1.5 to 2 hours after the start of infusion. Various studies have reported a half-life range of 2 to 24 minutes.^{48,76,77}

The primary pharmacodynamic effects of ularitide are preload and afterload reduction due to vasodilation of peripheral veins and arteries and increased diuresis and natriuresis at higher doses, lowering blood pressure. These effects result from its direct action on vascular smooth-muscle cells, causing dilation of renal, pulmonary, and coronary arterial vessels, and from inhibition of sodium reabsorption in the renal tubules. Ularitide activity is largely mediated by binding to NPR-A receptors, leading to increased intra-

cellular cGMP levels. Consistent with this mode of action, dose-dependent ularitide-induced increases in plasma cGMP levels have been observed in both healthy subjects and subjects with AHFS.⁷⁸

Ularitide restores fluid hemostasis by inducing diuresis and natriuresis, and vasodilation. In healthy volunteers, ularitide increased the renal filtration fraction by increasing GFR and reducing the effective renal plasma flow, and it increased the fractional excretion of sodium and the rate of urinary sodium excretion.⁴⁸ Additionally, administration of ularitide in healthy subjects at dosages up to 20 ng/kg/min leads to a decrease in plasma concentrations of renin, aldosterone, and angiotensin II, suggesting that ularitide may also have a downregulating effect on the RAAS that inhibits aldosterone secretion from the adrenal cortex.^{47,48} Ularitide infusion into healthy volunteers also led to reduced cardiac preload, pulmonary arterial pressure (PAP) and PCWP, increased CI, and reduced systemic vascular resistance (SVR).⁷⁹ These mechanisms suggest that ularitide may provide a potential benefit to patients with AHF characterized by elevated left and right ventricular filling pressures and neuroendocrine activation.

The clinical efficacy of ularitide in patients with ADHF was evaluated in SIRIUS II, a parallel-dose, placebo-controlled, double-blinded study in 221 patients randomized to placebo or one of three ularitide dosing arms. Ularitide was administered by 24-hour intravenous infusions at 7.5, 15, or 30 ng/kg/min. Compared with placebo for change from baseline to +6 hours, all three ularitide doses were associated with significantly greater reductions in the co-primary efficacy end point of mean PCWP. Dyspnea at 6 hours (the second of two co-primary end points) was rated moderately or markedly improved by a greater percentage of subjects in each ularitide dose group than in the placebo group.⁸⁰

Adverse effects of ularitide include increased sweating, nausea, dizziness, and hypotension (decreased blood pressure) with infusions of 5 ng/kg/min or greater. In the studies where these were observed, all side effects resolved without vasoconstrictor treatment. No apparent worsening of renal function was observed through 72 hours in the SIRIUS II study.

Conclusion

Natriuretic peptides are a family of peptide hormones with distinct biomolecular properties and clinical effects that have been well studied as a treatment modality for AHFS. Structurally, each has a 17-amino-acid loop differing in up to five positions among the different natriuretic peptides.

The vasodilators nesiritide and carperitide have been approved in the United States and Japan, respectively, for acute heart failure. The natural analogues of carperitide and nesiritide (ANP and BNP) are both produced by the atria and ventricles of the heart in response to increased blood pressure and stretching of the cardiac wall and generally cause vasodilation, RAAS inhibition, and reduction in blood pressure without affecting fluid volume. Plasma BNP has also been used as a diagnostic or prognostic marker for acute and chronic cardiac syndromes.

Ularitide, a synthetic form of the renal NP urodilatin, is currently undergoing clinical development. In contrast to the other peptides, urodilatin (ularitide), is produced in the kidney and acts in a paracrine fashion on collecting ducts, resulting in reduced Na^+ reabsorption and thereby increased natriuresis and diuresis. Intravenously applied ularitide also causes vasodilation, reduction in blood pressure, and bronchodilation.

Because of the capacity of the natriuretic peptides to restore hemodynamic balance and fluid homeostasis, they hold promise in the management of cardiopulmonary and renal symptoms of AHFS, although further studies are required to understand more completely their impacts on short- and long-term morbidity and mortality in AHFS patients.

References

1. Silver MA. The natriuretic peptide system: kidney and cardiovascular effects. *Curr. Opin. Nephrol. Hypertens.* 2006;15:14–21.
2. Stoupakis G, Klapholz M. Natriuretic peptides: biochemistry, physiology, and therapeutic role in heart failure. *Heart Dis.* 2003;5:215–23.
3. Saito Y, Nakao K, Arai H, et al. Augmented expression of atrial natriuretic polypeptide gene in ventricle of human failing heart. *J. Clin. Invest.* 1989;83:298–305.
4. D'Souza SP, Davis M, Baxter GF. Autocrine and paracrine actions of natriuretic peptides in the heart. *Pharmacol. Ther.* 2004;101:113–29.
5. Carstens J, Jensen KT, Pedersen EB. Effect of urodilatin infusion on renal haemodynamics, tubular function and vasoactive hormones. *Clin. Sci. (Lond.)* 1997;92:397–407.
6. Forssmann W, Meyer M, Forssmann K. The renal urodilatin system: clinical implications. *Cardiovasc. Res.* 2001;51:450–62.
7. Heer M, Drummer C, Baisch F, Gerzer R. Long-term elevations of dietary sodium produce parallel increases in the renal excretion of urodilatin and sodium. *Pflugers Arch.* 1993;425:390–94.
8. Meyer M, Richter R, Brunkhorst R, Wrenger E, et al. Urodilatin is involved in sodium homeostasis and exerts sodium-state-dependent natriuretic and diuretic effects. *Am. J. Physiol.* 1996;271(3 Pt 2):F489–97.
9. Drummer C, Fiedler F, König A, Gerzer R. Urodilatin, a kidney-derived natriuretic factor, is excreted with a circadian rhythm and is stimulated by saline infusion in man. *J. Am. Soc. Nephrol.* 1991;1:1109–13.
10. Drummer C, Kentsch M, Otter W, Heer M, Herten M, Gerzer R. Increased renal natriuretic peptide (urodilatin) excretion in heart failure patients. *Eur. J. Med. Res.* 1997;2:347–54.
11. Nakamura S, Naruse M, Naruse K, et al. Atrial natriuretic peptide and brain natriuretic peptide coexist in the secretory granules of human cardiac myocytes. *Am. J. Hypertens.* 1991;4:909–12.
12. Ogawa Y, Nakao K, Mukoyama M, et al. Natriuretic peptides as cardiac hormones in normotensive and spontaneously hypertensive rats. The ventricle is a major site of synthesis and secretion of brain natriuretic peptide. *Circ. Res.* 1991;69:491–500.
13. Hino J, Tateyama H, Minamino N, Kangawa K, Matsuo H. Isolation and identification of human brain natriuretic peptides in cardiac atrium. *Biochem. Biophys. Res. Commun.* 1990;167:693–700.
14. Schmitt M, Cockcroft JR, Frenneaux MP. Modulation of the natriuretic peptide system in heart failure: from bench to bedside? *Clin. Sci. (Lond.)* 2003;105:141–60.
15. Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. *Circulation* 1995;92:1558–64.
16. Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte

- hypertrophy. Evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. *J. Clin. Invest.* 1995;96:1280–87.
17. Boomsma F, van den Meiracker AH. Plasma A- and B-type natriuretic peptides: physiology, methodology and clinical use. *Cardiovasc. Res.* 2001;51:442–49.
 18. Scotland RS, Ahluwalia A, Hobbs AJ. C-type natriuretic peptide in vascular physiology and disease. *Pharmacol. Ther.* 2005;105:85–93.
 19. Sudoh T, Minamino N, Kangawa K, Matsuo H. C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. *Biochem. Biophys. Res. Commun.* 1990;168:863–70.
 20. Porter JG, Arfsten A, Fuller F, Miller JA, Gregory LC, Lewicki JA. Isolation and functional expression of the human atrial natriuretic peptide clearance receptor cDNA. *Biochem. Biophys. Res. Commun.* 1990;171:796–803.
 21. Shima M, Seino Y, Torikai S, Imai M. Intrarenal localization of degradation of atrial natriuretic peptide in isolated glomeruli and cortical nephron segments. *Life. Sci.* 1988;43:357–63.
 22. Bennett BD, Bennett GL, Vitangcol RV, et al. Extracellular domain-IgG fusion proteins for three human natriuretic peptide receptors. Hormone pharmacology and application to solid phase screening of synthetic peptide antisera. *J. Biol. Chem.* 1991;266:23060–7.
 23. Mukoyama M, Nakao K, Hosoda K, et al. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J. Clin. Invest.* 1991;87:1402–12.
 24. Ferrari R, Agnoletti G. Atrial natriuretic peptide: its mechanism of release from the atrium. *Int. J. Cardiol.* 1989;24:137–49.
 25. Gardner DG, Newman ED, Nakamura KK, Nguyen KP. Endothelin increases the synthesis and secretion of atrial natriuretic peptide in neonatal rat cardiocytes. *Am. J. Physiol.* 1991;261:E177–82.
 26. de Bold AJ, Bruneau BG, Kuroski de Bold ML. Mechanical and neuroendocrine regulation of the endocrine heart. *Cardiovasc. Res.* 1996;31:7–18.
 27. Bruneau BG, de Bold AJ. Selective changes in natriuretic peptide and early response gene expression in isolated rat atria following stimulation by stretch or endothelin-1. *Cardiovasc. Res.* 1994;28:1519–25.
 28. Ruskoaho H, Vakkuri O, Arjamaa O, Vuolteenaho O, Leppaluoto J. Pressor hormones regulate atrial stretch-induced release of atrial natriuretic peptide in the pithed rat. *Circ. Res.* 1989;64:482–92.
 29. Atlas SA, Maack T. Effects of atrial natriuretic factor on the kidney and the renin-angiotensin-aldosterone system. *Endocrinol. Metab. Clin. North Am.* 1987;16:107–43.
 30. Cody RJ, Atlas SA, Laragh JH, et al. Atrial natriuretic factor in normal subjects and heart failure patients. Plasma levels and renal, hormonal, and hemodynamic responses to peptide infusion. *J. Clin. Invest.* 1986;78:1362–74.
 31. de ZD, Janssen WM, de Jong PE. Atrial natriuretic factor: its (patho)physiological significance in humans. *Kidney. Int.* 1992;41:1115–33.
 32. Hobbs RE, Miller LW, Bott-Silverman C, James KB, Rincon G, Grossbard EB. Hemodynamic effects of a single intravenous injection of synthetic human brain natriuretic peptide in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am. J. Cardiol.* 1996;78:896–901.
 33. Janssen WM, de Zeeuw D, van der Hem GK, de Jong PE. Antihypertensive effect of a 5-day infusion of atrial natriuretic factor in humans. *Hypertension* 1989;13:640–6.
 34. Jensen KT, Carstens J, Pedersen EB. Effect of BNP on renal hemodynamics, tubular function and vasoactive hormones in humans. *Am. J. Physiol.* 1998;274:F63–72.
 35. Meyer M, Richter R, Brunkhorst R, et al. Urodilatin is involved in sodium homeostasis and exerts sodium-state-dependent natriuretic and diuretic effects. *Am. J. Physiol.* 1996;271:F489–97.
 36. van der Zander K, Houben AJ, Hofstra L, Kroon AA, de Leeuw PW. Hemodynamic and renal effects of low-dose brain natriuretic peptide infusion in humans: a randomized, placebo-controlled crossover study. *Am. J. Physiol. Heart. Circ. Physiol.* 2003;285:H1206–12.
 37. Adachi H, Tomoike H, Nishijima H, Egashira S, Nakamura M. Sustained dilatation of large coronary artery by alpha-human atrial natriuretic peptide in conscious dogs: a comparison with nitroglycerin. *Eur. J. Pharmacol.* 1989;161:189–96.
 38. Ishihara T, Aisaka K, Hattori K, et al. Vasodilatory and diuretic actions of alpha-human atrial natriuretic polypeptide alpha-hANP. *Life. Sci.* 1985;36:1205–15.
 39. D'Souza SP, Yellon DM, Martin C, et al. B-type natriuretic peptide limits infarct size in rat isolated hearts via KATP channel opening. *Am. J. Physiol. Heart Circ. Physiol.* 2003;284:H1592–600.
 40. Okumura K, Yasue H, Fujii H, et al. Effects of brain (B-type) natriuretic peptide on coronary artery

- diameter and coronary hemodynamic variables in humans: comparison with effects on systemic hemodynamic variables. *J. Am. Coll. Cardiol.* 1995;25:342–8.
41. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N. Engl. J. Med* 1998;339:321–8.
42. Riegger G, Elsner D, Forssmann WG, Kromer EP. Effects of ANP-(95–126) in dogs before and after induction of heart failure. *Am. J. Physiol.* 1990;259:H1643–8.
43. Schulz-Knappe P, Honrath U, Forssmann WG, Sonnenberg H. Endogenous natriuretic peptides: effect on collecting duct function in rat kidney. *Am. J. Physiol.* 1990;259:F415–8.
44. Gagelmann M, Hock D, Forssmann WG. Urodilatin (CDD/ANP-95–126) is not biologically inactivated by a peptidase from dog kidney cortex membranes in contrast to atrial natriuretic peptide/cardiodilatin (alpha-hANP/CDD-99–126). *FEBS Lett.* 1988;233:249–54.
45. Endlich K, Steinhausen M. Natriuretic peptide receptors mediate different responses in rat renal microvessels. *Kidney Int.* 1997;52:202–7.
46. Schramm L, Heidbreder E, Lukes M, et al. Endotoxin-induced acute renal failure in the rat: effects of urodilatin and diltiazem on renal function. *Clin. Nephrol.* 1996;46:117–24.
47. Bestle MH, Olsen NV, Christensen P, Jensen BV, Bie P. Cardiovascular, endocrine, and renal effects of urodilatin in normal humans. *Am. J. Physiol.* 1999;276:R684–95.
48. Carstens J, Jensen KT, Pedersen EB. Metabolism and action of urodilatin infusion in healthy volunteers. *Clin. Pharmacol. Ther.* 1998;64:73–86.
49. Fluge T, Forssmann WG, Kunkel G, et al. Bronchodilation using combined urodilatin-albuterol administration in asthma: a randomized, double-blind, placebo-controlled trial. *Eur. J. Med. Res.* 1999;4:411–5.
50. Abassi ZA, Tate J, Hunsberger S, Klein H, Trachewsky D, Keiser HR. Pharmacokinetics of ANF and urodilatin during cANF receptor blockade and neutral endopeptidase inhibition. *Am. J. Physiol.* 1992;263:E870–6.
51. Cowie MR, Jourdain P, Maisel A, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur. Heart J.* 2003;24:1710–8.
52. McCullough PA, Omland T, Maisel AS. B-type natriuretic peptides: a diagnostic breakthrough for clinicians. *Rev. Cardiovasc. Med.* 2003;4:72–80.
53. Suttner SW, Boldt J. Natriuretic peptide system: physiology and clinical utility. *Curr. Opin. Crit Care* 2004;10:336–41.
54. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N. Engl. J. Med.* 2002;347:161–7.
55. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;343:440–4.
56. Yu CM, Sanderson JE. Plasma brain natriuretic peptide—an independent predictor of cardiovascular mortality in acute heart failure. *Eur. J. Heart Fail.* 1999;1:59–65.
57. Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J. Am. Coll. Cardiol.* 2001;37:386–91.
58. Goetze JP, Christoffersen C, Perko M, et al. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J.* 2003;17:1105–7.
59. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult. *Circulation.* 2005 20;112(12):e154–235.
60. Gheorghiade M, Mebazaa A. Introduction to acute heart failure syndromes. *Am. J. Cardiol.* 2005a;96:1G–4G.
61. Gheorghiade M, Mebazaa A. The challenge of acute heart failure syndromes. *Am. J. Cardiol.* 2005b;96:86G–9G.
62. Bayram M, De LL, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am. J. Cardiol.* 2005;96:47G–58G.
63. Stough WG, O'Connor CM, Gheorghiade M. Overview of current noninodilator therapies for acute heart failure syndromes. *Am. J. Cardiol.* 2005; 96:41G–6G.
64. Gheorghiade M, Teerlink JR, Mebazaa A. Pharmacology of new agents for acute heart failure syndromes. *Am. J. Cardiol.* 2005;96:68G–73G.
65. Follath F, Franco F, Cardoso JS. European experience on the practical use of levosimendan in patients with acute heart failure syndromes. *Am J. Cardiol.* 2005;96:80G–5G.
66. Mebazaa A, Barraud D, Welschbillig S. Randomized clinical trials with levosimendan. *Am. J. Cardiol.* 2005;96:74G–9G.
67. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Pöder P, Kivikko M; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA.* 2007;297(17):1883–91.

