Best Practices for Optimally Treated Advanced Heart Failure

Michael L. Bristow, M.D., Ph.D.
Guest Editor

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Best Practices for Optimally Treated Advanced Heart Failure

MICHAEL L. BRISTOW, M.D., PH.D., Guest Editor

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ARTICLES IN BRIEF

Original Contributions

III-1 Maximizing Management of Patients with Decompensated Heart Failure

E. LOH, M.D.

Decompensated congestive heart failure is a complex clinical disorder that requires a multifaceted treatment approach. This article will review the role of pulmonary artery catheterization, the use of inotropic agents, and the role of left ventricular assist devices and heart transplantation as therapeutic options for patients who present with decompensated heart failure.

III-6 The Economic Burden of Heart Failure

J. B. O’CONNELL, M.D.

Heart failure, a major cause of morbidity and mortality among the elderly, is a serious public health problem. As the population ages and the prevalence of heart failure increases, expenditures related to the care of these patients will climb dramatically. As a result, the health care industry must develop strategies to contain this staggering economic burden. Strategies may include adopting approaches for preventing heart failure and implementing new treatment modalities with proven efficacy into large-scale clinical practice. Successful implementation of these strategies will require intensive physician and patient education and development of innovative approaches to fund support services.

III-11 Inotropes in the Beta-Blocker Era

B. D. LOWES, M.D., M. A. SIMON, M.D., T. O. TSVEKOV, M.D., M. R. BRISTOW, M.D., PH.D.

Beta-adrenergic blocking agents are now standard treatment for subjects with mild to moderate heart failure. However, subjects who decompensate on beta blockade often need treatment with a positive inotropic agent. Phosphodiesterase inhibitors (PDEIs) such as milrinone or enoximone retain their full hemodynamic effects in the face of complete beta blockade, because (1) the site of PDEI action is beyond the beta-adrenergic receptor, and (2) beta blockade reverses receptor pathway desensitization changes, which attenuate the PDEI hemodynamic response. Moreover, when PDEIs and beta-blocking agents are coadministered long term in chronic heart failure, their respective efficacies are additive and their adverse effects are subtractive. However, large placebo-controlled studies with PDEIs and beta blockers are needed to establish the efficacy and safety of this promising new treatment approach.
Introduction

Heart failure is a common disease and a major cause of morbidity and mortality. Since patients with advanced heart failure (AHF) are among the most critically ill cardiac patients and account for a large portion of health care costs, it is important to define the AHF population and identify appropriate treatment strategies for these patients. This supplement’s articles are based on a symposium held last March at the American College of Cardiology meeting. The articles focus on AHF from several different perspectives. The first article will address the effect of hospitalization and its economic impact on the cost of heart failure (HF). The subsequent paper deals with current approaches that optimize treatment and management of AHF. In the final article, the synergies of beta-blocking agents and phosphodiesterase inhibitors are highlighted to underscore how this combination might help to reverse/slow the heart failure disease process in AHF patients. It is hoped that this focus of attention on AHF will stimulate further investigation designed to deal effectively with this important health care problem.

Michael R. Bristow, M.D., Ph.D.
Chairperson
Maximizing Management of Patients with Decompensated Heart Failure

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Summary: Patients with decompensated congestive heart failure can be categorized into those with either acute or chronic presentations. Patients with acute decompensated heart failure most often have an acute injury that affects either myocardial performance (i.e., myocardial infarction) or valvular/chamber integrity (mitral regurgitation, ventricular septal rupture), which leads to an acute rise in left ventricular (LV) filling pressures resulting in pulmonary edema and dyspnea. Therapy for these patients is aimed at treating the underlying cause of the myocardial injury as well as pharmacologic strategies to reduce LV filling pressures and to improve cardiac performance. In contrast, the therapy of patients presenting with decompensated heart failure in the setting of chronic LV systolic dysfunction, treated with angiotensin-converting enzyme inhibitors, digoxin, diuretics, and maybe beta blockers, represent a poorly defined clinical entity that lacks clear guidelines for treatment. These patients can present with symptoms of volume overload and/or low cardiac output without evidence for a volume overloaded state. Potential diagnostic and therapeutic approaches include (1) a pulmonary artery catheter for invasive hemodynamic monitoring, (2) intravenous inotropic therapy, (3) LV mechanical assist device therapy, and (4) cardiac transplantation. This review presents some of the advantages and disadvantages of each of these interventions for patients with chronic systolic dysfunction who present with decompensated symptoms and require specialized management in the hospital setting.

Key words: heart failure, inotropic therapy, heart transplantation

Demographics of Decompensated Heart Failure

Nearly 500,000 Americans carry the diagnosis of congestive heart failure (CHF), which remains the single leading cause of hospitalization in the United States in adults > 65 years of age.1 Because the incidence of CHF doubles with each decade after age 45, many more patients will develop this disease as the U.S. population ages. The nearly 900,000 patients who are admitted annually to the hospital with CHF exceed those patients admitted for the second leading diagnosis-related group, pneumonitis, by a factor of two. Therefore, it is important to develop therapeutic and diagnostic management strategies to optimize the outcomes of patients with CHF in both hospital and outpatient settings.

Presentations of Acute versus Chronic Decompensated Congestive Heart Failure

Two categories of decompensated CHF exist: acute and chronic. Patients with acute decompensated CHF most often experience an acute myocardial injury that affects either myocardial performance (e.g., myocardial infarction) or valvular/chamber integrity (e.g., mitral regurgitation, ventricular septal rupture), which leads to an acute rise in left ventricular (LV) and diastolic pressure resulting in pulmonary edema, and dyspnea. Therapy for these patients is aimed primarily at the underlying cause of the injury with concomitant therapy to improve cardiac performance, reduce LV filling pressures, and reduce LV wall stress. Therapy to reverse these symptoms can include attempts to maximize coronary perfusion (thrombolytic therapy, angioplasty, or revascularization), to correct a new valvular lesion surgically, and/or to institute therapy for aggressive treatment of hypertension.

In contrast, patients with chronic decompensated CHF secondary to LV systolic dysfunction, treated with angiotensin-converting enzyme inhibitors (ACEIs), digoxin, diuretics, and maybe beta blockers, are a less clearly defined clinical entity without clear treatment guidelines. Potential approaches to be discussed include (1) pulmonary arterial catheterization for invasive hemodynamic monitoring, (2) intravenous inotropic therapy, (3) LV assistance device therapy, and (4) cardiac transplantation. This article will review some of the advantages and disadvantages of each of these interventions for
patients with chronic systolic dysfunction who present with symptoms of decompensation and require specialized care in the hospital setting.

