Contents

Preface: Emerging Comorbidities in Heart Failure **xi**

Antonio Cittadini, Eduardo Bossone and Hector O. Ventura

Thyroid Abnormalities in Heart Failure **139**

Sara Danzi and Irwin Klein

The effects of hyperthyroidism and hypothyroidism on the heart and cardiovascular system are well documented. It has also been shown that various forms of heart disease including but not limited to congenital, hypertensive, ischemic, cardiac surgery, and heart transplantation cause an alteration in thyroid function tests including a decrease in serum liothyronine (T_3). This article discusses the basic science and clinical data that support the hypothesis that these changes pose pathophysiologic and potential novel therapeutic challenges.

Anabolic Deficiencies in Heart Failure: Ready for Prime Time? **149**

Raffaele Napoli, Roberta D'Assante, Martina Miniero, Andrea Salzano, and Antonio Cittadini

Chronic heart failure (CHF) is a complex syndrome characterized by symptoms and signs supported by different forms of cardiac impairment. The link between multiple hormonal and metabolic derangements and the development of CHF and the beneficial effects seen with hormonal replacement therapy suggest that a reduction of anabolic pathways might contribute to the onset of CHF. Therefore, an imbalance between anabolic and catabolic forces could be responsible for the development of CHF. There are sufficient evidence to support the screening in patients with CHF of hormonal deficiencies and their correction with replacement therapy.

The Gut Axis Involvement in Heart Failure: Focus on Trimethylamine N-oxide **161**

Andrea Salzano, Shabana Cassambai, Yoshiyuki Yazaki, Muhammad Zubair Israr, Dennis Bernieh, Max Wong, and Toru Suzuki

A novel pathophysiological model of interest is the association between heart failure (HF) and the gastrointestinal system, the 'gut hypothesis'. The choline and carnitine metabolic by-product, Trimethylamine N-oxide (TMAO) is one of the more prominent molecules associated with the link between HF and the gut. Indeed, TMAO levels are increased in HF populations and higher TMAO levels are associated with poor prognosis, whereas low TMAO levels either at baseline/follow up confer better prognosis. Considering that TMAO levels seem not to be affected by guideline-HF treatment, this model could represent a novel and independent therapeutic target for HF.

Chronic Obstructive Pulmonary Disease and Heart Failure: A Breathless Conspiracy **171**

Pierpaolo Pellicori, John G.F. Cleland, and Andrew L. Clark

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are both common causes of breathlessness and often conspire to confound accurate diagnosis and optimal therapy. Risk factors (such as aging, smoking, and obesity) and clinical presentation (eg, cough and breathlessness on exertion) can be very similar, but the treatment and prognostic implications are very different. This review discusses the diagnostic challenges in individuals with exertional dyspnea. We also highlight the prevalence, clinical relevance and therapeutic implications of a concurrent diagnosis of COPD and HF.

Sleep Breathing Disorders in Heart Failure 183

Amanda C. Coniglio and Robert J. Mentz

Sleep-disordered breathing (SDB), including obstructive sleep apnea, central sleep apnea (CSA), and Cheyne-Stokes respiration, is common in patients with heart failure (HF) and associated with lower left ventricular ejection fraction (EF), increased arrhythmia burden, and increased mortality. Continuous positive airway pressure therapy improves short-term and long-term outcomes in HF patients. Adaptive servoventilation (ASV) therapy in patients with low-EF HF with predominant CSA is not recommended. Ongoing trials are evaluating whether ASV will have a role in SDB treatment. Phrenic nerve stimulation is an emerging treatment option that has shown promising outcomes. All HF patients should be screened for SDB.

When Pulmonary Hypertension Complicates Heart Failure 191

Alberto-Maria Marra, Nicola Benjamin, Antonio Cittadini, Eduardo Bossone, and Ekkehard Grünig

Pulmonary hypertension (PH) often complicates chronic left-sided heart failure, with a remarkable impact on quality of life, exercise capacity, and survival. PH in chronic left-sided heart failure (PH-LHD) is not only caused by backward transmission of pressures but also involves impairment of atrial function, inflammation, and vasoconstriction. Once the left atrium loses its reservoir capacity, usually pulmonary vascular resistances increase. Right atrial dilation commonly represents the first sign of PH-LHD, before right ventricle dilatation and systolic dysfunction develop, leading to right heart insufficiency, and ultimately, right heart failure.

