Report of the Task Force on Research in Heart Failure

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In 1992, the National Heart, Lung, and Blood Institute (NHLBI) convened a Task Force on Research in Heart Failure composed of national experts in basic, clinical, and population-based research on this condition. The task force’s charge was to assess the current state of research on heart failure and recommend future research approaches that are likely to lead to improved management or prevention of heart failure and, thereby, improved health for all Americans by the end of the decade. The task force presents its overall findings in the following summary that they prepared, highlighting especially promising areas for future research. Research accomplishments and specific recommendations in each of four major areas addressed by the task force—basic research, clinical research, population-based studies, and treatment—are described more fully in the main report. It is available on the NHLBI Gopher (accessible through one’s Internet Gopher client-Server: gopher.nhlbi.nih.gov, Port:70). A printed copy can be obtained from Charlene French, NHLBI, Building 31, Room 5A03, National Institutes of Health, Bethesda, MD, 20892 (telephone: [301]496-6331).

The Institute is very pleased to have this report to guide its heart failure research activities in the coming years. We are grateful to the task force chair, Dr Eugene Braunwald; the cochairs, Drs Arnold M. Katz, Francois M. Abboud, and Jay N. Cohn; and the members for their valuable contribution to this important and timely endeavor.

Introduction

During the past 10 years, scientists have made considerable progress in understanding the causes of and improving the treatment for heart failure. Because of this progress and recent technological advances, there are now outstanding opportunities for new research initiatives that will enable researchers to delineate populations at risk of developing heart failure and to design more effective preventive and therapeutic strategies. Expansion of research programs on the early detection and treatment of common precursors of heart failure, such as hypertension, atherosclerosis, and ventricular hypertrophy (thickening of the heart wall), offers great promise for reducing the morbidity and mortality from heart failure and the large human and financial costs associated with this condition.

Heart Failure: A Definition

The principal functions of the heart are to accept blood from the venous system, deliver it to the lungs where it is oxygenated (aerated), and pump the oxygenated blood to all body tissues. Heart failure occurs when these functions are disturbed substantially; it represents the “final common pathway” for all serious forms of heart disease. The cardinal clinical manifestations of heart failure are shortness of breath and exercise intolerance. The heart may fail when it has carried an excessive burden for a prolonged period of time, such as in patients with hypertension, valvular heart disease, and certain forms of congenital heart disease. Heart failure is a common consequence of ischemic heart disease in which portions of heart muscle have become infarcted (lost their viability) or in which surviving heart muscle does not receive adequate nourishment and thereby loses its normal contractile function. Heart failure is also observed in patients with a variety of infectious, inflammatory, and infiltrative conditions that affect heart muscle.

Heart Failure: A Major Health Problem

In 1990, Americans made almost 3 million visits to physicians because of heart failure. There were also about 750,000 hospital discharges in which patients were diagnosed with heart failure—a number that has doubled in just 12 years. Paradoxically, the prevalence of heart failure is increasing at the same time that more patients with heart disease are saved from premature death. However, because most of the treatments available slow the course of heart disease but do not abolish it, an increasing proportion of the population is living with heart disease and is therefore at risk of heart failure. Two important segments of the US population, elderly individuals and blacks, are at particular risk of developing heart failure. Because they constitute a growing proportion of the population, one can anticipate that the prevalence of heart failure and deaths from this condition, if unchecked, will continue to rise.

Heart failure is a progressive, fatal condition. Only about one half of patients survive after the development of severe symptoms. This bleak prognosis is comparable to that for patients with advanced cancer or acquired immunodeficiency syndrome (AIDS). By the time patients develop heart failure, some of their myocardial cells have already died or are seriously and irreversibly deteriorated, impairing the function of these cells and contributing to a poor prognosis for the patient.

Abundant opportunities lie ahead for improving the treatment of heart failure through basic, clinical, and

From the National Heart, Lung, and Blood Institute, Bethesda, Md.
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population-based research. Prevention remains the ultimate goal. Key opportunities are highlighted below in the areas of basic research, molecular biology, clinical research and treatment, and prevention.

