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PART I: INTRODUCTION

Heart Failure in the 1990s: Evolution of a Major Public Health Problem in Cardiovascular Medicine

REKHA GARG, MD, MS, MILTON PACKER, MD, FACC,* BERTRAM PITT, MD, FACC,†
SALIM YUSUF, MBBS, FRCP, DPHIL‡

Bethesda, Maryland, New York, New York, Ann Arbor, Michigan and Hamilton, Ontario, Canada

During the last decade, congestive heart failure has evolved into the most important public health problem in cardiovascular medicine. It is estimated that heart failure afflicts more than 3 million patients in the United States—nearly 1.5% of the adult population. The disease is at present the nation's most rapidly growing cardiovascular disorder; almost 400,000 people develop heart failure for the first time each year. Heart failure is a major cause of disability and morbidity. It impairs the ability of patients to carry out activities of daily living, care for themselves and support their families. In addition, it is responsible for the hospital admission of nearly 1 million Americans annually and is the most common reason for hospitalization of the elderly. Heart failure is a major contributor to the cost of health care—the country spends more than $8 billion in the care of these patients annually. Finally, it is a major cause of cardiovascular death; nearly 200,000 patients in the U.S. die of heart failure each year.

Given the enormous importance of heart failure, it would seem appropriate to channel considerable public and private resources to the conquest of this disease. Yet, to do so effectively, it is critical to review what we know and what we need to do. Such a review is particularly important today because our perspective of and our approach to the syndrome has undergone dramatic changes in recent years (1).

From the Clinical Trials Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; *Division of Circulatory Physiology, Columbia University College of Physicians and Surgeons, New York, New York; †Division of Cardiology, University of Michigan School of Medicine, Ann Arbor, Michigan, and the ‡Division of Cardiology, McMaster University, Hamilton, Ontario, Canada.

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Address for correspondence: Rekha Garg, MD, MS, Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, Federal Building, Room 5C10, 7550 Wisconsin Avenue, Bethesda, Maryland 20892.

Evolution of the Syndrome of Heart Failure

Heart failure in the 1990s is fundamentally a different disorder from what it was during most of this century. Thirty to 50 years ago, the most frequent causes of chronic heart failure were hypertensive heart disease and valvular heart disease, particularly mitral stenosis. At that time, physicians viewed heart failure as a slowly progressive disorder that remained compensated for many years. The major challenge for physicians was the control of pulmonary and peripheral edema, and numerous interventions were developed to deplete the body of excess fluid. In addition, many patients with heart failure had arrhythmias, which generally originated in the atria. It is noteworthy that digitalis gained popularity in the treatment of heart failure in part because of its ability to control the ventricular response to these arrhythmias (2). Yet despite the control of fluid retention and heart rate, heart failure progressed and the patient eventually died. The cause of death was commonly a pulmonary or cutaneous infection that resulted from interference with local defense mechanisms overwhelmed by the presence of edema.

This perspective of heart failure differs markedly from the syndrome of heart failure in the 1990s. Left ventricular dysfunction due to coronary artery disease is now the most common cause of chronic heart failure. Heart failure may evolve rapidly after the loss of a critical quantity of myocardium as the direct result of ischemic necrosis or it may develop gradually as a consequence of ventricular remodeling that follows a large myocardial infarction. In addition, heart failure may occur as the result of a dilated cardiomyopathy, the prevalence of which has increased during the last 20 years. In the 1990s, the major therapeutic challenge for the physician is no longer the control of fluid retention, because—with the advent of potent diuretic drugs—most patients with advanced symptoms do not have refractory edema. Now physicians direct their therapeutic efforts to the

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amelioration of effort intolerance (precipitated by activities of daily living) and the reduction of cardiovascular morbidity and mortality. Arrhythmias are still common in patients with heart failure, but these generally originate in the ventricles rather than the atria. Finally, the course of heart failure does not progress predictably from mild to severe disease, unfolding over a period of decades. Instead, advanced symptoms can develop in a matter of weeks or months (rather than years or decades), and sudden death may interrupt the course of the disease at any time.

Evolution of New Pathophysiologic Concepts of Heart Failure

As the syndrome of heart failure has evolved during recent decades, so has our understanding of the pathophysiology of heart failure. Thirty years ago, physicians believed that endogenous mechanisms activated during the course of heart failure played an important adaptive role in supporting the circulation as heart failure progressed. According to this traditional view, systemic vasoconstriction occurred in patients with heart failure to support the perfusion of vital organs; pulmonary vasoconstriction developed to reduce the rate of blood flow into the left heart chambers and thus lower pulmonary venous pressures; and the sympathetic nervous system was activated to enhance cardiac contractility. Physicians were advised not to interfere with these endogenous compensatory mechanisms because such interference would produce deleterious hemodynamic and clinical effects (3).

