

The **Cardioresenal Syndrome**

The Cardiorenal Syndrome

A Clinician's Guide to Pathophysiology and Management

editors

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Cardiotech Publishing, LLC
5405 W. 44th Street
Minneapolis, Minnesota 55410
USA
www.cardiotechpublishing.com

Any updates to this book may be found at:
www.cardiotechpublishing.com/titles/detail/9780979016479

Comments, inquiries, and requests for bulk sales can be directed to the publisher at:
info@cardiotechpublishing.com.

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Cover design by Beth Wright, Trio Bookworks
Book design by Ann Delgehausen, Trio Bookworks

Library of Congress Control Number: 2011940468

ISBN: 978-0-9790164-7-9

Printed in the U.S.A.

*This book would not have happened
without the myriad of individual patients
who teach me about medicine and life every single day.
Daily I learn, and my heart is touched by their complexity
and courage. In the final accounting, though,
it is not where you go in the morning that is most important
but those who welcome you at the end of the day.
Therefore, this book is dedicated to my dear wife, Stephanie,
and my wonderful daughters, Kazia, Magda, and Jana.*

—J. Thomas Heywood

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Abbreviations

| | | | |
|------|-----------------------------------|-------|--|
| ACE | angiotensin-converting enzyme | CI | confidence interval |
| ACEI | ACE inhibitor | CKD | chronic kidney disease |
| ACTH | adrenocorticotrophic hormone | CNP | C-type natriuretic peptide |
| ADHF | acute decompensated heart failure | CNS | central nervous system |
| ADP | antidiuretic hormone | CO | cardiac output |
| AGE | advanced glycation end-product | CrCl | creatinine clearance |
| AKI | acute kidney injury | CRP | C-reactive protein |
| AMI | acute myocardial infarction | CVD | cardiovascular disease |
| ANP | atrial natriuretic peptide | CVP | central venous pressure |
| AR | adenosine receptor | DNP | <i>Dendroaspis</i> natriuretic peptide |
| ARB | angiotensin receptor blocker | DRI | direct renin inhibitor |
| ATP | adenosine triphosphate | ECFV | extracellular fluid volume |
| AUC | area under the curve | EDPVR | end-diastolic pressure-volume relationship |
| AVP | arginine vasopressin | EF | ejection fraction |
| BMI | body mass index | ERPF | effective renal plasma flow |
| BNP | brain natriuretic peptide | ESRD | end-stage renal disease |
| BUN | blood urea nitrogen | FDA | Food and Drug Administration |
| CABG | coronary artery bypass grafting | GC | guanylyl cyclase |
| cAMP | cyclic adenosine monophosphate | GFR | glomerular filtration rate |
| cGMP | cyclic guanosine monophosphate | HR | hazard ratio |
| CHF | congestive heart failure | JVD | jugular venous distention |
| | | LOH | loop of Henle |

| | | | |
|------|---|---------------|--|
| LV | left ventricular | PRA | plasma renin activity |
| LVAD | left ventricular assist device | PRR | plasma refill rate |
| LVEF | left ventricular ejection fraction | PTCA | percutaneous transluminal coronary angioplasty |
| LVOT | left ventricular outflow tract | RAAS | renin-angiotensin-aldosterone system |
| MAP | mean arterial pressure | RAD | renal assist device |
| MI | myocardial infarction | RAP | right arterial pressure |
| MOF | multiorgan failure | RBF | renal blood flow |
| MSNA | muscle sympathetic nerve activity | RI | renal insufficiency |
| NGAL | neutrophil gelatinase-regulated lipocalin | RPF | renal plasma flow |
| NO | nitric oxide | RV | right ventricular |
| NP | natriuretic peptide | RVG | radionuclide ventriculography |
| NYHA | New York Heart Association | SNS | sympathetic nervous system |
| OR | odds ratio | TGF | tubuloglomerular feedback |
| PCI | percutaneous coronary intervention | TNF- α | tumor necrosis factor-alpha |
| PCWP | pulmonary capillary wedge pressure | TVI | time velocity integral |
| | | vWF | von Willebrand factor |
| | | WRF | worsening renal function |

Foreword

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During the last two decades, remarkable advances in the management of heart failure have resulted in considerable improvement in the mortality of patients with this very common disease. Nevertheless, clinical trial and registry data demonstrate that renal dysfunction is becoming increasingly common. The development of renal impairment, particularly in the setting of acute decompensated heart failure, is associated with poor outcomes. The term *cardiorenal syndrome* is often used to describe the renal insufficiency in heart failure, although previously the syndrome has not been well defined and it has been even less well understood. It is not surprising that renal dysfunction is an integral part of heart failure, given that the kidney plays such an important role in salt

and water regulation. The neurohormonal compensatory mechanisms activated in heart failure affect not just the heart but also the kidney in a complex interaction where the function of one organ influences that of the other.

The management of patients with cardiorenal syndrome remains unclear. On the one hand, until recently the focus has been largely on the heart despite the fact that drugs that “improve” cardiac function acutely often come at the cost of reduced survival. On the other, the therapy that is most obviously nephrocentric, namely diuretics, remains to this day the only means by which symptoms are improved most rapidly and effectively. When employed poorly, however, diuretics can worsen renal function and impair the very organ whose function is critical to symptom relief.