68. Suwa M, Seino Y, Nomachi Y, Matsuki S, Funahashi K. Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the "real world" of therapy. *Circ.* 2005; J. 69:283–90.
69. Kikuchi M, Nakamura M, Suzuki T, Sato M, Takino T, Hiramori K. Usefulness of carperitide for the treatment of refractory heart failure due to severe acute myocardial infarction. *Jpn. Heart.* 2001;J 42:271–80.
70. Schmitt M, Gunaruwan P, Payne N, et al. Effects of exogenous and endogenous natriuretic peptides on forearm vascular function in chronic heart failure. *Arterioscler. Thromb. Vasc. Biol.* 2004;24:911–7.
71. Scios, Inc. Nesiritide prescribing information. April 2005.
72. Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. *Am. Heart J.* 2002;144:1102–8.
73. Publication Committee for the VMAC Investigators Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA.* 2002;287:1531–40.
74. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005b;111:1487–91.
75. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA.* 2005a;293:1900–5.
76. Elsner D, Muders F, Muntze A, Kromer EP, Forssmann WG, Riegger GA. Efficacy of prolonged infusion of urodilatin [ANP-(95–126)] in patients with congestive heart failure. *Am. Heart J.* 1995; 129:766–73.
77. Kentsch M, Ludwig D, Drummer C, Gerzer R, Muller-Esch G. Haemodynamic and renal effects of urodilatin bolus injections in patients with congestive heart failure. *Eur. J. Clin. Invest* 1992a; 22:662–9.
78. Mitrovic V, Luss H, Nitsche K, et al. Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: a double-blind, placebo-controlled, ascending-dose trial. *Am. Heart J.* 2005a;150:1239.
79. Kentsch M, Ludwig D, Drummer C, Gerzer R, Muller-Esch G. Haemodynamic and renal effects of urodilatin in healthy volunteers. *Eur. J. Clin. Invest.* 1992b;22:319–25.
80. Mitrovic V, Seferovic P, Simeunovic, D, et al. A randomized, double-blind, placebo-controlled phase II study of ularitide in patients with decompensated congestive heart failure. *J. Card. Fail.* 2005b;11:S151.

Index

- A**
- Abciximab (ReoPro®), 641
- ACC. *See* American College of Cardiology
- Accelerated idioventricular rhythm (AIVR), 221
- ACD. *See* Active compression decompression
- ACE. *See* Angiotensin-converting enzyme
- ACEIs. *See* Angiotensin-converting enzyme inhibitors
- Acetazolamide, 366
- Acetylcholines, 821–822
- N*-Acetylcysteine (NAC), 121, 766
- Acid-base(s), arterial blood gas and
assessments of, 463–465
balance of, 457–458, 465–466
disturbances of, 461–463, 466
- Acidosis
lactic, 461–462
metabolic, 461, 463
respiratory, 461, 463
- Acinetobacter baumannii*, 253
- ACP. *See* Acute cor pulmonale
- Acromegaly
clinical presentations of, 291
definition of, 291
diagnosis of, 291
epidemiology of, 291
treatments for, 291
- ACS. *See* Acute coronary syndrome
- ACTH. *See* Adrenal tumors, excessive corticotropin
- Active compression decompression (ACD), 810–812, 813
- Acute coronary syndrome (ACS), 782–783
- AHF and, 202
- cardiac catheterization and, 170–171, 186
- classifications of, 171–172, 885–890
- clinical evaluation of, 170
- clinical scenarios associated with, 177–180
- coronary angiography of, 170–171, 186, 208
- hemodynamic monitoring of, 170, 171
- incidence/prognosis for, 168, 169
- pathophysiology of, 168–170
- treatments for, 172–177, 180
- ventilatory assistance for, 177
- levosimendan and, 176
- milrinone and, 174, 175–176
- Acute cor pulmonale (ACP), 66, 239
- Acute decompensated heart failure (ADHF), 371–374
- biomarkers and, 23–24
- diagnosis of, 23
- echocardiography and, 24–25, 28
- epidemiology of, 20–23
- management of, 25–26
- nitrates in
clinical trials of, 546–547
doses, 546–547
effects of, 545–546, 547
- therapies for, 26
- Acute Decompensated Heart Failure National Registry. *See* ADHERE
- Acute heart failure (AHF), 5, 13, 19
- ACS and
cardiac catheterization and, 170–171, 186
- classifications of, 171–172, 885–890
- clinical evaluation of, 170
- clinical scenarios associated with, 177–180
- coronary angiography of, 170–171, 186, 208
- hemodynamic monitoring of, 170, 171
- incidence/prognosis for, 168, 169
- pathophysiology of, 168–170
- treatments for, 172–177, 180
- ventilatory assistance for, 177
- amyloidosis and
other forms of, 315–316
- primary, 314–315
- prognosis for, 316
- antithrombotics and
case study on, 649
- conclusions on, 649–650
- management of, 644–649
- therapies for, 639–643
- thrombogenesis and, 643
- APS and, 307–308
- arrhythmias in
case presentation for, 231–232
- conclusions on, 232
- mechanisms of, 224–227
- outcome of, 224
- supraventricular, 221
- treatments for, 227–231
- ventricular, 221–224, 229–230

- Acute heart failure (AHF) (*cont.*)
 in Asia-Pacific region
 conclusions of, 25–27
 CVDs and, 20–21
 diagnosis of, 23
 epidemiology of, 20–23
 management of, 25–26
 BNP testing of, 468–469
 brain protection
 clinical case of, 700–702
 conclusions on, 702
 hypothermia and, 692–698
 pathophysiology of, 692
 treatments for, 699–700
 CAPL and, 308–309
 CHF and
 biomarkers and, 540–542
 clinical/therapeutic patterns
 for, 536–540
 conclusions on, 542
 signs/symptoms of, 540–542
 trends/treatments for,
 533–536
 clinical presentations of, 13,
 14–15
 coronary angiography
 cardiogenic shock and,
 451–452
 non-STEMI elevation and,
 453
 PCI and, 452–453
 STEMI elevation and, 451–452
 de novo, 14
 etiology/types of, 13–14
 hemochromatosis and, 317–318
 HES and, 312
 HLA and, 316–317
 immune system alterations in
 cellular/humoral responses
 and, 140–142
 humoral inflammatory
 mediators and, 137–138
 neurohormones/regulation of,
 136–137
 other humoral mediators and,
 138–140
 pathophysiology of, 134
 therapeutic implications for,
 142
 low-output, 679
 management of, 16
 MCTD and, 314
 mechanisms, 15
 mitochondria and
 conclusions on, 130
 functional improvement of,
 127–129
 involvement of, 126–127
 physiologic roles of, 124–126
 in postoperative period, 676
 conclusions on, 331
 definition/etiology of, 324
 diagnosis of, 324–325
 management of, 326–331
 monitoring of, 325–326
 mortality/prevalence of,
 323–324
 RA and, 309–310
 sarcoidosis and, 310–312
 SLE and, 306–307
 SSc and, 313–314
 systemic diseases and, 306–318
 Acute heart failure syndromes
 (AHFSs), 5, 6
 acromegaly and
 clinical presentations of, 291
 definition of, 291
 diagnosis of, 291
 epidemiology of, 291
 treatments for, 291
 analgesia for
 assessment of, 656–658
 clinical case of, 665–667
 complications of, 664–665
 conclusions on, 667
 medications, 658–664
 pain assessment and, 655–656
 arterial blood gas and
 acid-base assessments of,
 463–465
 acid-base balance and, 457–
 458, 465–466
 acid-base disturbances and,
 461–463, 466
 anion gap and, 458–459, 463,
 465
 BDE and, 458
 bicarbonate approach and,
 458
 clinical examples of, 460–461,
 464–466
 CO₂ and, 457
 conclusions on, 466
 gas exchange assessment of,
 456–457
 measurement/sampling of,
 455
 normal values of, 455, 456
 physiochemical approach to,
 459–460
 temperature correction of,
 455–456
 classifications of, 6
 clinical characteristics of
 hospitalized patients with,
 13, 14
 concepts
 new, 5–6
 old, 5
 conclusions on, 18–19
 Cushing's syndrome and
 clinical presentations of, 292
 definition of, 291–292
 diagnosis of, 292
 epidemiology of, 292
 treatments for, 292–293
 definitions of, 5, 6
 dobutamine and
 case study on, 567, 574
 clinical investigations/trials
 of, 569–572
 management of, 567
 mechanisms/metabolism of,
 567–569
 practical applications/
 considerations for, 572–574
 dopamine
 cardiovascular effects of, 579
 conclusions on, 580–581
 as modulator, 578–579
 pharmacology of, 577–578
 renal actions of, 579–580
 dyspnea and
 alternative diagnoses for,
 164–165
 conclusions on, 166–167
 probability of, 161–164
 echocardiography Doppler and,
 critically ill patients and,
 424–443
 economic consequences for, 18
 in elderly
 clinical case of, 375–376
 clinical features of, 373–374
 conclusions on, 376
 management of, 374–375
 pathophysiology of, 371–373
 endocrine disorders and,
 291–295
 endothelin receptor antagonists
 and, 626–627
 basis for, 628–629
 clinical studies of, 630–632
 clinical trials of, 632–634
 conclusions on, 634

- in preclinical studies, 629–630
 - euthyroid sick syndrome and, 294
- heart in, 5
- hyperparathyroidism and
 - causes of, 294
 - clinical presentations of, 294
 - definition of, 294
 - diagnosis of, 294
 - epidemiology of, 294
 - treatments for, 294
- hypocalcemia and
 - clinical presentations of, 295
 - definition of, 294
 - diagnosis of, 295
 - epidemiology of, 294
 - treatments for, 295
- hypothyroidism and
 - causes of, 293
 - clinical presentations of, 293
 - definition of, 293
 - diagnosis of, 294
 - epidemiology of, 293
 - treatments for, 294
- incidences of, 18
- inotropes in, 26
- in Latin America, 30
 - categories of, 30–31
 - Chagas disease and, 31–34
 - conclusions of, 36
 - DHF and, 30–31
 - management of, 31
- management of, 25–26
- in neonatal/pediatric
 - populations
 - clinical case of, 385–386
 - etiologies of, 379–383
 - features of, 378
 - presentation of, 379
 - prognosis for, 385
 - therapies for, 383–385
- NIV and, 26
 - BiPAP and, 477–480, 482
 - case report on, 482
 - contraindications for, 482
 - description of, 477–480
 - improvement mechanisms for, 480–481
 - PEEP and, 477–480, 482
 - side effects of, 482
 - uses of, 481–482
- nonthyroidal illness and, 294
- organ perfusion in
 - conclusions on, 153
 - impact of, 152–153
- models, 153
- neurohormonal pathways
 - and, 148–149
- regional circulations and, 150–152
- systemic, 148–149
- oxygen saturation
 - measurements in, 406–410
- pheochromocytoma and
 - clinical presentations of, 295
 - definition of, 295
 - diagnosis of, 295
 - epidemiology of, 295
 - treatments for, 295
- portable echocardiography and, 446–449
- risk models for, 7–12, 8, 9
 - clinical applicability of, 10–11
 - clinical management roles of, 11
 - conclusions on, 11–12
 - other, 9, 10
 - stratification, 7
- sedation for, 699
 - assessment of, 656–658
 - clinical case of, 665–667
 - complications of, 664–665
 - conclusions on, 667
 - medications, 658–664
 - pain assessment and, 655–656
- SRBDs and
 - clinical manifestations of, 361
 - conclusions on, 366
 - consequences of, 362–363
 - definitions of, 359–360
 - etiology of, 360
 - mechanisms of, 360–361
 - treatments for, 364–366
- β -thalassemia and
 - conclusions on, 304–305
 - factors linking, 301–303
 - pathophysiology of, 297–301
 - treatments/therapeutic considerations for, 303–304
- therapies for, 26
- Acute hypoxic hepatitis, 763
- Acute myocardial infarction (AMI), 121, 170, 613
 - complications, 674
 - effects on, 673
 - postmyocardial infarction, 678–679
 - STEMI and, 451–452
- Acute pericarditis
 - autoreactive, 248
- cardiac tamponade and
 - clinical picture of, 249–250
 - treatments for, 250
- causes of, 248
- clinical case on, 251–252
- clinical picture of, 247
- diagnosis of, 247–248
- treatments for, 248–249
- Acute respiratory distress
 - syndromes (ARDS), 66, 165
- Acute severe heart failure, 15
 - components of, 202
 - conclusions on, 205
 - definition of, 200
 - management of, 203–204, 212–214
 - minipumps and, 204–205
 - pathophysiology of, 201–203
 - ultrafiltration and, 204
 - vasopressors in
 - case study on, 589–591
 - clinical diagnosis of, 583–585
 - conclusions on, 591
 - as pharmacologic therapies, 586–587
 - specific, 587–589
 - as treatments, 585–586
- Acute severe pulmonary edema, 481–482
- Acute tubular necrosis (ATN), 580
- Adaptation to Intensive Care Environment (ATICE), 657, 658
- Adenosine, 77, 79, 276
- Adenosine diphosphate (ADP), 54, 79, 225
 - activation of, 126
 - consumption of, 124
 - increased, 115
- Adenosine triphosphatase (ATPase), 74, 75
 - inhibition of, 789
 - mitochondrial, 115
- Adenosine triphosphate (ATP), 54, 75
 - hydrolysis, 79
 - potassium, 595–596
- Adenylyl cyclase, 89
- ADH. *See* Alcohol dehydrogenase; Antidiuretic hormone
- ADHERE (Acute Decompensated Heart Failure National Registry), 9, 10, 11, 222, 371, 519