**Definition of Decompensated Congestive Heart Failure**

One important consideration, before deciding what therapies to use for patients with decompensated CHF, is to define the syndrome accurately. Currently, no universal definition of decompensated CHF exists. For example, the Vasodilator in Heart Failure (V-HeFT) studies found no relationship between left ventricular ejection fraction (LVEF) and peak exercise oxygen consumption [(VO2), a marker of cardiac reserve] in individuals with LV systolic dysfunction, indicating that LVEF is not a reliable surrogate for decompensated CHF. Isolated assessment of pulmonary and LV hemodynamics also does not reflect the diversity or the severity of the heart failure syndrome. Other factors to be considered include symptoms resulting from chronic low cardiac output, such as fatigue, peripheral changes in vascular tone, and loss of lean muscle mass. The use of an algorithm that incorporates hemodynamic criteria, New York Heart Association (NYHA) classification, and symptom score may be required for a more accurate guideline as to when to intervene prior to an acute hospitalization. More studies are needed to address chronic changes in hemodynamics in response to drug therapy and as a treatment target for the management of patients with decompensated CHF.

**Quality of Life versus Survival Considerations in Patients with Decompensated Congestive Heart Failure**

Current practice guidelines for the treatment of ambulatory patients with CHF published by the ACC/AHA Task Force on Practice Guidelines include recommendations for the use of ACEIs, other vasodilators, digoxin, diuretics, anticoagulation, and, potentially, beta blockers (Table I). It is important to remember that these recommendations deal specifically with the ambulatory population with stable chronic disease and do not address the group of patients with advanced end-stage decompensated CHF. Because of the clinical variability in presentations between compensated and decompensated CHF, management strategies for these two populations of patients differ greatly.

One important difference to consider between these two groups is the primary goal for treatment. The Framingham Heart Study, which turned 50 years old in 1998, demonstrated that once individuals develop their first symptoms of CHF, they continue down a fairly precipitous decline to their ultimate demise. The median survival duration was about 1.7 years for men and 3.2 years for women. Furthermore, in the Survival and Ventricular Enlargement (SAVE) trial, once individuals require hospitalization for symptomatic CHF, the overall mortality event rate increased from 20–25% at 4 years to nearly 60%. These data suggest that it is important to reconsider treatment goals when caring for patients with a history of repeated hospitalizations for decompensated CHF, so that focus is not placed merely on improving survival, but also on improving the quality of the patient’s life.

Patients’ views on accepting treatment strategies that can improve quality of life potentially at the cost of reducing survival duration are poorly understood. We recently performed an evaluation of patient treatment preferences for CHF therapy. Fifty patients (mean age 54 years), who had had a mean of 1.1 visits to an emergency room, required a mean of 1.4 hospitalizations, and about nine visits to the clinic during the year before being questioned. The mean LVEF was 24%, peak VO2 was 16 ml/min/kg, and their Minnesota Living with Heart Failure score was close to 50 (NYHA Class III functional status); CHF in 50% of these patients was caused by ischemia, and in 38% was due to dilated cardiomyopathy. Using a visual analog scale for symptoms of heart failure, four clinical categories were studied: fatigue, shortness of breath, depression, and survival. Using the analytical trade-off conjoint analysis technique, patients were asked whether they would accept a new therapy for heart failure if it improved their symptoms at the cost of either an increase or decrease in life span. Two-thirds of the patients were primarily symptom sensitive. In other words, the majority of patients would choose therapies that would improve their symptoms at the cost of potentially decreasing their survival time. No such relationship was found in a control group of 50 patients without cardiovascular disease. Therefore, consideration of patients’ viewpoint of their condition is important when deciding upon treatment strategies for decompensated CHF.

**Treatment Approaches for Decompensated Congestive Heart Failure**

Standard therapy for ambulatory patients with CHF includes the use of diuretics, ACEIs, second- and third-generation beta blockers, and digoxin. Diagnostic and treatment
choices currently available for patients with decompensated CHF include the use of invasive hemodynamic monitoring, intravenous inotropic therapy, ventricular assistance devices, and heart transplantation.

Invasive Hemodynamic Monitoring

One important issue is how aggressively to use right heart catheterization to manage patients with decompensated CHF. The current ACC/AHA Task Force recommendations for right heart catheterization include symptoms related to cardiogenic shock or near shock that is unresponsive to fluid challenge; acute pulmonary edema that is unresponsive to proper intervention or is complicated by systemic hypotension or shock; and use as a potential diagnostic tool to resolve the uncertainty of cardiogenic versus noncardiogenic pulmonary edema.

The treatment of decompensated CHF guided by invasive hemodynamic monitoring has been called into question by the recent findings of the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT). SUPPORT (Fig. 1) examined 30-day survival with and without the use of pulmonary arterial catheters in 5,735 patients treated in an intensive care unit (ICU) setting. The results demonstrated that patients who had right heart catheterization had a significantly reduced survival compared with individuals who did not undergo this invasive procedure. Some investigators have published recommendations for a moratorium on the use of right heart catheterization in patients who are ICU bound. It should be noted, however, that SUPPORT included patients who had multisystem organ failure with high Acute Physiology and Chronic Health Evaluation (APACHE) scores in the ICU in addition to CHF. Therefore, “confounding-by-indication” bias may have accounted for some of these results. Another very important issue is that only 11% of these patients had CHF as the primary reason for admission into the ICU; as a result, the question of the usefulness of invasive hemodynamic monitoring still has not been addressed prospectively in patients with CHF. Moreover, no randomized controlled trials have been conducted yet to prove the efficacy of this therapeutic approach in patients with decompensated CHF.

