Thyroid and Heart Failure
Ostinato rigore. Destinato rigore.
No’ si volta chi a stella è fisso

Ostinate rigour. To rigour destined.
Who is fixed to a star will nothing change

Leonardo da Vinci
The clinical significance of heart failure is enormous, and the need for novel therapeutic approaches compelling. In the United States alone, almost six million people are affected by the condition and another half million are newly diagnosed annually. Among those older than 65 years, heart failure is the most common indication for hospitalization. It is estimated that heart failure will account for more than $37 billion in U.S. healthcare costs in 2009. Overall, heart failure and other cardiovascular diseases are responsible for more deaths than accidents, cancer, and cerebrovascular accidents combined. Furthermore, in the decades ahead, the impact of heart failure on human health and healthcare economics is bound to increase due to aging of the population. Although the treatment of heart failure with beta-blockers, aldosterone antagonists, angiotensin I converting enzyme inhibitors and angiotensin II receptor blockers, implanted defibrillators, and cardiac resynchronization therapy has led to improvements in mortality and morbidity, the prognosis for patients afflicted with the condition is still poor. Consequently, the search for novel therapeutic targets to improve heart failure outcomes continues.

The earliest reports of patients with myxedema and thyrotoxicosis noted the profound effects of thyroid hormone deficiency and excess, respectively, on the cardiovascular system. Since then, our knowledge of how thyroid hormones regulate cardiac and peripheral vascular functions has progressively advanced from the physiological to the biochemical and molecular levels. Concurrently, our understanding of how systemic illnesses in general, and heart failure in particular, alter thyroid gland function, thyroid hormone metabolism, and triiodothyronine’s molecular actions has grown tremendously. Recent animal and pilot clinical studies have begun to examine the potential of thyromimetic agents—some naturally occurring and others in the form of synthetic analogues—with targeted actions that selectively affect or spare cardiovascular functions.

Consequently, a monograph comprehensively describing the interrelationships between thyroid hormones and heart failure is most timely. The distinguished authors recruited by editors Iervasi and Pingitore summarize the state of the art regarding the molecular and physiological actions of thyroid hormones on the heart and peripheral vasculature (Chap. 5); the pathophysiologial effects of mild and overt thyroid dysfunction on the cardiovascular system (Chaps. 3, 4, 12, 15, and 19) and cardiovascular risk factors (Chap. 14); the changes in thyroid function and thyroid hormone receptors and actions that accompany heart failure and are associated with its severity

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(Chaps. 7, 10, 11, 16, 17, and 18); and pilot studies investigating the application of
native thyroid hormones (Chaps. 13 and 21), their metabolites (Chap. 6), and their
analogos (Chaps. 9 and 20), and their downstream molecular and biochemical actions
(Chap. 22) as potential new approaches to heart failure treatment.

As we stand at the threshold of testing the applicability of all of this knowledge
about thyroid hormone actions to the enormous and incompletely addressed clinical
challenge of heart failure, this monograph represents an important scholarly map,
summarizing where we have been and plotting the most promising directions ahead.

Baltimore, April 2009

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The opportunity to look at old problems from a new angle is always welcome. Today, the possibility of investigating accepted, traditional paradigms in increasingly finer detail has been accompanied by the exponential development of research technologies. These, in turn, have largely been applied in attempts to explain the many and highly variable clinical observations within the already established framework while at the same time adding new information to it. Yet, major breakthroughs in our knowledge often occur by looking at problems from a different perspective, which not infrequently reveals that some long-held and broadly accepted notions are not universally true, such that new, unexpected avenues for research, diagnosis, and treatment are suddenly opened.

The relationship between the thyroid and the cardiovascular system has, until now, received insufficient attention because it remained outside the mainstream of cardiovascular thinking not only in clinical practice but also in research.

This very timely volume offers a unique focus and thereby a clearer understanding of clinical findings with intriguing research potential as well as relevant clinical applications. There is no doubt that this illuminating, very wisely assembled and coordinated volume will stimulate the work of investigators and provide clinicians with inquisitive minds new insights into their daily practice.

The book sets the stage very lucidly with a comprehensive analysis of the general aspects of the interrelationships between thyroid and cardiac failure and, more generally, between thyroid hormones and cardiovascular function. This novel, integrated approach also extends to proposals for new therapeutic strategies. The coordinators of this volume should be wholeheartedly congratulated for their wisdom and foresight in opening a new window of observation into the cardiovascular world. Their efforts will long be appreciated and gratefully acknowledged by all the readers of this volume.

Florence, April 2009

Prof. Attilio Maseri, MD
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In many fields of biomedicine there has been a virtual explosion of new knowledge over the past few years. Among these, a primary position is occupied by the physiological and pathophysiological neurohormonal control of the cardiovascular system, in which the state of the thyroid has assumed a prominent role. Extensive investigations that have made use of new technologies to study animal and human models of disease have focused on the modulation of cardiovascular function by the thyroid system. These results have supported and coincided with a growing understanding of the interacting biomolecular mechanisms that underlie the complex relationships between the thyroid system and cardiovascular function, although many aspects remain largely undefined.