- α_1 -Adrenergic receptors (α_1 - ARs), 91
- Adrenal tumors, excessive corticotropin (ACTH), 291–292
- β -Adrenergic receptors (β - ARs), 90–91, 567
 - decreased, 149
 - effects of, 192
 - roles of, 140, 723–724
- Adrenoceptors, 25
- Advance care planning, 705
- AEDs. *See* Automated external defibrillators
- Agency for Health Care Policy and Research (AHCPR), 885
- Aggrastat®. *See* Tirofiban
- Aging, 19, 372, 538. *See also* Elderly
- Agitation, 656–657
- AHA. *See* American Heart Association
- AHCPR. *See* Agency for Health Care Policy and Research
- AHF. *See* Acute heart failure
- AHFSSs. *See* Acute heart failure syndromes
- AHI. *See* Apnea hypopnea index
- Airways, 475
- AIVR. *See* Accelerated idioventricular rhythm
- Alanine aminotransferase, 724
- Albumin, 327, 460, 878
- Alcohol, 48, 122, 275
- Alcohol dehydrogenase (ADH), 122
- Aldolase, 312
- Aldosterone, 192, 227
 - antagonists, 534
 - levels, 554
 - serum, 202
- Alkalosis
 - metabolic, 461–462, 463
 - respiratory, 461, 463
- American Association of Poison Control Centers Toxic Exposure Surveillance System, 348
- American College of Cardiology (ACC), 257, 279, 452, 886
- American College of Chest Physicians, 280
- American Diabetes Association, 782
- American Heart Association (AHA), 257, 452, 809, 886
- AMI. *See* Acute myocardial infarction
- 126-Amino acid preprohormone, 609–610
- Aminophyllines, 821–822
- Aminopyridine, 355
- Amiodarone, 228, 230, 276, 311, 821
- Amrinone, 174
- Amyloidosis
 - AA, 315–316
 - AHF and
 - other forms of, 315–316
 - primary, 314–315
 - prognosis for, 316
- Analgesia, for AHFSSs
 - assessment of, 656–658
 - clinical case of, 665–667
 - complications of, 664–665
 - conclusions on, 667
 - medications, 658–664
 - pain assessment and, 655–656
- Anclrod, 309
- Anemia, 540
 - CHF and
 - additive effects of, 523–524
 - conclusions on, 525–526
 - correcting, 522–523
 - roles of, 519–526
 - Cooley's, 297
 - exacerbation, 301–302
 - Mediterranean, 297
- Anesthesia
 - for AHFSSs
 - clinical case on, 727–728
 - conceptual framework on, 719–721
 - conclusions on, 728
 - diagnoses of, 724
 - hemodynamic stability and, 725–727
 - perioperative concerns/awareness during, 727
 - practical issues concerning, 721–724
 - treatment decisions on, 725
 - procedures, 725
- Ang II. *See* Angiotensin II
- Angiography, coronary, 170–171, 186, 208
 - in AHF
 - cardiogenic shock and, 451–452
 - non-STEMI elevation and, 453
 - PCI and, 452–453
 - STEMI elevation and, 451–452
 - cardiogenic shock and, 451–452
- Angiotensin-converting enzyme (ACE), 16, 94, 534
 - dosages, 192
 - oral, 180
 - reactions to, 191
- Angiotensin-converting enzyme inhibitors (ACEIs), 16, 136, 534
- Angiotensin II (Ang II), 89, 93–94, 202, 753
- Anion gap, 458–459, 463, 465
- Ankylosing spondylitis (AS), 316–317
- ANP. *See* Atrial natriuretic protein
- Antiarrhythmics Versus Implantable Defibrillators (AVID), 226
- Antidiuretic hormone (ADH), 787
- Antinuclear antibodies (ANA), 308
- Antioxidants
 - endogenous, 125
 - ROS and, 123
 - systems, 125
- Antiphospholipid (aPL), 307
- Antiphospholipid syndrome (APS), 307–308
- Antithrombotics, AHF and
 - case study on, 649
 - conclusions on, 649–650
 - management of, 644–649
 - therapies for, 639–643
 - thrombogenesis and, 643
- Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *See* ATACS
- Anxiety, 868–872
- Aortic pressure, 671
- Aortic valve stenosis (AVS), 272
 - rheumatic, 274
- APL. *See* Antiphospholipid
- Apnea hypopnea index (AHI), 359
- Apoptosis, 129
- APS. *See* Antiphospholipid syndrome
- ARA. *See* Arm muscle area
- ARDS. *See* Acute respiratory distress syndromes
- Arginine vasopressin, 621, 787–788
- Arm muscle area (ARA), 877, 878
- Arrhythmias, 78, 302–303, 383

- in AHF
 - case presentation for, 231–232
 - conclusions on, 232
 - mechanisms of, 224–227
 - outcome of, 224
 - supraventricular, 221
 - treatments for, 227–231
 - ventricular, 221–224, 229–230
- cardiac, 165
- pregnancy and, 275–277
- α_1 -ARs. *See* α_1 -Adrenergic receptors
- β -ARs. *See* β -Adrenergic receptors
- Arterial blood gas, AHFSs and
 - acid-base assessments of, 463–464
 - acid-base balance and, 457–458
 - acid-base disturbances and, 461–463
 - anion gap and, 458–459, 463, 465
 - BDE and, 458, 459–460
 - bicarbonate approach and, 458
 - clinical examples of, 460–461, 464–466
 - CO₂ and, 457
 - conclusions on, 466
 - gas exchange assessment of, 456–457
 - measurement/sampling of, 455
 - normal values of, 455, 456
 - physiochemical approach to, 459–460
 - temperature correction of, 455–456
- Arteriography, coronary, 16
- Arteriosclerotic heart disease (ASHD), 226
- AS. *See* Ankylosing spondylitis
- Ascorbic acid, 118, 125
- ASHD. *See* Arteriosclerotic heart disease
- Asia-Pacific region, AHF/CVDs in, 20–21
 - conclusions of, 25–27
 - diagnosis of, 23
 - epidemiology of, 20–23
 - management of, 25–26
- Aspartate aminotransferase (AST), 765
- Aspirin, 639, 645
 - low-dose, 574
 - uses of, 249, 275, 307
- AST. *See* Aspartate aminotransferase
- Asthma
 - acute, 163
 - history of, 163
- ATACS (Antithrombotic Therapy in Acute Coronary Syndromes Research Group), 645
- Atenolol, 276
- ATP. *See* Adenosine triphosphate
- ATPase. *See* Adenosine triphosphatase
- Atrial fibrillation (AF), 221, 228, 643
- Atrial flutter, 228–229
- Atrial natriuretic protein (ANP), 54, 113
- Atrioventricular block (AV), 35
- Atropine, 821–822
- Australia, 20, 21–23
- Autoaggravation, 67
- Autoimmune diseases, 134
- Automated external defibrillators (AEDs)
 - clinical case of, 833–834
 - conclusions on, 834
 - feasibility of, 830–831
 - key caveats of, 832
 - training and, 831–832
- AV. *See* Atrioventricular block
- AVID. *See* Antiarrhythmics Versus Implantable Defibrillators
- AVS. *See* Aortic valve stenosis
- Azathioprine, 190, 195, 276, 306
- B**
- Base deficit/excess (BDE), 458, 459–460
- BDE. *See* Base deficit/excess
- Benznidazole, 35
- Benzodiazepines, 657, 660–661, 665
- Beta-blockers, 16, 226, 275, 541
 - intravenous, 228
 - safety of, 336–337
 - uses for, 293
- Bi-level positive airway pressure (BiPAP), 26, 203, 327, 365
 - NIV and, 477–480, 482
- Bilirubin, 724
- Biomarkers, 10
 - of cardiac failure, 23
 - CHF and, 540–542
 - serum, 23
- Biomechanical stress, 113
- BiPAP. *See* Bi-level positive airway pressure
- Bisphosphonates, 292, 294
- Biventricular assist device (BVAD), 278
- Blood
 - donors, 32
 - flow, 391, 672–673
 - glucose, 700, 782–783
 - lymphocyte count, 877
 - mixed venous, 418
 - pressure, 9, 178, 585–586
 - systemic, 573
 - volume, pulmonary, 400
- Blood urea nitrogen (BUN), 7, 9, 10, 231
- BNP. *See* B-type natriuretic peptide
- Body weight (BW), 877, 878
- Bolus
 - injection studies, 602–603
 - plus-injection studies, 603
- Bosentan, oral, 630
- Bradyarrhythmias, 35, 228
- Brain, 151–152
 - natriuretic peptides, 609
- Brain protection
 - AHF and
 - clinical case of, 700–702
 - conclusions on, 702
 - pathophysiology of, 692
 - treatments for, 699–700
 - hypothermia and, 692–698, 841–842
- Brazil, 30, 31
- Breathing, 480
- Breathing Not Properly study, 165
- Brugada syndromes, 349, 351
- B-type natriuretic peptide (BNP), 10, 520, 753, 755–756
 - benefits of, 23–24, 34
 - levels of, 7, 163, 373–374
 - Nesiritide (Natrecor®) and, 755–756
 - production of, 113
 - roles of, 23, 102
 - serum, 54
 - testing
 - of AHF, 468–469
 - for diagnosis, 469–471
 - in ER/ICU, 468–472
- Buffers, 822
- Bumetanide, 204, 903, 906

- BUN. *See* Blood urea nitrogen
- BVAD. *See* Biventricular assist device
- BW. *See* Body weight
- C**
- CABG. *See* Coronary artery bypass graft
- CADs. *See* Coronary artery diseases
- Caffeine, 275
- Calcineurin, 98, 99
- Calcitonin, 113
- Calcium, 75–76, 102, 537, 822
channel blockers, 16, 228, 337
homeostasis, 74–76
metabolism of, 125, 128–129
pathways, 127
-sensitive signaling pathways, 99–100, 553, 595
types of, 294
- Calcium Sensitizer or Inotrope on
None in Low-Output Heart
Failure. *See* CASINO
- Calciuresis, 294
- CAMP. *See* Cyclic adenosine monophosphate
- CAP. *See* Community-acquired pneumonia
- CAPL
See Catastrophic
Antiphospholipid
syndrome
- CAPRICORN study (Carvedilol
Port Infarct Survival
Control in Left Ventricular
Dysfunction), 128
- Carbon dioxide (CO₂), 457, 699
- Cardiac allograft, 676–677
- Cardiac arrhythmias, 165
- Cardiac catheterization
ACS and, 170–171, 186
pericardial effusion and, 258–259
pericardial tamponade and, 258–259
- Cardiac diseases, in pregnancy
anesthesiologic management of, 282–283
approach to, 269–270
arrhythmias and, 275–277
cardiac surgery and, 280–281
cardiomyopathy and, 277–279
conclusions on, 283–284
- congenital heart diseases and, 270, 271–273
eclampsia and, 281–282
endocarditis prophylaxis and, 282
hypertensive crisis and, 282
ischemic heart diseases and, 274–275
management of, 270–271
prosthetic heart valves and, 279–280
rheumatic heart disease and, 273–274
valvular heart diseases and, 273–274, 307
- Cardiac hypertrophy, 122–123
- Cardiac output, 148, 672
echocardiography Doppler, 428–430
measurement, 394
minimally invasive
assessment of, 397–398
conclusions on, 404
monitors, 398–399
pulse contour analysis and, 399–401
pulse power analysis and, 401–403
pulse pressure and, 403–404
- Cardiac remodeling, HF and, 112
biomechanical stress and, 113
remodeled heart and, 113–115
remodeled myocardium and, 116
remodeled ventricle and, 116
synthesis of, 116–117
- Cardiac resynchronization therapy (CRT), 48
clinical case of, 689–690
conclusions on, 690
implantation of devices in, 685–686
rationale for, 684–685
reports on
future of, 688–689
initial, 686–687
recent, 687–688
- Cardiac surgery, 602–603
postoperative, 783
- Cardiac tamponade, 179–180
acute pericarditis and
clinical picture of, 249–250
treatments for, 250
- Cardiac transplantation, 676
- Cardiogenic shock, 31, 178, 584–585, 674
case presentation for, 216–218
conclusions on, 218, 736
coronary angiography and, 451–452
definitions of, 207, 730
discussions on, 735–736
echocardiography Doppler and, 440–441
epidemiology of, 207–208
etiology of, 730–731
experiences, 733–735
myocardial reperfusion and, 214–216
newer developments in, 216
other settings for, 216
pathophysiology of, 208–209
patients with, 210–212
reversible myocardial
dysfunction and, 210
VADs for, 731–733
- Cardiologists, 525
- Cardiomyocytes, 55
- Cardiomyopathy(ies), 31, 48
diabetic, 122
dilated, 140
reactions to, 191
left ventricular, 300–301
in neonatal/pediatric
populations, 380–381
peripartum, 277–279
pregnancy and, 277–279
- Cardiopulmonary bypass (CPB), 280–281
- Cardiopulmonary resuscitation (CPR)
adequate compression forces
during, 814–816
circulation during, 809
conclusions on, 816
full chest wall recoil and, 810–812
hyperventilation during, 814
ICU/post-
clinical case of, 837–838
conclusions on, 842
life support withdrawal
during, 842
management of, 839–842
neurologic evaluation during, 842
pathophysiology of, 838–839
supportive care during, 840