Our view of the pathophysiology of heart failure has changed dramatically during the last 20 years. We now believe that systemic vasoconstriction can limit the systolic performance of the left ventricle and contribute to the development of heart failure. We believe that neurohormonal activation accelerates the rate of progression of heart failure, not only because of its ability to cause systemic vasoconstriction but because such activation leads to direct deleterious effects on the heart. This shift in our view of the pathophysiology of heart failure—from the original concept that endogenous mechanisms were adaptive to the present concept that such mechanisms are detrimental—has been supported by the results of clinical studies. Pharmacologic blockade of the alpha-adrenergic and angiotensin II receptors produces notable short-term hemodynamic benefits (4,5). Sustained interference with endogenous neurohormonal systems (produced by inhibition of the angiotensin-converting enzyme or blockade of the beta-adrenergic receptor) produces long-term symptomatic improvement (6,7). Finally, the long-term administration of vasodilators and converting enzyme inhibitors reduces morbidity and mortality (8,9). These (and many other) studies have proved conclusively that the activation of endogenous vasoconstrictor and neurohormonal mechanisms in heart failure can no longer be regarded as a beneficial homeostatic process.

The Development and Assessment of New Therapeutic Interventions

Changes in the clinical features and pathophysiology of heart failure during the last 20 years have been paralleled by a dramatic increase in the number of therapeutic strategies, many of which have challenged traditional approaches to management. Whereas in the past, physicians believed that bed rest was an important ingredient in the recovery of the patient with heart failure, we now encourage exercise to minimize the magnitude of deconditioning. Whereas in the past, physicians believed that systemic perfusion pressures had to be supported to preserve organ function, we now routinely decrease blood pressure with potent vasodilator drugs. Whereas in the past, physicians thought that the administration of inotropic drugs would address the fundamental defect in heart failure, we now worry about the long-term safety of inotropic agents (10) and even consider treating patients with drugs that depress the function of the heart (e.g., beta-blockers).

These advances in therapeutics have been paralleled by major advances in our ability to assess the efficacy and safety of new interventions. Twenty years ago, physicians believed that they could evaluate the utility of a new drug by measuring the change its administration produced on the symptoms and clinical status of a few patients. In the 1970s and 1980s, these subjective assessments were supplemented by objective measurements of left ventricular function, assessed using either invasive or noninvasive techniques. However, during the last decade, we have learned that such assessments can be misleading. Changes in symptoms in a small number of patients can be produced by placebo therapy, and changes in ventricular function (even if produced by a drug) do not reliably predict changes in the clinical status or outcome of patients. In the 1980s and 1990s, we have learned that interpretable information concerning the efficacy and safety of therapeutic interventions can be most readily obtained by performing large scale controlled clinical trials that evaluate clinically relevant endpoints.

Aim of the Supplement

Given these extraordinary changes in our perspective of heart failure during the last 20 years, it is appropriate to assess where we are and where we need to go. This is a particular appropriate time to do so because the recent completion of several large scale multicenter trials (8–14) has brought considerable new knowledge to the area of heart failure. These trials have affirmed the changes in clinical features and natural history of heart failure that have occurred during the last 20 years and have demonstrated the utility of interventions that have challenged traditional concepts of pathophysiology and therapeutics. Yet these trials have also shown us that, despite the optimal management, heart failure remains a disabling and lethal disease. Fortunately, we are better equipped than ever to meet this

challenge of heart failure with the development of new tools of molecular biology and experimental physiology.

The aim of this supplement to the *Journal of the American College of Cardiology* is to provide a comprehensive review of our present knowledge of the pathophysiology and treatment of chronic heart failure. Whereas other supplements have focused on specific aspects of the disorder or a specific approach to management, the present collection of manuscripts is intended to present a comprehensive overview of the syndrome. The articles in this supplement represent the proceedings of a 2-day symposium that was held on April 26 and 27, 1992 under the sponsorship of the Clinical Trials Branch of the National Heart, Lung, and Blood Institute. All articles in the supplement have undergone peer review. Two reports presented at the meeting have been published elsewhere (14,15) and are not reproduced in this supplement. Readers are referred to the primary publications for information regarding these presentations.

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