Basic Research on Heart Failure

Fundamental research continues to be needed to understand basic processes, explore promising hypotheses, and draw attention to the aging heart.

Understanding Basic Processes

During the past decade, enormous advances have been made in understanding the fundamental processes that underlie contraction and relaxation in normal and failing hearts. This understanding, vital to an ultimate solution to the problem of heart failure, is derived from research conducted on the hearts of intact animals, isolated hearts, strips of cardiac muscle, isolated myocytes (heart muscle cells), subcellular organelles, molecular mediators of heart failure, and, most recently, the genetic apparatus of cardiac cells. Studies in animal models of heart failure have been and continue to be valuable because they enable researchers to evaluate the feasibility of treatment options before they are applied in humans. Three research areas are highlighted below.

Models of Heart Failure

Two models of heart failure, caused by naturally occurring genetic abnormalities or electrical pacing, appear to be particularly promising for improving our understanding of human heart failure. They should be studied intensively. Transgenic models, in which a foreign gene is inserted into an animal for study, should be developed to elucidate the role of specific gene products in the initiation and progression of heart failure.

National Tissue Bank

The increasing availability of human myocardial tissue obtained during transplantation and autopsy offers important opportunities for studying the pathophysiology of clinical heart disease. Consideration should be given to creating a national tissue bank to coordinate the distribution of heart tissue obtained during cardiac transplantation and open-heart surgery. This bank would provide a unique database for studying human heart failure.

Components of the Myocardial Cell

The research agenda also should include identification of the mechanisms responsible for altered expression of contractile proteins, membrane pumps, and other proteins in failing hearts and elucidation of the functional consequences of these mechanisms in terms of cardiac pump function and survival of patients.

Exploring Promising Hypotheses

A number of provocative hypotheses for explaining the basic processes responsible for heart failure have emerged recently. For example, it has been proposed that cells of the failing heart are in an energy-deprived state that is secondary to an imbalance between energy production and energy utilization and not unlike an automobile that must climb a steep hill with limited fuel in its tank. Basic research has shown that hypertrophy of myocytes is an important adaptive response for reducing the load on the heart muscle. However, this increased mass of muscle must be nourished, and its demands may overtax a marginal energy supply. Research has also shown that normal contraction and relaxation of heart muscle depend on an orderly, well-synchronized movement of calcium and other ions into, out of, and among critical sites within the myocytes. Energy deprivation of myocardial cells interferes with these movements and usually causes, initially, a failure in relaxation of the heart muscle and, when more severe, a failure in contraction of the heart muscle. Three research areas are highlighted below.

Energy Deprivation in Heart Failure

More research must be conducted to establish the verity of the energy-deprivation theory of heart failure. If confirmed, this theory would have far-ranging implications for treatment. It would support the use of therapies that, over the long term, reduce cardiac workload and thereby the heart’s energy requirements while discouraging the use of measures that cause prolonged stimulation of the strength of contraction, which increases the heart’s energy requirements.

Cell Division in the Adult Heart

The division of heart muscle cells in the fetal heart generally ceases shortly after birth. For this reason, when a portion of the heart becomes necrotic, such as in myocardial infarction (heart attack), an excessive burden is placed on the surviving cells. This burden often leads to heart failure. The development of techniques to stimulate the orderly division of normal myocytes could prove decisive in preventing and treating heart failure in patients who have sustained damage to discrete portions of the heart.

Angiogenesis

Inadequate delivery of oxygen and nutrients to heart muscle through diseased coronary arteries (ischemic heart disease) is a major cause of energy deprivation and heart failure. A promising area of research, therefore, is the further development of small coronary vessels through angiogenesis (ie, stimulating the growth of new vessels).