- pharmacology in, 819–823
venous return during, 812–814
- Cardiorenal axis, 751–753
- Cardiorenal syndrome, 754
- Cardiotrophin-1, 95
- Cardiovascular diseases (CVDs)
in Asia-Pacific region, 20–21
conclusions of, 25–27
diagnosis of, 23
epidemiology of, 20–23
management of, 25–26
coexisting, 372
inflammatory responses to, 135
- Cardiovascular dysfunctions
at cellular level, 340–343
clinical manifestations of, 333–338
conclusions on, 343
etiology of, 338–340
- Cardiovascular regulatory systems, 135
- Cardioversion, 229
- β -Carotene, 118
- Carperitide, 615
- CART. *See* Classification and Regression Tree
- Carvedilol, 534–535
- CASINO (Calcium Sensitizer or Inotrope on None in Low-Output Heart Failure), 601
- Catastrophic Antiphospholipid syndrome (CAPL), 308–309
- Catecholamines
roles of, 772–773
uses of, 16, 25, 100, 137, 341
- Catheter(s). *See also specific types* in ICU
clinical use/description of, 413–420
complications/
contraindications of, 420–421
conclusions on, 421
critically ill patients and, 421
practical use of, 411–413
- PAC, 152, 165, 170, 333, 398, 406
- PICC, 24
- Swan-Ganz, 152, 165, 170, 411
- Catheterization, cardiac, 170–171, 186
pericardial effusion and, 258–259
pericardial tamponade and, 258–259
- CCU. *See* Coronary care unit
- Cell(s)
immune, 141
mast, 141–142
volume, 141, 786
- Central America, 32, 33
- Central oxygen saturation
measured in superior vena cava (ScvO₂), 406, 408–409
- Central sleep apnea (CSA), 359, 360, 362–365
- Central venous catheter (CVC), 406, 408–409
- Central venous pressure (CVP), 333
- Cephalosporins, 191
- CFM. *See* Continuous flow motion
- Chagas disease, 30
acute phase of, 32–33
chronic phase of, 33
diagnosis of, 33–34, 37
in Latin America, 31–34
treatments for
intravenous, 35–36
specific, 35
- CHDs. *See* Coronary heart diseases
- Chest pains, 439–440
- Chest x-ray (CXR), 161, 162, 166
limitations of, 497–498
normal, 494–497
- CHF. *See* Chronic heart failure
- Children, 32
- Chile, 32
- China, 20
- Chlorambucil, 312
- Chloride, 460
- Chloroquine, 351
- Chronic heart failure (CHF), 21–22, 630–632
AHF and
biomarkers and, 540–542
clinical/therapeutic patterns for, 536–540
conclusions on, 542
signs/symptoms of, 540–542
trends/treatments for, 533–536
anemia and
additive effects of, 523–524
conclusions on, 525–526
correcting, 522–523
roles of, 519–526
diagnosis of, 23
monitoring of, 23
phenotypes, 58–60, 61
severe, 648–649
studies, 519
treatments for, 25
vasopressin in, 621–622
- Chronic kidney insufficiency, 519
- Chronic obstructive pulmonary disease (COPD), 161
exacerbation of, 164
history of, 163–164
- c-Jun N-terminal kinases (JNKs), 96
- CK. *See* Creatine phosphate
- Classification and Regression Tree (CART), 9, 11
- Clopidogrel, 216, 574, 639–640, 645–646
- Clopidogrel in Unstable Angina to Prevent Recurrent Events. *See* CURE
- Coarctation of aorta, 272
- Cocaine, 48
- Colchicine, 350
- Collagen, 55
- Community-acquired pneumonia (CAP), 797–798
diagnosis of, 798–799
microbiological evaluation of, 799–800
- Comorbidities, 852–853
- Complement cascade, 80
- Complement system, 74
- Computed tomography (CT), 498
- Continuous flow motion (CFM), 449
- Continuous positive airway pressure (CPAP), 25, 177, 482
benefits of, 327
nasal, 364–365
uses of, 203, 212
- Continuous-wave (CW), 447
- Contraction-relaxation cycle, 52
- Cooley, Denton, 738
- Cooley's anemia, 297
- COPD. *See* Chronic obstructive pulmonary disease
- COPERNICUS (Carvedilol prospective randomized cumulative survival), 537, 541
- Copper (Cu), 118
- Coronary abnormalities, 381–382
- Coronary angiography, 170–171, 186, 208

- Coronary angiography (*cont.*)
 in AHF
 cardiogenic shock and, 451–452
 non-STEMI elevation and, 453
 PCI and, 452–453
 STEMI elevation and, 451–452
 cardiogenic shock and, 451–452
 Coronary angioplasty, 841
 Coronary arteriography, 16
 Coronary artery bypass graft (CABG), 127, 452
 Coronary artery diseases (CADs), 20, 21, 200
 Coronary care unit (CCU), 26
 Coronary heart diseases (CHDs), 21–23
 Corticosteroids, 249, 306
 Corticotropin-releasing hormone (CRH), 292
 Coumadin, 276
 Cocksackie B, 183, 184
 CPAP. *See* Continuous positive airway pressure
 CPB. *See* Cardiopulmonary bypass
 CPK. *See* Creatine phosphokinase
 CPR. *See* Cardiopulmonary resuscitation
 Cr. *See* Creatinine
 C-reactive protein (CRP), 23
 in AHF, 137–138
 roles of, 138
 Creatine phosphate (CK), 126
 Creatine phosphokinase (CPK), 114, 185
 Creatinine (Cr), 7
 levels of, 9
 serum, 9, 192, 309, 558–559
 CRH. *See* Corticotropin-releasing hormone
 Critical care
 levosimendan for, 604
 patients, 783
 CRP. *See* C-reactive protein
 CRT. *See* Cardiac resynchronization therapy
 Crystalloid solutions, 327
 CSA. *See* Central sleep apnea
 CT. *See* Computed tomography
 Cu. *See* Copper
 Cubitan (Nutricia), 882
 CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events), 645
 Cushing's syndrome
 clinical presentations of, 292
 definition of, 291–292
 diagnosis of, 292
 epidemiology of, 292
 treatments for, 292–293
 CVC. *See* Central venous catheter
 CVDs. *See* Cardiovascular diseases
 CVP. *See* Central venous pressure
 CW. *See* Continuous-wave
 CXR. *See* Chest x-ray
 Cyclic adenosine monophosphate (cAMP), 137, 213
 Cyclophosphamides, 48, 306, 312
 Cyclosporine, 99, 129
 effects of, 276
 uses for, 195
 Cysteines, 125
 Cytokine(s), 94, 95–96, 99, 119, 838
 activation of, 136, 137
 antagonists, 342
 expression, 137
 production of, 137
 release of, 149
 upregulation of, 142
 Cytosol, 77
- D**
 Dallas criteria, 195
 Darusentan, 632
 DCM, Dilated cardiomyopathy (DCM)
 DDI. *See* Dyspnea Differentiation Index
 DeBakey, Michael, 737
 Decisions to forgo life-sustaining therapies (DFLSTs)
 conclusions on, 711–712
 EOL and, 704, 705–712
 ethical debates/legal frameworks on, 705–707
 incidences/specificities of, 707
 Decompensated heart failure (DHF)
 chronic, 30
 refractory, 31
 clinical presentations of, 30–31
 definition of, 30–32
 general treatment for, 34, 37
 Deferoxamine, 317
 Defibrotide, 309
 Delirium, 657, 668
 Depression
 clinical case of, 872
 conclusions on, 872
 HF and, 867–868
 interventions addressing, 870–871
 Desferrioxamine, 121
 DeVries, William, 738
 Dexamethasone, 292
 Dexmedetomidine, 662
 DFLSTs. *See* Decisions to forgo life-sustaining therapies
 DHF. *See* Decompensated heart failure
 Diabetes, 59, 60, 122, 540
 Diaminopyridine, 355
 Diastole
 definition of, 52
 diastolic dysfunctions and, 52–54
 conclusions on, 60
 decreased compliance in, 54–55
 systolic dysfunction and, 55–58, 61
 Diastolic dysfunctions, diastole and, 52–54
 conclusions on, 60
 decreased compliance in, 54–55
 systolic dysfunction and, 55–58, 61
 Diastolic pressure-time index, 672
 Diazoxide, 129
 Digitalis, 350
 Digitalis Investigation Group, 226
 Digoxin, 191, 192
 effects of, 228, 276
 uses for, 230, 316, 341
 Dilated cardiomyopathy (DCM), 140, 299
 chronic, 379
 reactions to, 191
 Diltiazem, 230, 276, 330
 Dimethylthiourea, 121
 Disopyramide, 276
 Distributive shock, 584–585
 Diuresis, 204, 205
 Diuretic(s), 16, 176–177, 178, 302, 791–792
 effects of, 227, 276
 intravenous, 383
 loop, 503–510, 552, 754–755, 903, 906–907
 cardiovascular effects of, 507
 decreased renal functions and, 506–507

- metabolic effects of, 509
 - neurohormonal effects of, 507–509
 - pharmacodynamics of, 505
 - pharmacokinetics of, 505
 - renal effects of, 509
- reactions to, 191
- therapies, 552–553
- uses of, 327, 557
- DNR. *See* Do-not resuscitate
- DO₂I. *See* Oxygen delivery index
- Dobutamine, 36, 174–175, 560, 733, 903–904
 - administration of, 356
 - AHFSs and
 - case study on, 567, 574
 - clinical investigations/trials of, 569–572
 - management of, 567
 - mechanisms/metabolism of, 567–569
 - practical applications/considerations for, 572–574
 - infusion of, 409
 - reactions to, 191
 - studies, 598–599
- Do-not resuscitate (DNR), 704–705
- Dopamine, 174, 587–588, 733, 903–904
 - AHFSs and
 - cardiovascular effects of, 579
 - conclusions on, 580–581
 - as modulator, 578–579
 - pharmacology of, 577–578
 - renal actions of, 579–580
 - uses for, 193, 213
- Doppler, echocardiography,
 - AHHFs/critically ill patients and
 - cardiac output and, 428–430
 - cardiogenic shock and, 440–441
 - case presentation of, 442–443
 - chest pains and, 439–440
 - conclusions on, 443
 - EF and, 426–428
 - left heart failure and, 425–426
 - pulmonary edema and, 436–437
 - pulmonary venous congestion and, 430–436
 - with systemic venous congestion, 438–439
- Doppler technique, esophageal cardiac output measurement and, 394
- hemodynamic optimization of, 394–395
- learning curve/reproducibility of, 394
- limitations of, 394
- principles of, 391–394
- Doppler tissue imaging (DTI), 24, 56
- Doxorubicin, 48
- $dp/dt_{\max}$. *See* Maximal rate of isovolumic pressure development
- Drug(s), 129
 - absorption of, 850
 - antiarrhythmic, 192, 212, 311, 821, 840
 - anticoagulant, 641–643, 678, 838
 - antidepressant, 350
 - antiinflammatory, 249
 - antiplatelet, 639–641, 644–646
 - approval process, 899–907
 - cardiotoxic, 356
 - cardiotropic, 350
 - cardiovascular
 - assessment/diagnosis of, 349–350
 - case report on, 355–356
 - conclusions on, 356–357
 - ICU and, 350–351
 - management of, 351–354
 - pathophysiology of, 348–349
 - refractory ACFS and, 354–355
 - development, European regulatory views on, 892–896
 - distribution of, 850–851
 - dose initiation/titration, 849
 - efficacy/safety of, 901–903
 - excretion of, 851
 - interactions, 851–852
 - metabolism of, 851
 - neuromuscular blocking, 663–664
 - noncardiac, 373
 - nonsteroidal antiinflammatory, 192, 249
 - reconciliation, 853–854
 - selection of, 177, 849
 - therapies, 16, 172, 173–174
 - chronic inotropic, 26
 - immunosuppressive, 194–197
 - multidrug medical, 192
 - vasoactive, 733
- DTI. *See* Doppler tissue imaging
- Dyskinesis, regional, 49
- Dyspnea, AHFSs and
 - alternative diagnoses for, 164–165
 - conclusions on, 166–167
 - probability of, 161–164
- Dyspnea Differentiation Index (DDI), 164
- E
- E(t)*. *See* Time-varying ventricular elastance
- Earthquakes, 25
- East Timor, 20
- ECG. *See* Electrocardiogram
- Echocardiography, 212, 217, 248
 - ADHF and, 24–25, 28
 - pericardial effusion and, 257–258
 - pericardial tamponade and, 257–258
 - portable
 - AHFSs and, 446–449
 - conclusions on, 449
 - evaluation in ER, 447–449
 - handheld devices as, 446–447
 - transesophageal, 24, 212, 306–307
 - evaluation of, 425–427, 449
 - transthoracic, 24
- Echocardiography Doppler,
 - AHHFs/critically ill patients and
 - cardiac output and, 428–430
 - cardiogenic shock and, 440–441
 - case presentation of, 442–443
 - chest pain and, 439–440
 - conclusions on, 443
 - EF and, 426–428
 - left heart failure and, 425–426
 - pulmonary edema and, 436–437
 - pulmonary venous congestion and, 430–436
 - with systemic venous congestion, 438–439
- Eclampsia, 281–282
- ECM. *See* Extracellular matrix
- ECMO. *See* Extracorporeal membrane oxygenation
- EDP. *See* End-diastolic pressure
- EDPVR. *See* End-diastolic pressure-volume relation
- EDs. *See* Emergency departments
- EF. *See* Ejection fraction
- EFFECT (Enhanced Feedback for Effective Cardiac Treatment), 7–9