The planning of this book was initiated at the end of 2007, as researchers and clinicians became aware of the pathophysiological and clinical significance of thyroid function with respect to cardiac failure. At the same time, the implications of this relationship for public health, including the socioeconomic aspects, became clear. The driving considerations behind the book can be summarized as follows:

1) Cardiac failure worldwide represents a major public health problem.
2) Cardiac failure is the only common cardiovascular condition that is increasing in prevalence and incidence; it is responsible for about 1 million hospital admissions and 400,000 deaths annually in the United States and in Europe.
3) The critical role of the neuroendocrine system in the evolution of heart failure and in its prognosis is well defined; there is additional evidence that drugs able to modify the natural course of cardiovascular disease act on the neuroendocrine system, namely β-blockers and inhibitors of the renin-angiotensin-aldosterone system.
4) Thyroid hormones are essential for maintaining cardiovascular homeostasis. An altered thyroid hormone profile (including both the so-called low-T₃ syndrome and mild primary thyroid dysfunction) is observed in more than 30% of the total heart failure population.
5) The relationship between an altered thyroid hormone profile and cardiac failure is nowadays widely accepted: nonetheless, it is controversially interpreted by research scientists and clinicians.

Considering the importance of cardiac failure and its relationship to thyroid function, a traditional monographic publication would have been unable to integrate and give sufficient relevance to all the component inter- and multi-disciplinary issues. Instead, the task of bringing together the many different but equally significant aspects was given to the Institute of Clinical Physiology of the National Research Council of Pisa. The integration and merging of information from different disciplines to form a unified whole has been a particular specialty of the Institute since its founding, in 1968, by Professor Luigi Donato.
This book is therefore the result of a collaborative effort aimed at presenting a broad-ranging discussion of the relationship between thyroid and cardiac (dys)function, from the cellular mechanisms of thyroid-hormone action on the heart and vascular system to the clinical implications of their relatedness.

To facilitate the use of this book as a reference work, the contributions have been organized into four sections. Section one is a general introduction to the problem of heart failure with respect to thyroid function, while section two explores the basic aspects of the thyroid-hormone and cardiovascular systems in the normal and in the failing heart. Section three examines the clinical aspects, and section four the current and future therapeutic options for patients with thyroid and cardiac dysfunction.

Once the topics of the book were decided upon, we set about to identify the authors who could contribute to it by providing state-of-the-art information regarding the complex and widely debated emerging field of cardio-endocrinology. We sought to take into account the needs of medical students, post-graduates in the various medical disciplines (especially cardiology, internal medicine, and endocrinology), researchers working in the relevant fields of study, physicians of general medicine, and specialists who are confronted daily with the problem of heart failure associated with thyroid dysfunction. Accordingly, the scope of the book ranges from the cellular and subcellular mechanisms of thyroid-related cardiac disease to its clinical and epidemiological features. The authors who contributed to the volume are specialists in often very different, at times seemingly unrelated branches of medicine, such as biochemistry, cardiovascular physiology, endocrine physiology, experimental cardiology, experimental endocrinology, clinical cardiology, clinical endocrinology, nephrology, neuropsychiatry and cardiovascular epidemiology. They were invited exclusively on the basis of their internationally recognized authority and leadership, as pioneers and innovators in their areas of expertise. Without exception, they have transmitted their knowledge in a straightforward, exhaustive, and highly readable manner.

Fortunately, what had at first appeared to be a complicated task, joining these seemingly disparate chapters into a book, was greatly facilitated by the enormous enthusiasm and spirit of collaboration of the contributing authors, whom we warmly thank.

The reader of this book will notice that several topics of particular interest have been treated by authors, some from different specialties, with contrasting points of view. Rather than being a source of confusion, these differences prevent the book’s uniformity and coherence from becoming synonymous with a static and dogmatic vision. Certainty has no place in the medical sciences, and scientific curiosity represents a first and necessary step in innovation, which derives from a dynamic and critical exchange of ideas. In our opinion, these differences in opinion and interpretation are one of the strong points of the book rather than an element of weakness: they provide the reader with fresh points of view on important topics and reflect the lack of a common interpretation by the most competent authorities in the field. The same can be said for the slight overlaps in content that sometimes occur, as in many cases they present the same information from a different perspective and thus with different emphasis.

Moreover, as Editors of the book, we felt that it was important that the book’s individual chapters be able to stand alone in terms of subject matter. To this end, we gave the authors free hand to express their personal points of view and to develop their arguments in the context of their specialties.

The authors are particularly grateful to the Editorial Team of Springer, specifically, Drs. Donatella Rizza, Alessandra Born, and Angela Vanegas, who believed in
the goals of the project. Their competence, professionalism, constant support, patience, and kindness have made this book more than just an adventure but also a thoroughly enjoyable and stimulating experience.

If this multi-disciplinary but cohesive book is able to assist the clinician in his or her clinical practice, guide students and post-doctoral students of medicine, and encourage clinical as well as basic researchers towards new initiatives and explorations in the field, it will have certainly fulfilled its function.

*Pisa, April 2009*  
*Giorgio Iervasi*  
*Alessandro Pingitore*
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