The Aging Heart

Scientists have observed in aging rodents a progressive death of individual cardiac cells. This finding has important implications for human heart failure. The “dropout” of myocytes scattered throughout the heart places a greater workload on the remaining cells. This load may become excessive and cause heart failure, especially if hypertension or the loss of other viable cells, such as occurs in myocardial infarction, is superimposed on the normal aging process. This significant laboratory observation may explain why elderly persons have an increased prevalence of heart failure. It also underscores the great potential for preventing heart failure through early and vigorous treatment of hypertension, prevention of myocardial infarction, and limitation of infarct size by restoring blood flow early. A specific research area is highlighted below.
Molecular Effects of Age

In view of the growing public health impact of the aging US population, research should be undertaken to provide a better understanding of the molecular effects of age on the heart.

Molecular Biology and Heart Failure

Using the advanced techniques of molecular biology, scientists have made and will continue to make strides in exploring hereditary heart disease, individual and population differences, genetic predispositions, and potential gene therapies.

Genes and Inheritance

Increasingly, the powerful tools of modern molecular biology are being applied to research on the heart. Researchers have discovered alterations in the genes that express proteins vital for the contraction of overloaded hearts, and major advances are being made in understanding hereditary heart diseases. Specific heritable disorders of cardiac muscle, connective tissue, and the cardiac conduction system have been described. Many individuals in families known to be affected by these disorders are at a definable higher risk of manifesting specific cardiovascular diseases.

One significant discovery is that the mutation of a specific gene on chromosome 14 that encodes a key cardiac contractile protein, myosin heavy chain, is associated with and presumably responsible for some cases of familial hypertrophic cardiomyopathy. This condition is associated with abnormalities in cardiac contraction and relaxation and sometimes heart failure. This discovery makes possible the genetic diagnosis of familial hypertrophic cardiomyopathy in many patients and points the way to treating affected individuals in an early, "preclinical" stage of disease in the hope of ultimately preventing heart failure. Perhaps even more important, this discovery is an important lead in understanding the molecular basis of abnormal cardiac contraction. A specific research area is the molecular genetics of heart muscle disease. Idiopathic dilated cardiomyopathy, a relatively common form of heart muscle disease that leads to heart failure, is inherited in approximately 20% of cases. Efforts to elucidate the fundamental genetic abnormalities in this disorder should be encouraged. If successful, they could yield important information on the fundamental cause of heart failure and new methods of prevention.

Individual and Population Differences

It is not clear why some individuals, especially black Americans compared with white Americans, develop more severe ventricular hypertrophy (a forerunner of heart failure) with comparable degrees of blood pressure elevation. A key research area is identification of individuals at risk. By use of molecular biology techniques, it may be possible to identify a genetic basis for the wide differences observed among groups and individuals in the responses of the heart to various stresses. With this information, individuals at particular risk of developing heart failure could be identified so that preventive strategies could be targeted to these individuals.

Identifying the Genes Responsible

Although the main precursors of heart failure (atherosclerosis and hypertension) are complex, multigenic, and environmentally mediated, some forms of these conditions are associated with well-established and identified genetic abnormalities. A key research area is genetic predisposition to disease. Specific studies characterizing the human genome and its altered expression in atherosclerosis and hypertension should be undertaken because they are likely to produce new information on which genes are involved in the development of conditions that presage these diseases. The findings from these studies could lead to early and specific therapy for these precursors. Unraveling the genetic predisposition to expression of these important precursors and their response to therapy could pay rich dividends for preventing heart failure.

Gene Therapy

A major long-range goal that has potential for preventing and treating heart failure is the correction of abnormal cardiac gene expression. Building on evidence that the reduced density of calcium pump molecules in the sarcoplasmic reticulum (a structure within myocytes) impairs cardiac relaxation and filling in a failing heart, it may be possible, for example, through gene therapy to stimulate gene expression in the calcium pump. This would improve ventricular filling and prevent an important form of heart failure. Through gene therapy, it may also be possible to manipulate the internal repair mechanisms that are available to the heart. Two research areas are (1) introduction of foreign genes into the heart; Gene therapy offers considerable promise for preventing and treating heart failure. Application of such therapy to heart failure and its precursor conditions should be explored. Recent evidence showing that certain viruses are capable of transferring genes to nondividing cardiac muscle cells could make gene therapy for diseases of cardiac muscle realistic. (2) Restoring cell division: Because myocytes in the adult human heart have lost their capacity to divide, the response to cell injury is myocyte "dropout," which can lead to heart failure. Gene therapy should be explored as a method for restoring this capacity to adult myocytes. If successful, this approach could be applied widely in treating many conditions that lead to heart failure, including myocardial infarction.