- Effective refractory period (ERP), 225
- Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *See* ESSENCE
- Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan. *See* EVEREST
- EFICA (French Study of Acute Heart Failure), 13, 15
- Eisenmenger syndrome (ES), 269, 273
- Ejection fraction (EF), 426–428
- Elderly, AHFSs in
clinical case of, 375–376
clinical features of, 373–374
conclusions on, 376
management of, 374–375
pathophysiology of, 371–373
- Electrocardiogram (ECG), 161, 162, 166
abnormal, 190
necessity of, 349
- Electron paramagnetic resonance (EPR), 121
- ELISA (enzyme-linked immunosorbent assay), 165
- EMB. *See* Endomyocardial biopsy
- Emergency departments (EDs), 25, 161, 164
- Emergency room (ER), 468–472
- EMF. *See* Endomyocardial fibrosis
- End-diastolic pressure (EDP), 127
- End-diastolic pressure-volume relation (EDPVR), 45
- Endocardial viability ratio, 672
- Endocarditis prophylaxis, 282
- Endocrine disorders, 291–295
- Endocrinopathies, 303
- End of life (EOL)
abstract on, 704
care
communication/information and, 708–709
conclusions on, 711–712
development of, 710–711
multidisciplinary, 709–710
palliative, 707–708
DFLST at, 705–707
introduction to, 704–705
- Endomyocardial biopsy (EMB), 186, 187–188
- Endomyocardial fibrosis (EMF), 312
- Endothelin, 44, 89, 94
-1, 151, 820
- Endothelin receptor antagonists (ERAs), AHFSs and, 626–627
basis for, 628–629
clinical studies of, 630–632
clinical trials of, 632–634
conclusions on, 634
in preclinical studies, 629–630
- Endotoxin tolerance, 838
- Endotracheal tubes, 823
- End-systolic pressure-volume relation (ESPVR), 45, 46
- Enemas, 292, 294
- Enhanced Feedback for Effective Cardiac Treatment. *See* EFFECT
- Enoxaparin, 643, 645, 646, 649
- Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infusion. *See* EXTRACT
- Enterococcus faecalis*, 253
- Enteroviruses, 183
- Enzyme-linked immunosorbent assay. *See* ELISA
- EOL. *See* End of life
- EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), 554
- Epinephrines, 137, 819
administration of, 353, 356
levels of, 202–203
uses of, 383
- Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. *See* EPHESUS
- EPO. *See* Erythropoietin
- EPR. *See* Electron paramagnetic resonance
- Eptifibatide (Integrilin®), 641, 646
- ERAs. *See* Endothelin receptor antagonists
- Ergonovine, 274
- ERKs. *See* Extracellular regulated kinases
- ERP. *See* Effective refractory period
- Erythematosis, systemic lupus, 306–307
- Erythropoietin (EPO)
antioxidant effects of, 524–525
effects of, 523
nonhematopoietic actions of, 524
- ES. *See* Eisenmenger syndrome
- ESC. *See* European Society of Cardiology
- ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness), 152
- Esmolol, 228
- Esophageal Doppler technique
cardiac output measurement and, 394
hemodynamic optimization of, 394–395
learning curve/reproducibility of, 394
limitations of, 394
principles of, 391–394
- ESPVR. *See* End-systolic pressure-volume relation
- ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group), 645
- Estrogens, 789
- Ethacrynic acid, 903, 907
- Ethylene glycol, 787
- Etoposide, 312
- Euglycemia, 351–352
- Euro-Heart Failure Survey Programme (EuroHF), 13, 15–16, 19, 201
- EuroHF. *See* Euro-Heart Failure Survey Programme
- Europe, 5, 6, 13, 15–16, 18, 25, 183, 384
- European Resuscitation Council, 810
- European Society of Cardiology (ESC), 13, 486, 488, 536, 886
- European Society of Intensive Care Medicine, 5, 6

- Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness. *See* ESCAPE trial
- EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), 623, 757
- EVLW. *See* Extravascular lung water
- Extracellular matrix (ECM), 55
- Extracellular regulated kinases (ERKs), 96
- Extracorporeal membrane oxygenation (ECMO), 355, 385
- EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infusion), 646
- Extravascular lung water (EVLW), 400, 401
- Extubation, 490
- F**
- FACES scale, 656
- FADH. *See* Flavin adenine dinucleotide
- Fentanyl, 212, 658–659
- FGF. *See* Fibroblast growth factor
- Fibrinogen, 724
- Fibrinolysis, 822–823, 838
- Fibrinolytic therapy, 214
- Fibroblast growth factor (FGF), 95, 119
- Fibronectin, 55
- Fick principle, 408
- Finland, 598
- 1st Latin American Guidelines for the Assessment and Management of Decompensated Heart Failure, 30
- Flavin adenine dinucleotide (FADH), 119, 124
- Fluid restriction/resuscitation, 417
- Fondaparinux, 645
- Fragmin®, 645
- France, 17
- Frank-Starling relationship, 44
- Furosemide, 25, 28, 204, 903, 906
- G**
- Gadolinium, 225
- Ganglionic blockers, 150
- GDP. *See* Guanosine diphosphate
- Gender, female, 59, 60
- Germany, 16
- GFR. *See* Glomerular filtration rate
- Gibbon, John, 737
- GIK. *See* Glucose-insulin-potassium
- Global Registry of Acute Coronary Events (GRACE), 173
- Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-3), 208, 214, 645
- Glomerular filtration rate (GFR), 150, 373, 758
- Glucagon, 351–352
- Glucocorticoids, 293
- Glucose
- blood, 700, 782–783
 - disturbance, 781–783
 - insulin-potassium, 79, 127–128
 - oxidation of, 128
- Glucose-insulin-potassium (GIK), 79, 127–128, 781–782
- Glutathione, 118
- Glutathione peroxidase (GSHPx), 121, 125
- Glycoprotein IIb/IIIa receptor inhibitors, 641
- Glycosides, 16
- GPCRs. *See* G-protein-coupled receptors
- G-protein-coupled receptor kinases (GRKs), 92–93
- G-protein-coupled receptors (GPCRs), 89–90, 91
- G-proteins, 91–92
- GRACE. *See* Global Registry of Acute Coronary Events
- GRKs. *See* G-protein-coupled receptor kinases
- Growth factors, HF and, 94
- cytokines and, 94, 95–96, 99
 - RTKs and, 95
- GSHPx. *See* Glutathione peroxidase
- GTP. *See* Guanosine triphosphate
- Guanosine diphosphate (GDP), 89
- Guanosine triphosphate (GTP), 89
- GUSTO-3. *See* Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
- H**
- H₂O₂. *See* Hydrogen peroxide
- HATs. *See* Histone acetyltransferases
- Hb. *See* Hemoglobin
- HDACs. *See* Histone deacetylases
- Heart. *See also* Acute heart failure syndromes
- block, 190
 - in chronic heart failure, decompensated, 14
 - cycle, 45
 - rate, 329–330, 371, 672, 673
 - remodeled, 113–115
 - replacement, 737
 - rhythm, 371, 672
 - rupture, 179–180
- Heart Center, North Rhine Westphalia, 733
- Heart disease(s)
- congenital, in neonatal/pediatric populations, 381–382
 - cyanotic, 272
 - ischemic
 - levosimendan and, 603–604
 - pregnancy and, 274–275 - pregnancy and
 - congenital, 270, 271–273
 - ischemic, 274–275
 - rheumatic, 273–274
 - valvular, 273–274, 307
- Heart failure (HF). *See also* Chronic heart failure
- acute, 30
 - α₁- ARs and, 91
 - β- ARs and, 90–91
 - Ang II and, 93–94
 - cardiac remodeling and, 112
 - biomechanical stress and, 113 - remodeled heart and, 113–115
 - remodeled myocardium and, 116
 - remodeled ventricle and, 116
 - synthesis of, 116–117
 - conclusions on, 102–103
 - congestive, 612–613
 - depression and, 867–872

- Heart failure (HF) (*cont.*)
 diastolic
 definition of, 54
 mechanisms of, 54
 endothelin receptors and, 89, 94
 energy metabolism and, 771
 epidemiology of, 21–23
 GPCRs and, 89–90
 G-proteins and, 91–92
 GRKs and, 92–93
 growth factors and, 94
 cytokines and, 94, 95–96, 99
 RTKs and, 95
 hospitalizations for, 7, 14, 18, 200
 hyponatremia during, 790–793
 inflammatory mechanisms in, 135
 inflammatory syndrome and, 771–772
 intracellular signaling pathways and, 96–102
 left, echocardiography Doppler and, 425–426
 mortality associated with, 89
 phenotypes, 59–60
 risk scoring system, 8
 ROS in
 antioxidants and, 123
 biologic significance of, 118–119
 cardiac hypertrophy and, 122–123
 counterbalancing/generation of, 118
 NADPH oxidases and, 119, 120–121
 roles of, 121–122
 sources of, 119–120
 XO and, 119, 120
 transcription regulation of, 102
 Heart Failure Society of America, 5
 Heart failure with preserved ejection fraction time (HFpEF), 56
 HeartMate, 737, 738, 739
 Heart Outcomes Prevention Evaluation (HOPE), 123
 Heart rate (HR), 7, 9
 Heart Society of Cardiology, 5, 6
 Heat shock proteins (HSPs), 129, 130
 Hemochromatosis, 317–318
 Hemofiltration, high-volume, 841
 Hemoglobin (Hb), 7, 418
 levels, 521
 mean, 519
 Hemolysis, 297
 Hemoproteins, 119
 Heparins, 276, 455, 642
 low-molecular-weight, 280, 642
 unfractionated, 280
 Hepatocyte necrosis, 764
 HEPs. *See* High-energy phosphates
 HES. *See* Hypereosinophilic syndrome
 HF. *See* Heart failure
 HFpEF. *See* Heart failure with preserved ejection fraction time
 High-energy phosphates (HEPs), 126
 Histone acetyltransferases (HATs), 102
 Histone deacetylases (HDACs), 102
 HIV (human immunodeficiency virus), 183
 HLA. *See* Human leukocyte antigen
 Hong Kong, 20
 HOPE. *See* Heart Outcomes Prevention Evaluation
 Hospitalization(s)
 coronary care units in, 16
 data, 10
 frequency of, 16
 for heart failure, 7, 14, 18, 200
 ICU in, 16
 index, 16–17
 length of, 15
 mortality rates during, 15, 188
 preadmission, 15–16
 prognosis factors and, 16–18
 of patients with AHFSs, 13, 14
 in U.S., 7
 HOT. *See* Hypertension Optimal Treatment
 HR. *See* Heart rate
 HSPs. *See* Heat shock proteins
 Human immunodeficiency virus. *See* HIV
 Human leukocyte antigen (HLA), 295
 AHF and, 316–317
 B27 and, 316–317
 Hydralazine, 139
 Hydrogen peroxide (H₂O₂), 118, 121
 Hydromorphone, 659
 Hydroxychloroquine, 307
 Hydroxyethylstarch, 327
 Hydroxyl radicals (·OH), 118
 Hypereosinophilic syndrome (HES), 312
 Hyperglycemia, 781–782
 Hyperkalemia, 192
 Hyperlactatemia, 770–771
 conclusions on, 776
 without hypoxia, 771–773
 as marker, 771
 mechanisms of, 770–771
 practical interpretation of, 773–776
 treatments for, 776
 Hyperparathyroidism, 292
 causes of, 294
 clinical presentations of, 294
 definition of, 294
 diagnosis of, 294
 epidemiology of, 294
 treatments for, 294
 Hypertension, 59, 60, 200, 539
 pregnancy and, 282
 pulmonary, 273, 301
 arterial, 301
 Hypertension Optimal Treatment (HOT), 647
 Hypertrophy, 103
 calcium-sensitive signaling pathways and, 99–100
 ERKs as, 96
 heart failure and, 96–102
 intracellular signaling pathways and, 96–102
 JAK/STAT as, 99
 MAPKs as, 96
 PI3K and, 100–102
 SAPKs as, 96–99
 Hypocalcemia, 292
 clinical presentations of, 295
 definition of, 294
 diagnosis of, 295
 epidemiology of, 294
 treatments for, 295
 Hyponatremia
 classifications/treatments of, 789–790
 conclusions on, 793
 general considerations for, 786–789
 during HF, 790–793
 hypotonic, 789–790
 Hypotension, 77, 178

- Hypothermia
 for AMI, 698–699
 brain protection and, 692–698, 841–842
 clinical case of, 700–702
 clinical trials with, 693–695
 conclusions on, 702
 definition of, 692–693
 management, 695–698
 medical treatments for, 699–700
 resuscitative, 693
- Hypothyroidism, 292
 causes of, 293
 clinical presentations of, 293
 definition of, 293
 diagnosis of, 294
 epidemiology of, 293
 treatments for, 294
- Hypoxemia, 456
- Hypoxia, 771–773
- I**
- IABP. *See* Intraaortic balloon pump
- Ibuprofen, 249
- ICAM. *See* Intercellular adhesion molecule; Intracellular adhesion molecule
- ICD. *See* Implantable cardioverter-defibrillator
- ICU. *See* Intensive care unit
- I/E. *See* Inspiratory-to-expiratory time
- IGF-1. *See* Insulin-like growth factor
- Immune
 activation, 136
 cells, 141
- Immune system, 72–74
 alterations in AHF
 cellular/humoral responses and, 140–142
 humoral inflammatory mediators and, 137–138
 neurohormones/regulation of, 136–137
 other humoral mediators and, 138–140
 pathophysiology of, 134
 therapeutic implications for, 142
 RAAS and, 136–137
- IMPACT-HF. *See* Initiation Management PredischARGE: Process for Assessment of Carvedilol Therapy in Heart Failure
- Implantable cardioverter-defibrillator (ICD), 192
- IN-CHF. *See* Italian Network Registry on Congestive Heart Failure
- India, 20
- Indomethacin, 249, 314
- Indonesia, 20
- Infections, 302
- Inferior vena cava (IVC), 24
- Infliximab, 142
- Initiation Management
 PredischARGE: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF), 226, 536
- Inositol-1,4,5-triphosphate (IP₃), 89
- Inotropes, 559, 903–905
 classes of, 553
 positive, 565
 uses of, 26, 36, 178, 329, 356
- Inspiratory-to-expiratory time (I/E), 490
- Inspired fraction of oxygen, 488
- Insulin-like growth factor (IGF-1), 95, 113, 291
- Insulin-potassium, glucose, 79, 127–128, 781–782
- Integrilin®. *See* Eptifibatide
- Integrins, 139
- Intensive care unit (ICU), 16, 25, 471–472, 727
 BNP testing in, 468–472
 cardiovascular drugs and, 350–351
 critically ill patients in, EOL care for, 704–712
 PAC in
 clinical use/description of, 413–420
 complications/contraindications of, 420–421
 conclusions on, 421
 critically ill patients and, 421
 practical use of, 411–413
 post-CPR and
 clinical case of, 837–838
 conclusions on, 842
- life support withdrawal during, 842
 management of, 839–842
 neurologic evaluation during, 842
 pathophysiology of, 838–839
 supportive care during, 840
 right ventricular dysfunctions in
 case reports on, 242–244
 conclusions on, 244
 by depressed intrinsic contractility, 242
 diagnosis of, 238–242
 by increased afterload, 240–242
 mechanical ventilation and, 237–238
 physiology of, 237, 238
- Intensive therapy unit (ITU), 397
- Intercellular adhesion molecule (ICAM), 23
- Interferon-γ, 333
- INTERHEART study, 20–21
- Interleukin 1β, 333
- Internists, 525
- Intraaortic balloon pump (IABP), 177, 214, 330, 730
 clinical case on, 679
 clinical trials of, 674–677
 determinants of, 673–674
 effects
 hemodynamic, 671–672
 metabolic, 672–673
 treatment recommendations for, 677–679
- Intracellular adhesion molecule (ICAM), 139
- Intracellular signaling pathways, 103
 calcium-sensitive signaling pathways and, 99–100
 ERKs as, 96
 heart failure and, 96–102
 hypertrophy and, 96–102
 JAK/STAT as, 99
 MAPKs as, 96
 PI3K and, 100–102
 SAPKs as, 96–99
- Intrathoracic blood volume (ITBV), 400
- Intrathoracic volume (ITV), 400
- Intravenous immunoglobulins (IVIgGs), 306
- IP₃. *See* Inositol-1,4,5-triphosphate
- Irbesartan, 646