Intravenous Inotropic Therapy

Acute therapy: The early use of inotropic therapy is important because inotropic agents stabilize patients hemodynamically, augment organ perfusion, and may decrease the length of hospitalization (Table II). The two major classes of inotropic agents include (1) agents that stimulate the beta-adrenergic receptors (i.e., dopamine and dobutamine); and (2) phosphodiesterase inhibitors (PDIs) (i.e., milrinone). Phosphodiesterase inhibitors operate at the postreceptor level to inhibit phosphodiesterase, which prevents the degradation of cyclic adenosine monophosphate (cAMP), allowing more calcium to enter the myocyte, resulting in enhanced contractility. Phosphodiesterase inhibitors are not only potent inotropic agents, but possess important vasodilator properties as a result of their primary phosphodiesterase inhibitory effects in vascular smooth cells resulting in reduced systemic vascular resistance. Because of these effects on peripheral vascular resistance, PDIs can be considered inodilators. Treating pulmonary hypertension associated with decompensated CHF is also an important clinical goal. It is important to unload the right ventricle, and milrinone and other PDIs are extremely effective in reducing pulmonary vascular resistance.

Phosphodiesterase inhibitors also are important agents to bridge patients to heart transplantation. Because of the post-beta-adrenergic receptor site of action of PDIs, they are not strongly associated with the problems of desensitization that are seen with the chronic use of beta-adrenergically active inotropic agents. Finally, another advantage of PDI use in the treatment of decompensated CHF is the preserved inotropic response seen in patients treated with chronic beta-blocker therapy. As even more patients are treated with beta blockers, and many patients with decompensated symptoms are on these agents, phosphodiesterase inhibition may be the best choice to overcome these effects of beta blockade. Finally, in patients with refractory class IV heart failure symptoms, the oral PDI, enoximone, has been used to “bridge” patients pharmacologically to chronic beta-blocker therapy.

Outpatient intermittent therapy with inotropic agents: Outpatient intermittent inotropic therapy for patients with decompensated CHF remains a controversial treatment strategy. The data available have been generated from very small numbers

![Fig. 1 SUPPORT Trial: 30-day survival with and without pulmonary artery catheter (n = 2,016). RHC = right heart catheterization. Reprinted with permission from the Journal of the American Medical Association, Vol. 276 (11), 889–897. Copyright 1996, American Medical Association.](image)
TABLE III  Intermittent outpatient inotropic therapy for heart failure [milrinone (n = 32) and dobutamine (n = 4)]

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<th>Baseline</th>
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<td>ER visits</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>75</td>
<td>34</td>
</tr>
<tr>
<td>Hospital days</td>
<td>528</td>
<td>150</td>
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Recent data from a group of patients who were treated primarily with home-administered intermittent milrinone therapy demonstrated that numbers of both emergency room (ER) visits and hospitalizations decreased, as did the total days of hospitalization. Reprinted with permission from the American Heart Journal, 1996;132:805–808.

of patients, and there remains no consensus on dosage, duration, and the clinical usefulness of this form of treatment.\textsuperscript{12} However, many algorithms for the treatment of heart failure are now guided by case-management controls or health- and disease-management programs, which include administration of intermittent inotropic therapy in the home setting. These efforts are aimed at improving symptoms and quality of life. Recent data (Table III) from a group of patients who were treated primarily with home-administered intermittent milrinone therapy demonstrated that numbers of both emergency room visits and hospitalizations decreased, as did the total days of hospitalization.\textsuperscript{13} There still remain no data to suggest that chronic, long-term use of either oral\textsuperscript{14, 15} or intravenous therapy with inotropes prolongs survival. Therefore, the decision to use these agents should be taken following detailed discussion with the patient about the risks and limited survival benefits of this approach.

Cost versus clinical efficacy in choosing an inotropic agent: As previously mentioned, inotropic therapy is an important bridge therapy for patients with decompensated heart failure awaiting heart transplantation. The choice of long-term continuous infusion with an inotropic agent must be balanced between cost and clinical efficacy. A group of patients awaiting heart transplantation who were treated chronically with milrinone or dobutamine were studied to determine the comparative total cost of treating these patients.\textsuperscript{16} Despite the fact that the pharmacy charges were greater for milrinone than for dobutamine, the procedural and laboratory costs associated with milrinone therapy were lower, suggesting a more stable clinical course for these patients. The total per diem cost of care was not different between the groups of patients treated with milrinone and those treated with dobutamine despite the clearly greater drug acquisition costs for milrinone. These preliminary data suggest that preliminary acquisition costs should not be the only factor in determining which inotropic agent to use.

Promises and pitfalls of intravenous inotropic therapy: Despite the many benefits provided by inotropic agents, they must be used judiciously. The use of PDIs in particular, with their vasodilatory properties, requires careful consideration of the etiologic factors underlying the low-output state. For example, because PDIs have potent vasodilator properties, they are generally not the best choice to use in the setting of low systemic vascular resistance (i.e., sepsis) or states of hypovolemia (i.e., over-diuresis, gastrointestinal bleeding). The use of PDIs will result in excessive vasodilation and potentially significant systemic hypotension.

Other caveats to consider when using inotropic agents are that single hemodynamic goals are inadequate to judge an agent’s efficacy and that every patient has a variable response. The efficacy and toxicity of these agents are dosage dependent—larger dosages induce greater cardiac output but potentially generate more arrhythmias and other side effects. In addition, the combination of different classes of inotropic agents, such as dobutamine and milrinone, creates synergistic toxicity. Finally, dose adjustment is always important when using these agents, especially when end-organ perfusion is compromised.

Recent studies have demonstrated dramatic improvements in survival of patients with CHF treated with beta blockers;\textsuperscript{17–19} beta blockers are now recommended for chronic CHF management.\textsuperscript{3} Therefore, beta-blocker therapy is more commonly seen in patients who present to the hospital with decompensated CHF. The choice of inotropic agents in the setting of patients already treated with chronic beta-blocker therapy should be dictated by an understanding of the beta-adrenergic receptor-cAMP cascade. For the reasons discussed earlier, very high doses of dobutamine have to be used to overcome the effects of chronic beta-blockade therapy. These large doses can have significant arrhythmic side effects. Due to the fact that PDIs act beyond the level of the receptor, retaining its full hemodynamic effect, these agents should be favored for use in these patients.

Left Ventricular Assist and Heart Replacement Devices

Left ventricular assistance devices, such as the TCI HeartMate (Thermocardiodynamics, Inc., Chelmsford, Mass.), are clearly important in the care and treatment of patients who have advanced compensated CHF. These devices have the ability to reverse significant end-organ damage in the setting of inpatient cardiac failure despite high doses of inotropic therapy in patients awaiting heart transplantation.\textsuperscript{20}

Heart Transplantation

The Registry of the International Society of Heart and Lung Transplantation clearly demonstrates that heart transplantation improves survival compared with traditional therapy. As medical therapy for end-stage heart disease, heart transplantation is the preferred treatment option for eligible patients. Despite the success of heart transplantation as a therapy for end-stage CHF, donor numbers in the US have remained flat, and, therefore, other pharmacologic and device therapy for these patients must be evaluated.