Clinical Research and Treatment

Advances in understanding the compensatory mechanisms involved in heart function and in developing effective drug therapies have led to a number of exciting treatment strategies for the future.

Compensatory Mechanisms

The natural history of heart failure, in general, consists of three phases: myocardial injury, activation of compensatory mechanisms, and overt heart failure owing to inadequate or maladaptive compensation. Beginning in the second phase, a series of neural (nervous) and humoral (hormonal) responses are triggered. Whereas a healthy heart is able to secrete active substances into the circulation, these "endocrine" functions are altered in a failing heart, and an excess secretion of
substances such as atrial natriuretic peptide and brain natriuretic peptide is released, affecting target organs such as the kidney, vascular endothelium, and smooth muscle. A failing heart also releases into the bloodstream excess amounts of the catecholamine norepinephrine, which may activate adrenergic receptors. A variety of other molecules, including β-endorphins, vasopressin, and endothelin, and increased activity of the renin-angiotensin-aldosterone system constrict blood vessels and appear to play important roles in the impaired tissue perfusion that occurs in heart failure. It is now known that overactive neurohumoral responses, a hallmark of heart failure, support the circulation and may be helpful to patients with acute heart failure, but they also tend to increase the burden on the failing heart by increasing the resistance against which the heart contracts. Over the long term, these compensatory mechanisms are deleterious.

Drug Therapy

A number of drugs have been developed that interfere with neurohumoral activation. Among these are the angiotensin-converting enzyme inhibitors. These drugs have been used successfully over the past decade to treat hypertension and relieve heart failure symptoms. A major recent advance is the finding that these drugs also prolong survival in patients with heart failure and delay the onset of heart failure and death in patients who have impaired heart function but not heart failure. Researchers have also shown, in small pilot trials, that β-adrenergic receptor blockers, another class of neurohumoral antagonists, have a beneficial effect on patients with heart failure. These drugs may be helpful when combined with angiotensin-converting enzyme inhibitors in prolonging the life of patients with heart failure and patients with heart disease at risk of developing heart failure. The NHLBI, in collaboration with the Department of Veterans Affairs, is about to launch a clinical trial to test the role of β-adrenergic receptor blockers in managing patients with moderate-to-severe heart failure. The results of this trial could profoundly affect the management of heart failure.

Treatment Strategies

There are a number of exciting research opportunities for improving the treatment of patients with established heart failure. Several key opportunities are described below.

Prevention of Cardiac Rhythm Disturbances

Arrhythmias are a common cause of death in patients with heart failure. A number of drugs that might prevent lethal arrhythmias by altering the movement of ions through the membranes of cardiac cells are becoming available. Others can be “designed” as more is learned about the molecular configuration of ion channels in failing myocytes. The most promising drugs should be tested carefully. It is important also to determine whether catheter ablation of rhythm disturbances or implantation of internal cardioverter defibrillators (electrical means of treating arrhythmias) can prolong life in patients with heart failure who have already experienced a serious arrhythmia and are therefore at high risk of sudden death.

Treatment of Hibernating Myocardium

Another potentially useful treatment for many patients with heart failure (ie, those with ischemic, poorly contracting, yet viable — so-called hibernating — myocardium) is myocardial revascularization. Research should be undertaken to identify the mechanisms responsible for the development of myocardial hibernation, and cost-effective techniques should be developed for detecting this state in the failing heart.

Transplantation Across Species

Fundamental research on overcoming the formidable immunological barriers to cardiac xenotransplantation (hearts transplanted across species) should be encouraged. This treatment strategy has the greatest long-term potential for significantly broadening the use of cardiac transplantation.