- Iron, 317
 - chelation treatment, 298
 - overload, 297
- Ischemia, 227
 - calcium homeostasis and, 74–76
 - conclusions on, 81
 - mechanisms of, 70–71, 72
 - myocardial, 613–614
 - other intercellular events
 - around, 76–77
 - reperfusion syndrome, 838–839
 - ROS and, 72–74
 - therapeutic approaches for, 77–81
- Isoproterenol, 353
- Isosorbide, 28
 - dinitrate, 139
- Isosource (Novartis), 882
- Isovolumic relaxation time (IVRT), 54
- Italian Network Registry on Congestive Heart Failure (IN-CHF), 533, 536, 538
- Italy, 13
- ITBV. *See* Intrathoracic blood volume
- ITU. *See* Intensive therapy unit
- ITV. *See* Intrathoracic volume
- IVC. *See* Inferior vena cava
- IVIGs. *See* Intravenous immunoglobulins
- IVRT. *See* Isovolumic relaxation time
- J**
- JAK. *See* Janus kinases
- JAK/STAT pathways, 99
- Janus kinases (JAK), 95
- Japan, 20, 21, 23, 25
- Jarvik-7 TAH, 738
- JCAHO. *See* Joint Commission on Accreditation of Healthcare Organizations
- JNKs. *See* c-Jun N-terminal kinases
- Joint Commission on Accreditation of Healthcare Organizations (JCAHO), 655
- K**
- K⁺. *See* Potassium
- Kerley's B lines, 165
- Ketoconazole, 293
- Kidney(s), 519
 - cardiorenal axis and, 751–753
 - cardiorenal syndrome and, 754
 - conclusions regarding, 759–760
 - conventional strategies for, 754–756
 - single nephron and, 751–753
 - therapeutic strategies for, 756–759
- Korea, 20, 21
- Krebs cycle, 119, 126–128, 768
- L**
- LAC. *See* Lupus anticoagulant test
- Lactate
 - metabolism, 768–769
 - turnover, 769–770
- Lactic acidosis, 461–462
- Laminin, 55
- Laos, 20
- Laplace's law, 43, 56
- Lasix, 231
- LATAREA study, 705
- Latin America
 - AHFSs in, 30
 - categories of, 30–31
 - Chagas disease and, 31–34
 - conclusions of, 36
 - DHF and, 30–31
 - management of, 31
 - Chagas disease in, 31–34
- Laxatives, 292, 294
- LBBB. *See* Left bundle branch block
- LDL. *See* Low-density lipoprotein
- Left bundle branch block (LBBB), 178
- Left ventricle (LV), 112
- Left ventricular assist devices (LVADs), 26, 189
 - challenges with, 742–744
 - conclusions regarding, 744
 - historical perspectives on, 737–739
 - mechanical circulatory support for, 740–742
 - future of, 744–745
- Left ventricular diastole
 - conclusions on, 60
 - pathophysiology/physiology of, 52–60
- Left ventricular ejection fraction (LVEF), 7, 24, 59, 61, 334–336, 671–672
- Left ventricular end-diastolic area (LVEDA), 24, 56
- Left ventricular end-diastolic pressure (LVEDP), 58, 671
- Left ventricular end-diastolic volume (LVEDV), 56, 58, 334–336
- Left ventricular filling pressure, 431–436
- Left ventricular function, 334–336
- Left ventricular hypertrophy (LVH), 375
- Left ventricular outflow tract (LVOT), 24, 448
- Left ventricular systole
 - background on, 43
 - conclusions on, 49–50
 - definition of, 43–44
 - diagnosis of, 43–44
 - $dP/dt_{\max}$ and, 44
 - force-frequency relation and, 48
 - pathophysiology of, 48–49
 - PV loop and, 44–46
 - systolic performance of, 47–48
 - time-varying ventricular elastance and, 46–47
- Leukemia inhibitory factor (LIF), 113
- Leukocytes, 141
- Levosimendan, 204, 213–214, 223
 - ACS and, 176
 - action mechanisms of, 595–596
 - cardiac surgery and, 602–603
 - clinical trials of, 597–602
 - for critical care, 604
 - ischemic heart diseases and, 603–604
 - pharmacokinetics of, 596–597
 - uses of, 26, 34, 36, 37, 553
- LiDCO-Plus System, 398, 400, 402–403
- LIDO (Levosimendan Infusion Versus Dobutamine Study), 204, 598–599
- Lidocaine, 259, 276, 821, 823
- LIF, Leukemia inhibitory factor
- Life support withdrawal, 842
- Likelihood ratio (LR), 161
- Lipoic acid, 118
- Lipopolysaccharide (LPS), 137
- Lipoxygenases, 119
- Lithium, 402
- Liver
 - lesions
 - conclusions on, 766–767
 - etiology of, 764

- general course/prognosis for, 765–766
 management of, 766
 manifestations of, 764–765
 pathophysiology of, 763–764
 transplantation, 317–318
 Löffler's endocarditis, 191
 Low-density lipoprotein (LDL), 307
 Low-molecular-weight heparin, 280, 642
 Low-output syndrome, 178
 LPS. *See* Lipopolysaccharide
 LR. *See* Likelihood ratio
 Lungs, 417, 475, 480
 Lupus anticoagulant test (LAC), 307
 LV. *See* Left ventricle
 LVADs. *See* Left ventricular assist devices
 LVEDA. *See* Left ventricular end-diastolic area
 LVEF. *See* Left ventricular ejection fraction
 LVH. *See* Left ventricular hypertrophy
 LVOT. *See* Left ventricular outflow tract
 Lymphocytes, 141
M
 MADIT-II. *See* Multicenter Automatic Defibrillator Implantation Trial-II
 Magnesium, 821
 Magnetic resonance imaging (MRI), 186
 Malaysia, 20
 Maldigestion, 879
 Mammalian target of rapamycin (mTOR), 95
 Manganese SOD (Mn SOD), 118
 Mannitol, 787
 Maori, 21–22
 MAP. *See* Mean arterial pressure
 MAPKs. *See* Mitogen-activated protein kinases
 Marfan syndrome, 272–273
 Matrix metalloproteinases (MMPs), 49, 54, 116
 Maximal rate of isovolumic pressure development ($dp/dt_{\max}$), 44
 MCTD. *See* Mixed connective tissue disease
 MDSs. *See* Myocardial depressant substances
 Mean arterial pressure (MAP), 398, 399
 Mechanical ventilation
 adjustments, 488–490
 clinical case of, 491–492
 conclusions on, 492
 extubation/weaning of, 490
 indications for, 488
 physiologic effects of, 486–488
 right ventricular dysfunctions, in ICU, 237–238
 Mediterranean anemia, 297
 MEF2. *See* Myocyte enhancer factor-2
 Melagatran, 642–643
 N-2-Mercaptopropionyl glycine (MPG), 121
 Metabolic acidosis, 461, 463
 Metabolic alkalosis, 461–462, 463
 Methadone, 659
 Methanol, 787
 Methotrexate, 306
 Metoprolol
 CR/XL, 59, 61
 effects of, 228, 276
 β -MHC. *See* β -Myosin heavy chain
 MI. *See* Myocardial infarction
 Mid-America Heart Institute, 214
 Milrinone, 26, 223, 560, 571–572, 903–905
 for ACS, 174, 175–176
 uses for, 34, 36, 193, 341, 383
 Minipumps, 204–205
 Mitochondria, 596
 AHF and
 conclusions on, 130
 functional improvement of, 127–129
 involvement of, 126–127
 physiologic roles of, 124–126
 Mitochondrial permeability transition (MPT), 124–125
 Mitochondrial permeability transition pore (MPTP), 76
 Mitogen-activated protein kinases (MAPKs), 90, 96, 123, 137
 Mitral regurgitation, 179
 Mitral valve prolapse (MVP), 274
 Mitral valves, 447–448
 Mitral valve stenosis (MVS), 274
 Mixed connective tissue disease (MCTD), 314
 MKK kinases (MKKKs), 96–97
 MKKKs. *See* MKK kinases
 MMPs. *See* Matrix metalloproteinases
 Mn SOD. *See* Manganese SOD
 MODs. *See* Multiple organ dysfunctions
 Monitors
 minimally invasive, 398–399
 PICCO-Plus, 398, 399, 400
 Vigileo, 398, 403
 Monocytes, 141
 Morphine, 658–659
 Mortality, 168
 associated with AHF, 323–324
 associated with HF, 89
 rates during hospitalizations, 15, 188
 preadmission, 15–16
 prognosis factors and, 16–18
 MPG. *See* N-2-Mercaptopropionyl glycine
 MPTP. *See* Mitochondrial permeability transition pore
 MRI. *See* Magnetic resonance imaging
 mTOR. *See* Mammalian target of rapamycin
 MTP. *See* Mitochondrial permeability transition
 Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II), 226
 Multiple organ dysfunctions (MODs), 333
 Muscle(s)
 respiratory, 150–151
 vasculature of, 152
 MVP. *See* Mitral valve prolapse
 MVS. *See* Mitral valve stenosis
 Myanmar, 20
 Myocardial depressant substances (MDSs), 340
 Myocardial dysfunctions
 mechanisms of, 839
 reversible, 210
 Myocardial infarction (MI), 135, 208. *See also* Acute myocardial infarction
 Myocardial inflammation, 135
 Myocardial ischemia, 168–170, 613–614

- Myocardial reperfusion, 214–216
injury
calcium homeostasis and, 74–76
conclusions on, 81
definition of, 70
mechanisms of, 70–71, 72
other intercellular events around, 76–77
ROS and, 72–74
therapeutic approaches for, 77–81
- Myocardial stunning, 210
- Myocarditis, 140, 299–300, 677
active, 186–187
borderline, 186–187
causes of, 184
clinical course/prognosis for, 188–189
clinical presentation of, 185–186
conclusions on, 194–197
DCM and, 191
definition of, 183
diagnosis of, 186–188
eosinophilic, 190–191
forms of, 184
fulminant, 189
general management of, 191–194
giant cell, 190
hypersensitivity, 190–191
immunosuppressive therapies for, 194–197
in neonatal/pediatric populations, 379–380
pathogenesis of, 184–185
- Myocarditis Treatment Trial, 195
- Myocardium
anti-stunning effects on, 596
remodeled, 116
- Myocyte enhancer factor-2 (MEF2), 102
- Myocyte, remodeled, 113–115
- β -Myosin heavy chain (β -MHC), 102, 114
- N**
- Na^+ . *See* Sodium
- NAC. *See* N-acetylcysteine
- $\text{Na}^+\text{Ca}^{2+}$ (NCE), 75
- NADH. *See* Nicotinamide adenine dinucleotide
- NADPH. *See* Nicotinamide adenine dinucleotide phosphate
- National Registry of Myocardial Infarction-2 (NIRMI-2), 215, 216
- Natrecor®. *See* Nesiritide
- Natriuretic peptides
atrial, 610–611
biochemistry of, 608
brain, 609
clinical significance of, 612–614
conclusions on, 614
C-type, 609–610, 612
pharmacology/physiology of, 610–611
receptors, 610
as therapeutic agents, 614
- Natriuretics, 21, 27
- Natural killer (NK), 23
- NCE. *See* $\text{Na}^+\text{Ca}^{2+}$
- Neonatal populations
AHFSs in
clinical case of, 385–386
etiologies of, 379–383
features of, 378
presentation of, 379
prognosis for, 385
therapies for, 383–385
cardiomyopathies in, 380–381
coronary abnormalities in, 381–382
myocarditis in, 379–380
- NEP. *See* Neutral endopeptidase
- Nepal, 20
- Nervous system, sympathetic, 137
- Nesiritide (Natrecor®), 34, 176, 223, 572, 615–616, 903, 905–906
ADHF and, 551
BNP and, 554–555
conclusions/recommendations for, 560–561
risk-benefit profile of, 558–560
therapeutic options for, 555–558
therapies for, 552–554
uses of, 328, 383–384
- Neurohormones
pathways associated with, 148–149
regulation of, 136–137
- Neutral endopeptidase (NEP), 757–758
- Neutrophils, 72–73
- New York Heart Association (NYHA), 10, 17, 58, 141, 309
- New Zealand, 20, 21, 23
- NF. *See* Nuclear factor
- NFAT. *See* Nuclear factor of activated T cells
- NF- κ B. *See* Nuclear factor κ B
- Nicardipine, 328
- Nicorandil, 129
- Nicotinamide adenine dinucleotide (NADH), 120, 124, 126–127
- Nicotinamide adenine dinucleotide phosphate (NADPH), 119, 120–121
- Nifedipine, 274, 316
- NIPPV. *See* Noninvasive positive pressure ventilation
- NIPSV. *See* Noninvasive pressure support ventilation
- Nitrates, 16, 173–175
in ADHF
clinical trials of, 546–547
doses, 546–547
effects of, 545–546, 547
effect of, 26
uses of, 275, 327
- Nitric oxide (NO), 54, 758
dependent pathways, 96
production of, 138–139
regulation of, 138–139
uses for, 80
- Nitric oxide synthetase (NOS), 138
forms of, 340
inducible, 209
- Nitrogen balance, 878
- Nitroglycerin (NTG), 173–175, 328, 553, 903, 905
therapies, 556–557, 560
uses of, 173–175, 328, 553
- Nitroprusside, 174, 175, 553, 903, 905
- NIV. *See* Noninvasive ventilation
- NK. *See* Natural killer
- NO. *See* Nitric oxide
- Nociceptives, 727
- Noninvasive positive pressure ventilation (NIPPV), 177
- Noninvasive pressure support ventilation (NIPSV), 477–480, 482
- Noninvasive ventilation (NIV), 26
AHFSs and, 26
BiPAP and, 477–480, 482
case report on, 482