Future Treatment Strategies for Decompensated Congestive Heart Failure

Future advances in inotropic therapy are being studied today. An intravenous form of the positive inotropic agent ves-
narinone (OPC-8212) has been studied and may become available soon. Levosimendan is a new class of inotropic agents with phosphodiesterase inhibitory activity but presumably acts primarily via a troponin-C agonist mechanism to increase contractility. This agent has both an intravenous and oral formulation that is being tested in patients with advanced CHF. Another strategy approach currently being studied is the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) trial, which, in patients admitted to the hospital with decompensated CHF, investigates the benefit of up-front use of milrinone versus placebo in reducing the total number of days of hospitalization for cardiovascular events within 60 days following therapy.

Conclusion

Decompensated CHF is a complex, multifaceted clinical syndrome. With advances in outpatient therapy for stable, ambulatory patients with CHF, new challenges are now being seen in patients who are admitted with decompensated heart failure symptoms. They are often sick, with more advanced hemodynamic decompensation requiring potentially more aggressive invasive hemodynamic intervention combined with the use of intravenous inotropic agents. Guidelines need to be developed to simplify existing care algorithms for the treatment of these patients. Finally, as some of these therapies can improve symptoms at the cost of possibly shortening survival, a detailed understanding of individual patient preferences is needed to align patient and physician treatment goals.

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The Economic Burden of Heart Failure

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Summary: Heart failure, a major cause of morbidity and mortality among the elderly, is a serious public health problem. As the population ages and the prevalence of heart failure increases, expenditures related to the care of these patients will climb dramatically. As a result, the health care industry must develop strategies to contain this staggering economic burden. Strategies may include adopting approaches for preventing heart failure and implementing new treatment modalities with proven efficacy into large-scale clinical practice. Successful implementation of these strategies will require intensive physician and patient education and development of innovative approaches to fund support services.

Key words: heart failure, economic burden, aging population, angiotensin-converting enzyme inhibitors, beta blockers, hospitalization costs

Prevalence and Prognosis of Heart Failure

Introduction

Heart failure is a major public health issue. It is highly prevalent among the elderly population, and its prevalence is projected to rise markedly over the next decade.1, 2 Even with the commitment to excellence in health care that exists in the United States, resources and personnel are limited; the economic burden of managing heart failure is staggering. It is, therefore, imperative that the medical profession examines the impact of developing technology and new therapeutic modalities on heart failure management. Efforts must be made to develop novel strategies to reduce the burgeoning cost of care of these patients without compromising the effectiveness of that care.3, 4

Prevalence

Heart failure is a clinical syndrome that has become more prevalent in recent years. In 1996, almost 4.8 million Americans were afflicted with congestive heart failure (CHF), and each year approximately 400,000 new cases of CHF were diagnosed.5 Disease prevalence is expected to reach 10 million cases in the U.S. alone by the year 2007.5 Enhanced public awareness and advances in the management of acute myocardial infarction, diabetes, hypertension, and heart failure have led to decreased early mortality rates from these disorders while increasing the incidence of heart failure.2 In 1979, there were 377,000 hospital discharges of patients with primary heart failure; this number increased to 870,000 in 1996, accounting for 2.8% of all hospital discharges and 22% of all discharges for cardiovascular disease in the U.S. In 1991, there were 2.3 million hospital discharges of patients with a primary or secondary diagnosis of heart failure, and examination of nonfederal hospital discharge records for that year indicated an average length of stay of 7.7 days for such patients.4

Prognosis

Mortality rates from CHF continue to be high, with a 6-year mortality rate secondary to heart failure of 84% in men and 77% in women.7 In 1996, heart failure caused 43,837 deaths; women accounted for a larger proportion (62%) than men (38%).5 Following the development of systolic dysfunction, heart failure usually progresses unpredictably and symptoms worsen. Once cardiac muscle loss and fibrosis become irreversible, disease advance becomes inexorable and death inevitably follows (Fig. 1).

Impact of Aging Population

As the population ages, the incidence of heart failure and its resulting mortality will continue to increase.7 In 1940, only 7% of Americans were expected to live to the age of 90 years; by 1980, 24% of Americans were expected to reach the age of 90; however, the long-awaited aging of the 75 million baby boomers born between 1947 and 1964 is still to come. The
number of Americans over the age of 65 is expected to double in the next 30 years.\(^8\) The incidence of CHF approaches 1% in those over the age of 65 years,\(^5\) and has been reported at 4% in the 70- to 79-year age group.\(^9\)

**Economic Impact of Heart Failure**

The costs related to heart failure management are difficult to assess. Hospital charges for heart failure management were approximately $10,000 per discharge, based on a mean length of stay of 6.3 to 7.7 days.\(^4\) According to the Medicare program, Health Care Financing Administration (HCFA) expenditures for heart failure in 1991 were higher than those for cancer (based on the five most common diagnosis-related groups (DRGs) for cancer combined) and higher than those for myocardial infarction (based on two DRGs for myocardial infarction combined) (Fig. 2).\(^4\) Almost 75% of costs associated with a typical heart failure-related hospitalization (excluding hotel charges) accumulate within the first 48 h. It is interesting that payer mix does not have a major impact on charges or length of stay, even when HMOs, indemnity insurance, and government programs were considered.

Heart failure-related readmission rates range from 15 to 30% at 90 days; data suggest that half of these readmissions could be prevented.\(^10,11\) Although approximately 70% of patients with heart failure are classified as New York Heart Association (NYHA) class I or II and do not experience recurrent hospitalizations, the total expenditure in 1991 for heart failure hospitalizations alone (federal hospitals excluded) was $23 billion.\(^4\) However, in addition to hospitalization charges, outpatient expenses exceeded $4,000 per patient per year. With an average of 3.4 outpatient visits per patient per year, total ambulatory costs exceeded $13 billion.\(^4\) Transplantation costs ($250 million) are a relatively small proportion of the total expenditure; a limited number of heart transplant procedures are performed each year.\(^12\)

In summary, the annual expenditure on heart failure management, encompassing hospitalization costs (including inpatient care and pharmacy costs) and outpatient visits, for the 4.8 million patients in the U.S. approached $38 billion in 1991.\(^4\) A more recent study of 29,000 patients with heart failure reported an average cost of almost $11,000 per patient per hospitalization (Heart Failure BOI Analysis 1997, Merck & Co., data on file). Thus, costs have not been reduced despite advances in medical treatment. Based on an increase in the number of patients with heart failure since 1990, the total cost for heart failure management in 1999 is estimated to approach $56 billion. As the population ages and the number of patients with heart failure increases, the economic burden of managing these patients may become unmanageable.