“Bridges” to Heart Transplantation

Although transplantation is an effective treatment for patients with end-stage heart failure, the lack of donor hearts limits its application to relatively few patients. Ventricular assist pumps that serve as a “bridge to transplantation” appear to be a promising, although complex and costly, method of preventing the death of terminally ill patients who have heart failure and are awaiting a donor heart. Efforts to improve and simplify these pumps should be undertaken.

Quality of Life and Costs of Care

The treatment of heart failure is most commonly evaluated in terms of its ability to extend life. However, therapy must also be evaluated in terms of quality of life and costs of care. The development of reliable, valid, and reproducible measures of quality of life related to heart failure should be encouraged, and these measures should be used in assessing and comparing the costs and effectiveness of various therapies.

Prevention of Heart Failure

Two areas in which significant progress has been made are detection and diagnosis of heart failure and noninvasive imaging.

Detection and Diagnosis

In the long term, the prevention of heart failure is likely to have a far more salutary effect on public health than treatment. Prevention of heart failure requires early, vigorous treatment of precursor conditions, such as hypertension, hyperlipidemia, and diabetes mellitus, and lifestyle changes to retard or reverse the development of coronary atherosclerosis. Prevention also requires improved, safe, and cost-effective screening techniques that can be applied broadly in populations to identify individuals who have an altered ventricular mass, chamber size, or function and who are at risk of developing heart failure. Vital to any program of prevention is the identification of patients with structural heart disease who have hypertrophied, dilated, or ischemic hearts; these individuals are at considerably higher risk of developing heart failure. Better diagnostic criteria also are needed for early detection of heart failure and application in population screening.
Noninvasive Imaging

During the past decade, a number of imaging techniques have been developed for detecting cardiac abnormalities associated with or presaging heart failure. These include a variety of ultrasonographic methods, high-speed computed tomography, nuclear magnetic resonance imaging, and various radionuclide methods, including positron emission tomography. The costs of applying these techniques vary enormously, and their relative diagnostic accuracy has not been determined. Especially promising areas of research on the prevention of heart failure are (1) cost-effective care: Cost-effective strategies should be developed for applying noninvasive techniques to appropriate populations to identify patients at risk of developing heart failure. (2) Thrombolytic therapy to prevent heart failure: An important cause of heart failure, acute myocardial infarction, can be prevented or reduced in severity by early administration of clot-dissolving (thrombolytic) drugs. Although the efficacy of this therapy is well established, many patients who could potentially benefit from the therapy still do not receive it. A concerted effort should be made to identify the reasons—psychological, social, logistic, and financial—why victims of heart attack do not receive thrombolytic drugs.

Conclusions

Heart failure is a major and growing health problem in the United States. Scientists are at the brink of making major advances that could control this condition. A vigorous, multipronged effort against heart failure is likely to yield important dividends and should now be undertaken. This effort should involve intensification of fundamental research on the genetic and cellular causes of heart failure; development, improvement, and use of new pharmacological agents for treating heart failure; and development of a preventive strategy that includes identifying patients at risk of heart failure and instituting appropriate interventions to reduce or abolish this risk. The task force is confident that such efforts will be rewarded by a reduction in the enormous toll of heart failure on the American people.

Appendix

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General References

The following references are provided as a guide for individuals interested in obtaining additional information on the research areas mentioned in this report. The list provided is not intended to be comprehensive or to reflect all of the important and wide-ranging studies in heart failure research. The references are listed alphabetically for each of the five main sections of the report.

Introduction


Basic Research


Langer GA. Calcium and the heart: exchange at the tissue, cell, and organelle levels. FASEB J. 1992;6:893-902.


Clinical Research


Population-Based Studies


Treatment


Key Words • Cardiovascular News • heart failure
Report of the Task Force on Research in Heart Failure.
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Circulation. 1994;90:1118-1123
doi: 10.1161/01.CIR.90.3.1118
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
http://circ.ahajournals.org/content/90/3/1118.citation

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