- contraindications for, 482
 - description of, 477–480
 - improvement mechanisms for, 480–481
 - PEEP and, 477–480, 482
 - side effects of, 482
 - uses of, 481–482
- Nonsteroidal antiinflammatory drugs (NSAIDs), 306, 310, 658
- Nonsustained ventricular tachycardia (NSVT), 221, 230–231
- Noradrenaline, 174, 586–587, 588, 733
- Norepinephrines, 137, 176
 - levels of, 202–203
 - α -methyl, 820
 - uses for, 383
- North America, 183
- NOS. *See* Nitric oxide synthetase
- Novacor, 737, 739
- NRMI-2. *See* National Registry of Myocardial Infarction-2
- NRS. *See* Numeric rating scale
- NSAIDs. *See* Nonsteroidal antiinflammatory drugs
- NSVT. *See* Nonsustained ventricular tachycardia
- N-terminal Pro-BNP, 471–472
- NTG. *See* Nitroglycerin
- Nuclear factor (NF), 119
- Nuclear factor κ B (NF- κ B), 140
- Nuclear factor of activated T cells (NFAT), 98
- Numeric rating scale (NRS), 656
- Nursing
 - conclusions on, 865
 - education/licensure in, 857–860
 - roles, 857–858
 - services, 858–865
- Nutrition
 - assessments, 877–879
 - clinical case of, 881
 - comments on, 882
 - concerns regarding, 876–877
 - enteral, 879–880
 - therapies, 879–881
- NYHA. *See* New York Heart Association
- O**
- Obstructive sleep apnea (OSA), 360–361, 362–365
 - Obstructive sleep apnea hypopnea syndrome (OSAHS), 359, 360–361
 - Odds ratio, 214
 - $\cdot$ OH. *See* Hydroxyl radicals
 - ONOO $\cdot$. *See* Peroxynitrite
 - Opiates, 665
 - Opioids, 727
 - OPTIME-CHF. *See* Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
 - OSA. *See* Obstructive sleep apnea
 - OSAHS. *See* Obstructive sleep apnea hypopnea syndrome
 - Osmolality, 787
 - Osmolarity, 75, 787
 - Osmoregulation, 788
 - Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), 10, 12, 26, 221, 224
 - Overlap syndrome, 314
 - Oxygen, 391
 - assessment of, 456–457, 464
 - free radicals, 333
 - paradox, 70
 - saturation, 341
 - measurements in ACFSS, 406–410
 - supplementary, 25
 - therapies, 456
 - Oxygen delivery index (DO $_2$ I), 397
 - Oxygen saturation venous (SvO $_2$)
 - low, 406, 408–409
 - measurement of, 418
 - mixed, 418, 586
 - significance/use of, 418–419
- P**
- PAC. *See* Pulmonary artery catheter
- Pacemakers, 192
- PAF. *See* Platelet-activating factor
- Parathyroid hormone (PTH), 294
- PARP. *See* Poly-ADP ribosyl polymerase
- PARS. *See* Poly ADP-ribose synthetase
- Partial pressures of oxygen (PO $_2$), 455
- Patient(s)
 - assessment of, 862–863
 - critical care, 783
 - critically ill
 - AHFSs/echocardiography Doppler and, 424–443
 - EOL care for, 704–712
 - PAC in ICU and, 421
 - end-stage, 855
 - pharmacists and, 853–855
 - PBV. *See* Pulmonary blood volume
 - PCI. *See* Percutaneous coronary intervention
 - PCO $_2$. *See* Venoarterial carbon dioxide tension
 - PCP. *See* Pulmonary capillary pressure
 - PCR. *See* Polymerase chain reaction
 - PCWP. *See* Pulmonary capillary wedge pressure
 - PDGF. *See* Platelet-derived growth factor
 - Peak expiratory flow (PEF), 164
 - PECAM. *See* Platelet endothelial cell adhesion molecule
 - Pediatric populations
 - AHFSs in
 - clinical case of, 385–386
 - etiologies of, 379–383
 - features of, 378
 - presentation of, 379
 - prognosis for, 385
 - therapies for, 383–385
 - cardiomyopathies in, 380–381
 - coronary abnormalities in, 381–382
 - myocarditis in, 379–380
 - PEEP. *See* Positive end expiratory pressure
 - PEF. *See* Peak expiratory flow
 - Peptides, 21, 148
 - GsMtx-4, 225
 - natriuretic
 - atrial, 610–611
 - biochemistry of, 608
 - brain, 609
 - clinical significance of, 612–614
 - conclusions on, 614
 - C-type, 609–610, 612
 - pharmacology/physiology of, 610–611
 - receptors, 610
 - as therapeutic agents, 614

- Percutaneous balloon
 pericardiotomy, 255
 complications of, 263
 management after, 263
 outcomes data of, 263
 technique, 262–263
- Percutaneous coronary
 intervention (PCI), 172
 coronary angiography and,
 452–453
- Pericardial effusion, 165
 cardiac catheterization and,
 258–259
 clinical presentation of, 256–257
 echocardiography and, 257–258
 etiology of, 255–256
- Pericardial tamponade, 165
 cardiac catheterization and,
 258–259
 clinical presentation of, 256–257
 echocardiography and, 257–258
 etiology of, 255–256
- Pericardiocentesis, 180, 255
 complications of, 261
 indications of, 259
 management after, 261
 recurrent, 261–262
 technique, 259–261
- Pericarditis, 299–300. *See also*
 Acute Pericarditis
- Pericardium, 247
- Pericardial balloon pericardial
 window. *See* Percutaneous
 balloon pericardiotomy
- Peripherally inserted central
 catheter (PICC), 24
- Peripheral vascular resistance,
 672
- Peroxidases, 119
- Peroxynitrite (ONOO⁻), 118
- PET. *See* Positron emission
 tomography
- PFK. *See* Phosphofructokinase
- PGSL-1. *See* P-selectin glycoprotein
 ligand-1
- PHARM. *See* Pharmacist
 Assessment
 Recommendation and
 Monitoring
- Pharmacist Assessment
 Recommendation and
 Monitoring (PHARM),
 847
- Pharmacists
 conclusions on, 855
 drugs/medications and
 prescribed by physicians,
 848–853
 used by patients, 853–855
 roles of, 847–855
- Phentolamines, 137
- Phenylephrines, 137, 589
- Pheochromocytoma, 292
 clinical presentations of, 295
 definition of, 295
 diagnosis of, 295
 epidemiology of, 295
 treatments for, 295
- Philippines, 20
- Phlebotomy, 317
- Phosphocreatine, 115
- Phosphodiesterase inhibitors, 226
- Phosphofructokinase (PFK), 768
- Phosphoinositide-3-kinase (PI3K),
 90, 100–102
- Phosphoinositide kinase (PIK),
 100–102
- Phospholipase C β (PLC β), 89
- PICC. *See* Peripherally inserted
 central catheter
- PICCO-Plus monitor, 398, 399,
 400
- PIK. *See* Phosphoinositide kinase
- PI3K. *See*
 Phosphoinositide-3-kinase
- PKA. *See* Protein kinase A
- PKB. *See* Protein kinase B
- PKC. *See* Protein kinase C
- Placebo, 26
- Plasma, 141
 exchange, 309
 fresh frozen, 309
 toxicity, 787
- Platelet-activating factor (PAF), 73
- Platelet-derived growth factor
 (PDGF), 95, 113
- Platelet endothelial cell adhesion
 molecule (PECAM), 139
- PLC β . *See* Phospholipase C β
- Pneumonia
 aspiration, 800–801
 clinical case of, 804–805
 community-acquired, 797–798
 diagnosis of, 798–799
 microbiological evaluation of,
 799–800
 conclusions on, 805
 diagnosis of, 803–804
 ventilator-associated, 801–803
- Pneumothorax, spontaneous, 165
- PO₂. *See* Partial pressures of
 oxygen
- Poiseuille's law, 348
- Poly ADP-ribose synthetase
 (PARS), 129
- Poly-ADP ribosyl polymerase
 (PARP), 126
- Polymerase chain reaction (PCR),
 35, 187
- Portable echocardiography
 AHFSs and, 446–449
 conclusions on, 449
 evaluation in ER, 447–449
 handheld devices as,
 446–447
- Positive end expiratory pressure
 (PEEP), 152, 414–415,
 489–490
 NIV and, 477–480, 482
- Positron emission tomography
 (PET), 210
- Potassium (K⁺), 231
 ATP, 595–596
 -channel antagonists, 355
 glucose-insulin-, 79, 127–128,
 781–782
 metabolism of, 128–129
 sensitive, 79
 serum, 192–193
- Prealbumin, 878
- PRECEDENT (Prospective
 Randomized Evaluation of
 Cardiac Ectopy with
 Dobutamine or Natreacor
 Therapy), 226, 556, 558
- Prednisone, 190, 194, 195
- Pregnancy, cardiac diseases in
 anesthesiologic management of,
 282–283
 approach to, 269–270
 arrhythmias and, 275–277
 cardiac surgery and, 280–281
 cardiomyopathy and, 277–279
 conclusions on, 283–284
 congenital heart diseases and,
 270, 271–273
 eclampsia and, 281–282
 endocarditis prophylaxis and,
 282
 hypertensive crisis and, 282
 ischemic heart diseases and,
 274–275
 management of, 270–271
 prosthetic heart valves and,
 279–280

- rheumatic heart disease and, 273–274
 - valvular heart diseases and, 273–274, 307
 - Pressure-volume area (PVA), 46
 - Pressure-volume loop (PV loop), 44–46
 - Primary myocardial dysfunctions, 48
 - PROACTION (Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Failure Treated Initially as Outpatients with Nesiritide), 557, 558
 - Procainamide, 230
 - Progesterones, 789
 - PROMISE. *See* Prospective Randomized Milrinone Survival Evaluation
 - Propanolol, 137, 276
 - Prophylaxis, 35, 309
 - antibiotic, 282
 - endocarditis, 282
 - Propofol, 661–662, 727
 - Propylthiouracil, 293
 - Prospective Randomized
 - Evaluation of Cardiac Ectopy with Dobutamine or Natrekor Therapy. *See* PRECEDENT
 - Prospective Randomized Milrinone Survival Evaluation (PROMISE), 22
 - Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Failure Treated Initially as Outpatients with Nesiritide. *See* PROACTION
 - Prostacyclin, 309
 - Prostaglandins, 150, 274
 - Prosthetic heart valves, 279–280
 - Protein kinase, 77
 - Protein kinase A (PKA), 89, 90
 - Protein kinase B (PKB), 123
 - Protein kinase C (PKC), 89, 90, 123
 - Proteoglycans, 55
 - Prothrombin time, 724
 - P-selectin glycoprotein ligand-1 (PGSL-1), 74
 - PTH. *See* Parathyroid hormone
 - Pulmonary arterial hypertension (PAH), 301
 - Pulmonary artery, 406, 408–409
 - Pulmonary artery catheter (PAC), 152, 165, 170, 333, 398, 406
 - in ICU
 - clinical use/description of, 413–420
 - complications/contraindications of, 420–421
 - conclusions on, 421
 - critically ill patients and, 421
 - practical use of, 411–413
 - Pulmonary artery occlusion pressure (PAOP)
 - clinical purpose/usage of, 416–417
 - measurement of, 414–416
 - physiologic relevance of, 413
 - Pulmonary blood volume (PBV), 400
 - Pulmonary capillary pressure (PCP), 171
 - Pulmonary capillary wedge pressure (PCWP), 24, 188, 334, 554
 - Pulmonary circulation, 672
 - Pulmonary congestions, 177–178
 - Pulmonary edema, 31
 - acute, 177–178, 481
 - severe, 481–482
 - causes of, 416–417
 - echocardiography Doppler and, 436–437
 - noncardiogenic, 165
 - weaning-induced, 417
 - Pulmonary embolism, 165, 648
 - Pulmonary gradient, 448
 - Pulmonary hypertension (PH), 301
 - Pulmonary infections, 165
 - Pulmonary valves, 448–449
 - Pulmonary vascular resistance (PVR), 271
 - Pulmonary venous congestion, 430–436
 - Pulse
 - oximeters, 456
 - power analysis, 401–403
 - pressure, 403–404
 - wave, 447
 - PVA. *See* Pressure-volume area
 - PV loop. *See* Pressure-volume loop
 - PVR. *See* Pulmonary vascular resistance
 - Pyruvate, 768–769
- Q**
- Q10. *See* Ubiquinone
 - Quinidine, 276
- R**
- RA. *See* Rheumatoid arthritis
 - RAAS. *See* Renin-angiotensin aldosterone system
 - RALES (Randomized Aldactone Evaluation Study), 554
 - Randomized Aldactone Evaluation Study. *See* RALES
 - Randomized Intravenous Tezosentan (RITZ), 632–634
 - RAP. *See* Right atrial pressure (RAP)
 - Rapamycin, 95
 - RAS. *See* Renin-angiotensin system
 - RBF. *See* Renal blood flow
 - RCA. *See* Right coronary artery
 - Reactive oxygen species (ROS), 129
 - in HF
 - antioxidants and, 123
 - biologic significance of, 118–119
 - cardiac hypertrophy and, 122–123
 - counterbalancing/generation of, 118
 - NADPH oxidases and, 119, 120–121
 - roles of, 121–122
 - sources of, 119–120
 - XO and, 119, 120
 - modulation of, 79–80
 - production of, 125
 - roles of, 71, 72–74, 121–122
 - Receptor tyrosine kinases (RTKs), 95
 - Regional wall motion
 - abnormalities (RWMA), 48, 426
 - Remifentanyl, 659
 - Renal blood flow (RBF), 150
 - Renal dysfunctions, 539–540
 - Renal failure, 302
 - Renin, 521
 - aldosterone system, 202
 - Renin-angiotensin aldosterone system (RAAS), 54, 55
 - adrenergic system and, 533–534
 - immune system and, 136–137
 - kidneys and, 751–753