**Strategies for Managing the Burden of Heart Failure**

**Economic-Based Targets**

Since hospitalization costs account for a major portion of expenses related to heart failure management, decreasing hospital length of stay may be desirable. However, economic gains realized by shortening hospital length of stay may potentially be compromised by increases in hospital readmission rates or emergency room visits. Efforts directed at decreasing hospital length of stay do not affect the majority of hospitalization costs (75% of non-hotel costs occur within the first 48 h). Thus, it may be more cost effective to stabilize patients in the hospital, allowing for short increases in hospital length of stay, but reducing overall hospital readmission rates and number of emergency room visits. In Michigan, health care systems are encouraged to prevent frequent hospitalizations; Medicare DRG reimbursements for a rehospitalization with 15 days of discharge are not granted.
The incidence of heart failure is higher than average in 75% of patients with heart failure have antecedent hypertension; about 20% of these patients become disabled with heart failure within 6 years. The survivors of myocardial infarction; intensive home monitoring to delay disease progression; and prompt management of underlying cardiac disorders.

Initiated after the onset of LV dysfunction or cardiac disease, but before CHF.13

Before onset of left ventricular dysfunction or coronary artery disease.13

After onset of heart failure to delay progression and prevent clinical events.13

Abbreviations: ACE = angiotensin-converting enzyme, CHF = congestive heart failure.

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Medical-Based Targets

Health care professionals need to improve implementation of primary, secondary, and tertiary strategies (Table I) for preventing the onset and progression of heart failure. Nearly 75% of patients with heart failure have antecedent hypertension. The incidence of heart failure is higher than average in survivors of myocardial infarction; about 20% of these patients become disabled with heart failure within 6 years. The primary prevention strategy, introduced before the onset of left ventricular (LV) dysfunction, includes treatment of diabetes, hypertension, and hyperlipidemia; discontinuation of smoking; and prompt management of underlying cardiac disorders including coronary artery disease or valvular heart disease. Initiated after the onset of LV dysfunction but before clinical heart failure, secondary prevention involves treatment with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, aspirin, antihyperlipidemic agents, anticoagulation therapy, and coronary revascularization, if appropriate. After the onset of clinical heart failure, tertiary prevention/treatment involves pharmacologic therapy with ACE inhibitors, beta blockers, digoxin, and diuretics; prevention of recurrent myocardial infarction; and intensive home monitoring to delay disease progression and prevent clinical events.

Use of ACE inhibitors: Results of the Studies of Left Ventricular Dysfunction (SOLVD), Veterans Administration Cooperative Vasodilator–Heart Failure Trial (V-HeFT II), and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trials demonstrated that ACE inhibitors reduce disability, improve functional capacity, and prolong life among patients with heart failure. Furthermore, this drug class was well tolerated in more than 80% of study patients. Angiotensin-converting enzyme inhibitor treatment reduced hospital readmission rates; ACE-inhibitor therapy decreased the risk of 90- and 180-day rehospitalizations in patients with heart failure. However, reductions in morbidity and mortality associated with ACE-inhibitor and beta-blocker treatment have not yet translated into reduced mortality in national heart failure statistics.

Underutilization of ACE inhibitors may contribute to the absence of the reduction in national heart failure morbidity and mortality. The overall use of ACE inhibitors in Medicare patients admitted to acute care hospitals with a principal diagnosis of heart failure ranges from 48 to 57%. Ideal candidates for ACE inhibitor therapy include patients with low ejection fraction (EF) (<40%), normal renal function, and normal serum potassium. However, only 73% of patients most likely to benefit from and tolerate such therapy are prescribed ACE inhibitors at hospital discharge. Advanced age was associated with decreased prescription rates among ideal candidates; 78% of patients 65 to 74 years and 67% of those ≥85 years were prescribed ACE inhibitors at hospital discharge. Physician specialty also affects prescribing practices. Cardiologists prescribe ACE inhibitors to their patients with CHF more often (46%) compared with all other physicians (22%); cardiologists also tend to prescribe these agents earlier in the course of CHF treatment than do internists and family or general practitioners.

Obtaining an objective assessment of LV systolic function is associated with ACE inhibitor use. Of hospitalized Medicare patients with CHF, 48% lacked documentation of LV function in the medical record. Patients with an objective assessment of LV function were prescribed ACE inhibitors more often at hospital discharge than patients without an LV assessment (56 vs. 48%, p = 0.006). In addition, when LV function was assessed at hospital admission, significantly more patients were prescribed ACE inhibitors at hospital discharge than patients without an assessment of LV function, even if EF was low (36 vs. 26%, p = 0.004).

Appropriate ACE inhibitor dosing is also an important determinant of clinical outcome. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared the effects of low- and high-dose ACE inhibitors on the survival of patients with heart failure. Compared with low-dose lisinopril, treatment with high-dose lisinopril resulted in small reductions in both total mortality (42.5 vs. 44.9%, p = 0.128) and cardiovascular mortality (37.2 vs. 40.2%, p = 0.073). However, treatment with high doses of the ACE inhibitor reduced heart failure-related hospitalizations by 24% compared with the low-dose therapy (p = 0.003).

In a retrospective outpatient chart audit evaluating guideline implementation in the management of CHF, 50% of 16,603 patients with CHF were prescribed an ACE inhibitor, but overall only 26% of patients received the recommended target dose.