It is therefore important that physicians involved in the care of patients with heart failure better understand the definition, epi-

The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management, 1st ed. © 2012
J. Thomas Heywood and John C. Burnett Jr., eds.
Cardiotext Publishing, ISBN: 978-0-9790164-7-9.

demiology, pathogenesis, clinical features, and mechanisms underlying various evolving novel therapies for this increasingly common and serious condition: the cardiorenal syndrome. It is equally important that investigators, whether basic or clinical scientists, also understand the relationship between abnormalities at the molecular, cellular, organ, and clinical level.

The publication of *The Cardiorenal Syndrome: A Clinicians' Guide to Pathophysiology and Management* is most timely in fulfilling the need and lacuna in the field. Indeed, it is greatly welcomed. Drs. Heywood and Burnett, both distinguished and highly respected experts in this area, have assembled comprehensive chapters by eminent investigators and clinicians covering all aspects of this perplexing syndrome. Areas of certainty, of controversy, and of future research are addressed. Each chapter is complete in its own right and includes an invaluable up-to-date reference list. Pathophysiology and epidemiology are well covered, providing an excellent basis for the later chapters that describe the essential aspects of the disease from drug and mechanical therapies to transplant of either or both organs. Here, clinicians will readily find what has been learned about

the cardiac and renal interactions in heart failure. Dr. Heywood's own chapter provides the clinicians a very useful and practical approach to heart failure patients who present with worsening renal function. Perhaps the most useful lesson from the book is that there are many diverse varieties of this disorder with radically different therapies. For example, worsening renal function can be the result of either too little or too much diuretic. The skill lies in the ability to assess the difference in a particular patient. The authors endeavor to give the reader knowledge for making this key distinction. Left ventricular assist devices can definitively cure renal failure in carefully chosen patients, but they can expensively fail to do so when deployed in the wrong patient.

This book stands as a landmark in the study of the cardiorenal syndrome. It will no doubt be extremely useful to the cardiovascular specialist and internist caring for the growing number of these patients. And it will be just as useful to the scientists and the trainees interested in this condition. The authors are to be congratulated for their success in putting together, with such dexterity and finesse, so much relevant and crucial information on the subject in one volume.

Preface

The last several decades have seen important successes in the effort to treat those suffering from congestive heart failure. Ironically, because heart failure is both so deadly and yet so common, it is particularly well suited for the discovery of new therapies by means of randomized controlled trials. Dating back to the early 1980s, a few key treatments have been identified and vindicated while considerably more procedures and medications have been studied and abandoned. Stable heart failure patients enrolled in clinical trials and benefiting from evidence-based therapy and devices currently have yearly mortalities of 5% or less.¹

This steady progress can in no way allay the sad reality that heart failure remains a frequent cause for hospital admission and

is the direct cause of 50,000 deaths per year in the United States alone. In the past decade appreciation of the role of worsening renal function both as a risk factor and also as a cause of poor outcomes in congestive heart failure have been increasing. The term *cardiorenal syndrome* has been applied to the concurrence of significant renal and cardiac dysfunction, which portends a marked increase in mortality. In the Acute Decompensated Heart Failure National Registry (ADHERE) study, an elevated BUN (blood urea nitrogen) and creatinine were 2 of the 3 most significant predictors of in-hospital mortality.² Of course, it is not surprising that renal dysfunction is an integral part of the syndrome of congestive heart failure given the key role that the kidney plays in fluid and electrolyte balance in mammalian physiology. However, the same clinical trials that so importantly crafted modern therapy for heart failure via neurohormonal blockade and later device implantation at the same

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time obscured the role of renal dysfunction in the progression of heart failure for the simple reason that patients with significant kidney dysfunction were routinely excluded from these trials.

Recognition of the role of renal dysfunction in the progression of heart failure is a critical advance, but it is only a first step; many questions remain. How to define cardiorenal syndrome: is it a cardiovascular problem (low blood pressure, low cardiac output) or one renal pathophysiology? Is blockade of the renin-angiotensin-aldosterone system useful or detrimental in this syndrome? Is cardiorenal syndrome a medical emergency requiring organ transplantation, or a should hospice be utilized instead? Cardiac function can currently be largely supported by implantation of a left ventricular assist device. In these cases clinicians must make critical decisions about the potential reversibility of renal dysfunction before inserting these costly devices.

Of course there are no single answers to these questions. But that does not mean they are the wrong questions or should not be asked. The first line of Tolstoy's *Anna Karenina* is: "Happy families are all alike, every unhappy family is unhappy in their own way." In the same way each patient with cardiorenal syndrome is unique and often requires very different treatment than the patient who appears tomorrow with the same BUN, creatinine, and ejection fraction.

From this realization, *The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management* took its genesis. In an era when information technology is changing rapidly,

it still seemed that a book was the best way to collect key information about what is known and not known about this complex and deadly syndrome, that is, What is cardiorenal syndrome clinically, and how should it be defined and recognized? Are there therapies to counteract it and when, and more importantly, for whom should they be applied? The book contains very clinically oriented chapters on the risks and benefits of organ transplantation and assist device implantation in high-risk individuals; there are also intriguing suggestions that new therapies may be added to our armamentarium in the form of designer peptides and stem cell technologies.

At the core of *The Cardiorenal Syndrome: A Clinician's Guide to Pathophysiology and Management* is the realization that for practicing clinicians, an understanding of the syndrome is not an academic exercise. The well-being and at times the lives of people depend on it. Our hope and belief is that wrestling this most dangerous foe and winning a bit more often will reduce suffering and save lives.

References

1. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention heart-failure events. *New Eng J Med*. 2009;361:1329-1338.
2. Fonarow GC, Adams KF Jr, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005; 293:572-580.