- Renin-angiotensin system (RAS), 150–151, 153
- ReoPro®. *See* Abciximab
- Reperfusion injury
definition of, 70
myocardial
calcium homeostasis and, 74–76
conclusions on, 81
mechanisms of, 70–71, 72
other intercellular events around, 76–77
ROS and, 72–74
therapeutic approaches for, 77–81
- Respiratory acidosis, 461, 463
- Respiratory alkalosis, 461, 463
- Respiratory conditions, 164–165
- Respiratory distress, 480–481
- Respiratory rate (RR), 7, 490
- Respiratory tract infections, lower, 797–798
- REVIVE (Randomized Evaluations of Levosimendan), 26, 176, 553, 600–601
- Rheumatic heart disease, 273–274
- Rheumatoid arthritis (RA), 309–310
- Ribonucleoprotein (RNP), 308
- Right atrial pressure (RAP), 24, 239–240
- Right coronary artery (RCA), 64
- Right heart, RV of
failure of, 64
pressure values of, 64
vascularization of, 64
- Right ventricle (RV), 672
ARDS and, 66
conclusions on, 68
pathophysiology/physiology of, 63–68
right heart and
failure of, 64
pressure values of, 64
vascularization of, 64
right ventricular and
afterload of, 63–64, 66
contractile impairment of, 64–66
volume, 66
RVF and, 63, 66–68
- Right ventricular afterload, 240–242
- RV and, 63–64, 66
contractile impairment of, 64–66
volume, 66
- Right ventricular dysfunctions, in ICU
case reports on, 242–244
conclusions on, 244
by depressed intrinsic contractility, 242
diagnosis of, 238–242
by increased afterload, 240–242
mechanical ventilation and, 237–238
physiology of, 237, 238
- Right ventricular failure (RVF), 63, 66–68
- Right ventricular function, 336–337
- Right ventricular infarction, 179
- Right ventricular preload, 63
- Right ventricular volumes, 63, 418
- Ritodrine, 274
- RNP. *See* Ribonucleoprotein
- ROS. *See* Reactive oxygen species
- ΔPCO_2 . *See* Venous arterial carbon dioxide tension difference
- RR. *See* Respiratory rate
- RTKs. *See* Receptor tyrosine kinases
- RUSLAN trial, 176, 603–604
- RVF. *See* Right ventricular failure
- RWMAs. *See* Regional wall motion abnormalities
- Ryanodine receptor (RyR), 99, 758
- RyR. *See* Ryanodine receptor
- S**
- SAC. *See* Stretch-activated channel blockers
- Saline, 400, 792
- SAPKs. *See* Stress-activated protein kinases
- Sarcoendoplasmic reticulum Ca^{2+} -ATPase. *See* SERCA
- Sarcoidosis, 310–312
- Saturation of hemoglobin with oxygen (SpO_2), 455
- Scars, 227
- Scleroderma (SSc), 313–314
- ScvO₂. *See* Central oxygen saturation measured in superior vena cava
- Sedation, 699
for AHFSs
assessment of, 656–658
clinical case of, 665–667
complications of, 664–665
conclusions on, 667
medications, 658–664
pain assessment and, 655–656
- Sedation Agitation Scale, 657
- Seizures, 699
- Selectins, 139
- Septic myocardial depression, 334
- Septic shock
etiology of, 338–340
prognostic factors in, 337–338
- SERCA (sarcoendoplasmic reticulum Ca^{2+} -ATPase), 102, 114–115, 119
- Serum sodium concentration, 7
- SHAPE study, 19
- SHOCK. *See* Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock
- Shock
cardiogenic, 31, 178, 584–585, 674
case presentation for, 216–218
conclusions on, 218, 736
coronary angiography and, 451–452
definitions of, 207, 730
discussions on, 735–736
echocardiography Doppler and, 440–441
epidemiology of, 207–208
etiology of, 730–731
experiences, 733–735
myocardial reperfusion and, 214–216
newer developments in, 216
other settings for, 216
pathophysiology of, 208–209
patients with, 210–212
reversible myocardial dysfunctions and, 210
VADs for, 731–733
distributive, 584–585
septic
etiology of, 338–340

- prognostic factors in, 337–338
- Should We Emergently
Revascularize Occluded
Coronaries for Cardiogenic
Shock (SHOCK), 207, 208,
209, 215–216, 452, 674, 730,
735
- Shunts
intrapulmonary, 486
left-to-right, 271–272
residual, 272
- SID. *See* Strong ion difference
- Signal transducer and activator of
transcription (STAT), 95,
99, 102
- Singapore, 20, 21
- Sitaxsentan, 632
- SLE. *See* Systemic lupus
erythematosus
- Sleep-related breathing disorders
(SRBDs), AHFSs and
clinical manifestations of,
361
conclusions on, 366
consequences of, 362–363
definitions of, 359–360
etiology of, 360
mechanisms of, 360–361
treatments for, 364–366
- SMASH. *See* Swiss Multicenter
Trial of Angioplasty
Shock
- Smoking, 275
- SNP. *See* Sodium nitroprusside
- Sodium (Na⁺), 10, 12, 302
bicarbonate, 351, 353, 356
levels, 460
serum, 622–623
- Sodium nitroprusside (SNP), 276,
328, 383
clinical trials on, 548
dosages, 548
effects of, 547–548, 549
- SODs. *See* Superoxide dismutases
- Soluble guanylate cyclase (sGC),
758–759
- SOLVD (Studies of Left Ventricular
Dysfunction), 621
- Somatostatin receptor agonists
(SRS-A), 291
- Sotalol, 276
- South America, 32
- South Korea, 21
- Spironolactone, 16, 192, 227
- SpO₂. *See* Saturation of
hemoglobin with oxygen
- SPORTIF III, 647
- SRBDs. *See* Sleep-related breathing
disorders
- SRS-A. *See* Somatostatin receptor
agonists
- SSc. *See* Scleroderma
- STAT. *See* Signal transducer and
activator of transcription
- Statins, 226–227, 574
- ST elevation myocardial infarction
(STEMI), 168, 170
early, 172
elevation/coronary angiography,
451–452
evolution of, 173
non-, 453
- Stem cell therapy, 35
- STEMI. *See* ST elevation
myocardial infarction
- Steroids, 309
- Stewart approach, 459–460
- Stewart-Hamilton principle,
411
- Streptomycin, 225
- Streptozotocin, 122
- Stress-activated protein kinases
(SAPKs), 96–99
- Stretch-activated channel blockers
(SAC), 225
- Stroke volume (SV), 399, 673
- Stroke work (SW), 46
- Strong ion difference (SID),
459
- Studies of Left Ventricular
Dysfunction. *See* SOLVD
- Sulfonamides, 191
- Sulfonylurea, 227
- Superior vena cava, 406,
408–409
- Superoxide, 118
- Superoxide dismutases (SODs),
118, 125
- Supraventricular tachycardias
(SVTs), 229
- Surgery, 699, 727
cardiac, 602–603
pregnancy/cardiac, 280–281
- SURVIVE (Survival of Patients
with Acute Heart Failure in
Need of Intravenous
Inotropic Support), 26, 176,
204, 213, 553, 601
- SV. *See* Stroke volume
- SvO₂. *See* Oxygen saturation
venous
- SVR. *See* Systemic vascular
resistance
- SVTs. *See* Supraventricular
tachycardias
- SW. *See* Stroke work
- Swan-Ganz catheters, 152, 165,
170, 411
- Sweden, 19
- Swiss Multicenter Trial of
Angioplasty Shock
(SMASH), 215–216
- Sympathetic nervous system, 137
- Systemic inflammatory response
syndrome, 838–839
- Systemic lupus erythematosus
(SLE), 306–307
- Systemic vascular resistance
(SVR), 272
- Systemic venous congestion,
438–439
- Systole, 52
- Systolic blood pressure (SBP), 7, 9
- T
- Tachycardia(s)
supraventricular, 229
ventricular, 221
clinical case of, 833–834
conclusions on, 834
feasibility of, 830–831
key caveats of, 832
management of, 827–829
pathophysiology of, 827
polymorphic, 231
special clinical features of,
829–830
sustained, 231
training and, 831–832
- Tacrolimus, 99
- TAH. *See* Total artificial heart
- Taiwan, 21
- TBARS. *See* Thiobarbituric acid
reactive substances
- TBW. *See* Total body water
- TCAs. *See* Tricyclic antidepressants
- TEE. *See* Transesophageal
echocardiography
- Tei index, 315
- Tension-time index, 672
- Terlipressin, 589
- Tezosentan, 223, 631, 632–634

- TGF- β . *See* Transforming growth factor- β
- Thailand, 20
- β -thalassemia
- ACFS and
 - conclusions on, 304–305
 - factors linking, 301–303
 - pathophysiology of, 297–301
 - treatments/therapeutic considerations for, 303–304
 - intermedia, 303–304
 - major, 299, 303
- Thallium, 312
- Theophylline, 350, 366
- Thienopyridines, 640
- Thiobarbituric acid reactive substances (TBARS), 121
- Thorax, 400, 412
- Thrombogenesis, 643
- Thrombolytic therapies, 840–841
- Ticlopidine, 639–641
- Tidal volume, 489
- Time-varying ventricular elastance ($E(t)$), 46–47
- TIMPs. *See* Tissue-inhibitor metalloproteinases
- Tirofiban (Aggrastat®), 641
- Tissue-inhibitor metalloproteinases (TIMPs), 23, 49, 116
- TMZ. *See* Trimetazidine
- TNF- α . *See* Tumor necrosis factor- α
- TNFR1. *See* Tumor necrosis factor receptor type 1
- TNFR2. *See* Tumor necrosis factor receptor type 2
- Tolvaptan, 227, 792–793
- Torsemide, 204, 903, 906–907
- Total artificial heart (TAH), 737
- Total body water (TBW), 786
- TOX-ACLS. *See* Toxicologic-oriented advance cardiac life support
- Toxicologic-oriented advance cardiac life support (TOX-ACLS), 349
- Transesophageal echocardiography (TEE), 24, 212, 306–307
- evaluation of, 425–427, 449
- Transforming growth factor- β (TGF- β), 113
- Transposition of great vessels, 273
- Transthoracic echocardiography (TTE), 24
- Transthyretin (TTR), 316
- Triceps skinfold thickness (TST), 877, 878
- Tricuspid valves, 448
- Tricyclic antidepressants (TCAs), 356
- Triiodothyronine, 294
- Trimetazidine (TMZ), 128
- Troponin, 338
- I, 185
 - T, 185–186
- Trypanosoma cruzi*, 32, 33
- TST. *See* Triceps skinfold thickness
- TTE. *See* Transthoracic echocardiography
- TTR. *See* Transthyretin
- Tumor necrosis factor- α (TNF- α), 23, 73, 96, 119, 333
- Tumor necrosis factor receptor type 1 (TNFR1), 136
- Tumor necrosis factor receptor type 2 (TNFR2), 136
- U
- Ubiquinone (Q10), 118
- Ularitide, 616
- Ultrafiltration, 204
- conclusions of, 515
 - intermittent isolated, 513–515
 - process of, 510–511
 - rationale for, 511–512
 - techniques, 512–513
- United Kingdom, 16
- United States (U.S.), 7, 25, 598
- Urate, 118
- Urodilatin, 608–609, 611–612
- Uruguay, 32
- U.S. *See* United States
- U.S. Food and Drug Administration, 384, 662, 899
- V
- VADs. *See* Ventricular assist devices
- Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study. *See* VERITAS
- Valves
- pressure of RV, 64
 - prosthetic heart, 279–280
 - pulmonary, 448–449
 - tricuspid, 448
- Vascular adhesion molecule (VCAM), 139
- Vascular endothelial growth factor (VEGF), 95
- Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC), 547, 556
- Vasodilators, 173–175, 178–179, 531, 903, 905–906
- effects of, 545
 - induced-, 327
- Vasopressin, 570, 588–589, 819–820
- antagonists, 756–757, 792–793
 - arginine, 621, 787–788
 - in CHF, 621–622
 - conclusions on, 624
 - effects of, 622–623
 - receptor antagonists, 623–624
- Vasopressors, 565, 819
- in acute severe heart failure case study on, 589–591
 - clinical diagnosis of, 583–585
 - conclusions on, 591
 - as pharmacologic therapies, 586–587
 - specific, 587–589
 - as treatments, 585–586
 - infusions, 213
 - options, 570
 - therapies, 176, 341, 354
- VCAM. *See* Vascular adhesion molecule
- VEGF. *See* Vascular endothelial growth factor
- Venoarterial carbon dioxide tension (PCO₂), 419
- Venoarterial carbon dioxide tension difference (Δ PCO₂), 419–420
- Venous oximetry
- case report on, 409–410
 - conclusions on, 410
 - hemodynamic instability and, 408–409
 - measurement of, 406–408
 - normal values of, 406
 - physiopathology of, 406
- Ventilation mechanical
- adjustments, 488–490
 - clinical case of, 491–492
 - conclusions on, 492
 - extubation/weaning of, 490
 - in ICU, 237–238

- indications for, 488
 - physiologic effects of, 486–488
 - right ventricular dysfunctions, 237–238
 - noninvasive, 26
 - BiPAP and, 477–480, 482
 - case report on, 482
 - contraindications for, 482
 - description of, 477–480
 - improvement mechanisms for, 480–481
 - PEEP and, 477–480, 482
 - side effects of, 482
 - uses of, 481–482
 - Ventricle, remodeled, 116
 - Ventricular assist devices (VADs), 193–194, 330–331
 - for cardiogenic shock, 731–733
 - Ventricular beats, premature, 221, 230–231
 - Ventricular fibrillation (VF), 221
 - AEDs and
 - clinical case of, 833–834
 - conclusions on, 834
 - feasibility of, 830–831
 - key caveats of, 832
 - training and, 831–832
 - management of, 827–829
 - pathophysiology of, 827
 - polymorphic, 231
 - special clinical features of, 829–830
 - sustained, 231
 - Ventricular function, 334
 - Ventricular interdependence, 66–67
 - Ventricular muscular pump system, 52–54
 - Ventricular premature beats (VPBs), 221
 - Ventricular relaxation, 54–55
 - Ventricular septal rupture, 179
 - Ventricular tachycardia (VT), 221
 - AEDs and
 - clinical case of, 833–834
 - conclusions on, 834
 - feasibility of, 830–831
 - key caveats of, 832
 - training and, 831–832
 - management of, 827–829
 - pathophysiology of, 827
 - polymorphic, 231
 - special clinical features of, 829–830
 - sustained, 231
 - Verapamil, 293, 316, 330
 - Verbal rating scale (VRS), 655–656
 - VERITAS (Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study), 634
 - VF. *See* Ventricular fibrillation
 - Vietnam, 20
 - Vigileo monitor, 398, 403
 - Vincristine, 312
 - Virchow's triad, 643
 - Vitamin(s)
 - C, 118, 317
 - E, 118, 123, 125
 - K antagonists, 641–642
 - VMAC. *See* Vasodilatation in the Management of Acute Congestive Heart Failure
 - vMF. *See* von Willebrand factor
 - von Willebrand factor (vMF), 23
 - VPBs. *See* Ventricular premature beats
 - VRS. *See* Verbal rating scale
 - VT. *See* Ventricular tachycardia
- W**
- Warfarin, 280, 307
 - Water
 - restriction of, 791–792
 - retention, 302
 - Weaning, 490, 678
- X**
- Xanthine oxidase (XO), 119, 120
 - Xanthine oxidoreductase (XOR), 120
 - XO. *See* Xanthine oxidase
 - XOR. *See* Xanthine oxidoreductase
- Z**
- Zinc (Zn), 118
 - Zn. *See* Zinc