<table>
<thead>
<tr>
<th>TABLE 1 Strategies to prevent heart failure and its progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary prevention</strong> a</td>
</tr>
<tr>
<td>1. Treat hypertension (especially systolic hypertension)</td>
</tr>
<tr>
<td>2. Treat hyperlipidemia</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong> b</td>
</tr>
<tr>
<td>1. ACE inhibitors</td>
</tr>
<tr>
<td>2. Beta blockers</td>
</tr>
<tr>
<td>3. Secondary prevention after myocardial infarction</td>
</tr>
<tr>
<td>(a) Aspirin</td>
</tr>
<tr>
<td>(b) Beta blockers</td>
</tr>
<tr>
<td>(c) Antihyperlipidemic therapy</td>
</tr>
<tr>
<td>(d) Anticoagulation therapy</td>
</tr>
<tr>
<td>(e) Coronary revascularization (in appropriate patients)</td>
</tr>
<tr>
<td><strong>Tertiary prevention</strong> c</td>
</tr>
<tr>
<td>1. ACE inhibitors</td>
</tr>
<tr>
<td>2. Beta blockers</td>
</tr>
<tr>
<td>3. Digoxin</td>
</tr>
<tr>
<td>4. Secondary prevention after myocardial infarction</td>
</tr>
<tr>
<td>5. Intensive home monitoring and intervention</td>
</tr>
</tbody>
</table>

a Before onset of left ventricular dysfunction or cardiac disease.
b After onset of left ventricular dysfunction or coronary artery disease, but before CHF.
c After onset of heart failure to delay progression and prevent clinical events.

Use of ACE inhibitors: Results of the Studies of Left Ventricular Dysfunction (SOLVD), Veterans Administration Cooperative Vasodilator–Heart Failure Trial (V-HeFT II), and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trials demonstrated that ACE inhibitors reduce disability, improve functional capacity, and prolong life among patients with heart failure. Furthermore, this drug class was well tolerated in more than 80% of study patients. Angiotensin-converting enzyme inhibitor treatment reduced hospital readmission rates; ACE-inhibitor therapy decreased the risk of 90- and 180-day rehospitalizations in patients with heart failure. However, reductions in morbidity and mortality associated with ACE-inhibitor and beta-blocker treatment have not yet translated into reduced mortality in national heart failure statistics.

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Improved timing and accuracy of heart failure diagnosis: It is recommended that all patients with heart failure undergo a complete diagnostic evaluation to (1) determine the type and severity of their cardiac dysfunction, (2) uncover correctable etiologic factors, (3) determine prognosis, and (4) guide treatment. Routine diagnostic studies for adult patients with heart failure include complete medical history; physical examination; exercise stress testing to assess functional capacity and symptomatic limitations; transthoracic echocardiography for specific assessment of ventricular mass, chamber size, systolic and diastolic function, and valvular abnormalities; and other noninvasive tests to detect ischemia and assess myocardial viability. These diagnostic tests are essential to evaluate patients with heart failure and to determine an underlying cause that can be appropriately treated by specific therapies; improvements in the definition and detection of heart failure classes are also needed.

Compliance-Based Targets

Patients’ failure to comply with physician instructions frequently contributes to disease-related complications. Patients are often noncompliant with prescribed medication regimens; 15% of hospital readmissions are related to medication noncompliance. The Merck Study defined compliance as refilling 80% of prescriptions on time and continuing prescriptions for a 1-year period; only 46% of patients with heart failure were compliant. Proprietary issues that affect patient compliance include regimen complexity, prescription size, side-effect profile, patient education, medication effectiveness, cost, and physician factors. It is interesting that DiMatteo et al. reported that the most important physician factor was physician global job satisfaction. Physicians who were happier in their work appeared to improve patient adherence.

Only 10% of eligible patients with heart failure follow appropriate ACE inhibitor medication regimens when factors are combined for patient noncompliance and inaccurate medication dosing. Savings would be enormous if all eligible heart failure patients were prescribed the correct ACE inhibitor regimen and adhered to physicians’ recommendations. Consider the following analysis: for 1,000 patients with heart failure taking enalapril at a cost of $540 per person per year, the total 3-year cost would be $1.6 million. Approximately 350 hospitalizations would be prevented over these years, and, at an average cost of $10,770 per hospitalization, the savings would amount to $3.7 million. The net savings (prevented hospitalization minus enalapril costs) would be $2 million per 1,000 patients over 3 years. For the entire population of 4.78 million patients with heart failure in the U.S., the net 3-year savings would be $10 billion.

Clinical trials, which contain the necessary infrastructure, ensure that a large percentage of patients receive medication prescriptions, maintain appropriate medication regimens, and require patient compliance. However, routine clinical practice lacks such an infrastructure. Managed care and discounted fee-for-service do not allow direct funding of support services such as follow-up visits, home visits, or education. Fee-for-service arrangements are limited primarily to physician encounters and hospitalizations. During a patient’s hospitalization, physicians receive a daily fee. It is in the interest of the hospital, however, to discharge the patient as soon as possible; thus, a divergence in economic outlook is created. Although a huge financial benefit exists for managed care providers to ensure patient compliance, patient compliance issues are not properly addressed under the current system.

Conclusion

There are 4.78 million patients with heart failure in the United States, of whom 1.4 million are in NYHA class III or IV at any given time. More than $56 billion is spent annually on the treatment and management of heart failure, 70% of which covers the hospitalization of patients. There is a need to develop innovative solutions to keep this growing population out of the hospital and to improve the overall management of the patients. Success in this endeavor will have a beneficial impact on our entire health care system.

References


Inotropes in the Beta-Blocker Era

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Division of Cardiology, University of Colorado Health Sciences Center, Denver, Colorado, USA

Summary: Beta-adrenergic blocking agents are now standard treatment for mild to moderate chronic heart failure (CHF). However, although many subjects improve on beta blockade, others do not, and some may even deteriorate. Even when subjects improve on beta blockade, they may subsequently decompensate and need acute treatment with a positive inotropic agent. In the presence of full beta blockade, a beta agonist such as dobutamine may have to be administered at very high (> 10 µg/kg/min) doses to increase cardiac output, and these doses may increase afterload. In contrast, phosphodiesterase inhibitors (PDEIs) such as milrinone or enoximone retain their full hemodynamic effects in the face of beta blockade. This is because the site of PDEI action is beyond the beta-adrenergic receptor, and because beta blockade reverses receptor pathway desensitization changes, which are detrimental to PDEI response. Moreover, when the combination of a PDEI and a beta-blocking agent is administered long term in CHF, their respective efficacies are additive and their adverse effects subtractive. The PDEI is administered first to increase the tolerability of beta-blocker initiation by counteracting the myocardial depressant effect of adrenergic withdrawal. With this combination, the signature effects of beta blockade (a substantial decrease in heart rate and an increase in left ventricular ejection fraction) are observed, the hemodynamic support conferred by the PDEI appears to be sustained, and clinical results are promising. However, large-scale placebo-controlled studies with PDEIs and beta blockers are needed to confirm these results.