Cardiac Cachexia Revisited: The Role of Wasting in Heart Failure 199

Miroslava Valentova, Stefan D. Anker, and Stephan von Haehling

Cardiac cachexia is a co-morbidity of heart failure (HF) defined by a non-edematous weight loss of $\geq$6% within the previous 6–12 months. Cachexia affects about 10-39% patients with HF and occurs typically in advanced stages of HF, especially in the presence of congestive right ventricular dysfunction. This review elucidates the approaches and pitfalls in the diagnosis of cachexia. It summarizes the prevalence and impact of cardiac cachexia. It also discusses changes in body composition over the course of HF and provides an overview of the mechanisms involved in wasting in HF.

The Impact of Obesity in Heart Failure 209

Salvatore Carbone, Carl J. Lavie, Andrew Elagizi, Ross Arena, and Hector O. Ventura

Overweight and obesity adversely impact cardiac structure and function, affecting systolic and diastolic ventricular function. Epidemiologic studies have documented an obesity paradox in large heart failure cohorts, where overweight and obese individuals with established heart failure have a better short- and medium-term prognosis compared with leaner patients; this relationship is strongly impacted by level of cardiorespiratory fitness. There are implications for therapies aimed at increasing lean mass as well as weight loss and improvements in quality of diet for the prevention and treatment of heart failure and concomitant obesity to improve cardiorespiratory fitness.

The Cardiorenal Syndrome in Heart Failure 219

Maria Rosa Costanzo

Abnormal fluid handling leads to physiologic abnormalities in multiple organ systems. Deranged hemodynamics, neurohormonal activation, excessive tubular

sodium reabsorption, inflammation, oxidative stress, and nephrotoxic medications are important drivers of harmful cardiorenal interactions in patients with heart failure. Accurate quantitative measurement of fluid volume is vital to individualizing therapy for such patients. Blood volume analysis and pulmonary artery pressure monitoring seem the most reliable methods for assessing fluid volume and guiding decongestive therapies. Still the cornerstone of decongestive therapy, diuretics' effectiveness decreases with progression of heart failure. Extracorporeal ultrafiltration, an alternative to diuretics, has been shown to reduce heart-failure events.

Hypertension and Heart Failure: Prevention, Targets, and Treatment **237**

Katherine E. Di Palo and Nicholas J. Barone

Hypertension is possibly the most powerful, modifiable risk factor for the development of heart failure. Chronic hypertension drives cardiac remodeling within the left ventricle resulting in hypertensive heart disease, which ultimately manifests as heart failure. Early detection and appropriate management are necessary to prevent heart failure as well as other cardiovascular diseases. Achieving blood pressure goals in conjunction with using evidence-based treatments can improve clinical outcomes for patients with comorbid hypertension and heart failure.

Atrial Fibrillation in Heart Failure: Focus on Antithrombotic Management **245**

Mohammed Obeidat, Malcolm Burgess, and Gregory Y.H. Lip

Heart failure (HF) and atrial fibrillation (AF), increasingly common in the aging population, are closely related and commonly found together. This article explores the relationship between AF and HF and the thromboembolic effect of these diseases. Morbidity and mortality are increased when the 2 conditions are seen together. Stroke risks are significant with AF and all subtypes of HF. This article suggests that all patients with AF and HF should be considered for anticoagulation. Current evidence suggests that non–vitamin K antagonist oral anticoagulants are effective and safe in AF and HF in comparison with warfarin.

Sex and Gender-Related Issues in Heart Failure **259**

Giulio Francesco Romiti, Fabrizio Recchia, Andrea Zito, Giacomo Visioli, Stefania Basili, and Valeria Raparelli

Understanding the role of sex- and gender-related factors, when dealing with a global growing epidemic such as heart failure, is a much needed and unmet goal for health care providers and scientists in order to design targeted strategies, aimed at improving both clinical and patient reported outcomes measures in women and men with heart failure. The present review provides an overview of the current available evidence on sex- and gender-related differences in heart failure.

Psychological Disorders in Heart Failure **269**

Katherine E. Di Palo

The occurrence of depression, anxiety, and insomnia is strikingly high in patients with heart failure and is linked to increased morbidity and mortality. However, symptoms are frequently unrecognized and the integration of mental health into cardiology care plans is not routine. This article describes the prevalence, identification, and treatment of common comorbid psychological disorders.