Key words: beta blockers, phosphodiesterase inhibitors, heart failure, milrinone, enoximone

Introduction

Beta-adrenergic blocking agents are standard treatment for patients with mild to moderate chronic heart failure (CHF).1, 2 The benefits of beta blockade include time-dependent improvements in myocardial function and remodeling, and a decrease in hospitalizations and mortality.1, 2 The U.S. Carvedilol Trials reported a composite 65% reduction in mortality and a reduction in cardiovascular hospitalizations.3 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)4 recently reported a 32% reduction in all-cause mortality when a beta blocker was added to standard therapy. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) demonstrated a 34% reduction in all-cause mortality as well as significant improvements in cardiovascular mortality, sudden death, and worsening heart failure.5 These findings have led to the recommended use of beta blockers in patients with CHF with a primary or secondary dilated cardiomyopathy phenotype and New York Heart Association Class II or III symptoms.1, 2

However, because of the degree to which the failing heart is dependent on adrenergic support,6 there is also the potential for adverse effects of antiadrenergic agents in the subset of patients with advanced or severe CHF. The Moxonidine in Congestive Heart Failure (MOXCON)7 trial was recently stopped early due to higher mortality in the active arm8 moxonidine is a centrally acting inhibitor of sympathetic outflow that reduces systemic and cardiac norepinephrine.9 In MOXCON, a marked reduction in cardiac adrenergic support to heart rate, contractility, and/or blood pressure may have been deleterious to patients with more advanced CHF leading to an early increase in mortality.10

As with moxonidine, there is also potential for adverse effects of beta-blocking agents in subjects with more advanced heart failure. Some patients do not tolerate initiation and titration of beta blockade, others exhibit a decrease in left ventricular (LV) function, which has been associated with increased mortality,11 and some subjects who improve go on to decompensate. In these decompensated patients who develop a clinically significant low cardiac output state, inotropic support is often necessary to improve hemodynamics. Thus, for optimal therapeutic management of CHF it is important to un-
understand the interaction between positive inotropes and beta blockers. This paper reviews the pharmacologic, hemodynamic, and clinical effects of beta blockers and positive inotropes acting within the beta-receptor pathways, and discusses how the interactions between these two classes of agents may be used to improve clinical outcomes of patients in advanced CHF.

Myocardial Beta-Receptor Signal Transduction in Congestive Heart Failure

The general schema for beta-adrenergic receptor coupled signal transduction is given in Figure 1. Agonist occupancy of both beta1- and beta2-adrenergic receptors stimulates adenylyl cyclase (AC), which leads to increased intracellular concentration of second messenger cyclic adenosine monophosphate (cAMP). Increases in intracellular cAMP activate protein kinase A (PKA), which, through phosphorylation of molecular targets such as phospholamban and calcium channels, increases contractile function. The coupling of beta1 and beta2 receptors to AC stimulation and to subsequent changes in systolic and diastolic function is mediated via G proteins that either stimulate (Gs) or inhibit (Gi) AC activity. In model systems, the beta1-adrenergic receptor is predominantly coupled to Gs, whereas the beta2 receptor is uniquely coupled to both Gs and Gi.12 In addition, the beta1 receptor may be coupled to ion channel activation by cAMP independent mechanisms,13 and may also have exclusive coupling to apoptotic pathways.14 This heterogeneity of signal transduction pathway coupling creates the potential for the beta1 receptor being selectively coupled to more adverse biological effects than the beta2 receptor.1

Congestive heart failure is characterized by desensitization of the beta-receptor pathways due, at least in part, to sustained increased cardiac adrenergic stimulation. In this setting, beta-receptor pathways undergo several alterations, which result in reduced response to adrenergic stimulation (Table I). Normal, nonfailing ventricular myocardium contains 75 to 80% beta1 receptors and 20 to 25% beta2 receptors.15, 16 In failing myocardium, the percentage of beta1 receptors is reduced to 60 to 70% and the beta2-receptor population is proportionately increased to 30 to 40%.15, 16 This redistribution is a result of a selective downregulation of beta1-adrenergic receptors in the failing heart, with little or no change in beta2-receptor numbers.15, 16 Downregulation of beta1 receptors is marked in right ventricles failing in the setting of primary pulmonary hypertension,16 moderate in both ventricles with idiopathic dilated cardiomyopathy,15, 17 and mild in ischemic dilated cardiomyopathy.17 In failing ventricular myocardium, levels of beta1-receptor protein are reduced in all cellular compartments, including the cell membrane.16 In addition, a partial uncoupling of beta2-17, 18 and beta1-adrenergic receptors17 from functional response occurs secondary to at least two regulatory changes, upregulation in Gαi19–21 and receptor phosphorylation.22

As a result of these signal transduction changes the response to both beta agonists and phosphodiesterase inhibitors (PDEIs) is decreased in the failing heart.23–25 This can be observed in Figure 2, which gives the responses of several PDEIs, including enoximone and milrinone, as well as the beta agonist isoproterenol, in isolated tissue preparations of nonfailing versus failing human hearts. As can be observed in Figure 2, the response to PDEIs and isoproterenol is attenuated in failing right ventricular trabeculae, while the response to the Na channel agonist BDF-9148 is not decreased. The reason for the decreased response of PDEIs is upregulation in Gαi17, 19–21

![FIG. 1 Beta-adrenergic signal transduction in human cardiac myocytes. β1-AR = β1-adrenergic receptor; β2-AR = β2-adrenergic receptor; AC = adenylyl cyclase; Gi = stimulatory G protein with α, β, and γ subunits; Gs = inhibitory G protein with α, β, and γ subunits; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PDEc = cyclic phosphodiesterases; PDEp = particulate, SR-associated PDE III; SR = sarcoplasmic reticulum; PHLMBN = phospholamban; PKA = cAMP-dependent protein kinase A; CAMK = calmodulin-activated kinase; AMP = adenosine monophosphate.](image)

**TABLE I** Summary of beta-adrenergic pathway abnormalities in various kinds of dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>IDC (LV, RV)</th>
<th>ISCDC (LV, RV)</th>
<th>PPH (RV only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downregulation of β1-adrenergic receptors</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Uncoupling of β2-adrenergic receptors</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Uncoupling of β1-adrenergic receptors</td>
<td>—</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Upregulation of βARK-1</td>
<td>++</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Increased activity of Gi</td>
<td>+</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Decreased adenylyl cyclase catalytic activity</td>
<td>+ (RV only)</td>
<td>—</td>
<td>++</td>
</tr>
</tbody>
</table>

*Abbreviations: IDC = idiopathic dilated cardiomyopathy, ISCDC = ischemic dilated cardiomyopathy, LV = left ventricular, RV = right ventricular, PPH = primary pulmonary hypertension.*
Sites of Action of Myocardial Inotropes

The target of action of positive inotropic agents and their interaction with beta-blocking agents differs depending on the class of drug and pharmacologic mechanism of action. As shown in Figure 1, beta agonists exert their effects through beta1- and beta2-receptor occupancy on the surface of cardiac myocytes, with subsequent signal transduction resulting in stimulation of adenylyl cyclase and in activation of cAMP dependent and independent pathways. As shown in Figure 2, preparations of human failing hearts given isoproterenol demonstrate an attenuated systolic tension response when compared with nonfailing controls. In the intact failing heart, the response to the partial beta agonist dobutamine is likewise altered. As discussed above, the attenuation of beta-agonist responses in the failing human heart is due to changes in beta-adrenergic receptors and Gi. Although beta-blocker therapy may reverse some of the desensitization changes, when a beta agonist is administered in the presence of full-dose beta blockade, no effect of the beta agonist will be realized until the antagonist has been displaced from the receptor via mass action.

Phosphodiesterase type III, which milrinone and enoxime selectively inhibit, is a particulate fraction-associated enzyme, which is anchored to the sarcoplasmic reticulum and is unaltered in the failing human heart. The PDEI-based inotropes are selective, competitive inhibitors of PDE-III and exhibit positive inotropic and vasodilatory effects by inhibiting intracellular degradation of cAMP. In cardiovascular tissues, the increases in cAMP activate myocardial protein kinase A (PKA) and in vascular smooth muscle cGMP-dependent protein kinase (PKG). In myocardial cells sarcoplasmic reticulum (SR)-associated PDE inhibition leads to PKA-mediated phosphorylation of phospholamban, resulting in increased reuptake of calcium and subsequently increased sarcoplasmic reticulum Ca2+ release. In vascular smooth muscle, activation of PKG results in vasodilation. Thus, these agents can stimulate cardiac function and produce vasodilation in the absence of beta-adrenergic receptor activation. Because PDE-III is SR associated and PKA is compartmentalized close to the SR via A-kinase anchoring proteins (AKAPs), a selective PDEI-III inhibitor has a relatively specific effect on the SR. Compared with beta agonists, this leads to a preferential effect on systolic and diastolic function versus heart rate. Because the site of action is beyond beta-adrenergic receptors, beta blockade will not attenuate the favorable hemodynamic actions of PDEIs.

Concomitant Use of Inotropes and Beta Blockers in Advanced Heart Failure: Theoretical Considerations

The concomitant use of a beta agonist and a beta-blocking agent is not rational, since agonist action is blocked by the antagonist. On the other hand, there are theoretical advantages to the concomitant use of PDEIs and beta blockers in advanced CHF. Based on their site of action, the overall response to PDEIs in patients on beta blockade is preserved or even enhanced. This is, at least in part, because beta blockers can reduce the upregulation of the inhibitory Gi protein. Table II compares the positive and negative properties of beta blockers and PDEIs. The profile for beta blockers includes eventual biologic improvement of intrinsic systolic function, a biologically based reversal of remodeling, lowering of heart rate, favorable metabolic effects, antiarrhythmic properties, and anti-ischemic effects. However, as noted earlier, the use of beta blockers can present difficulties in patients with advanced heart failure (HF) due to myocardial depression and worsening of heart failure. Moreover, in some patients on high-dose beta blockers, there is impairment in exercise tolerance and other adverse effects, which may preclude their use.

On the other hand, the pharmacologic action of PDEIs produces favorable hemodynamic effects and an improvement in exercise performance attributable to hemodynamic improvement. However, at higher doses, PDEIs may increase heart rate and myocardial metabolic requirements and exacerbate ischemia. In addition, the proarrhythmic effects of PDEIs have led to an increase in mortality in multiple randomized studies. As shown in Table II, when given in combination, the potential adverse effects of PDEIs or beta-blocking agents are “cancelled” by the beneficial effects of the other class. Moreover, the pharmacologically based favorable hemodynamic effects of PDEIs and the salutary biologic effects of beta blockers on left ventricular (LV) function are theoretically (Table II) and operationally additive.

Hemodynamic Effects of Dobutamine versus Phosphodiesterase Inhibitors in Patients Treated with Beta Blockade

Several studies have described the concomitant use of the partial beta agonist dobutamine and beta-blocking agents in subjects with heart failure. In one study, nine patients with HF treated chronically with the beta1-, beta2, and alpha-receptor-blocking agent carvedilol were given a graded dobutamine infusion (5, 10, 15, and 20 µg/kg/min) and were eval-
TABLE II Cardiovascular effects of beta-adrenergic blocking agents, phosphodiesterase inhibitors, or their combination in subjects with heart failure

<table>
<thead>
<tr>
<th>Effect</th>
<th>Beta blocker</th>
<th>PDEI</th>
<th>Beta blocker + PDEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓ ↓</td>
<td>← or ↑</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Systolic function</td>
<td>↓ then ↑</td>
<td>↑</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Diastolic function</td>
<td>← ← or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Arterial vasodilation</td>
<td>↑ ← or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Venodilation</td>
<td>↑ ↑ ↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LV filling pressure</td>
<td>← or ↑, then ↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MVO₂</td>
<td>↓ ↓</td>
<td>← or ↑</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Exercise capacity</td>
<td>← or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Proarrhythmia</td>
<td>↓ ↓</td>
<td>← or ↑</td>
<td>↓ ↓</td>
</tr>
</tbody>
</table>

Abbreviations: PDEI = phosphodiesterase inhibitor, LV = left ventricular, MVO₂ = maximal venous oxygen (consumption).

Unfortunately, beta-blocker treatment. However, in metoprolol-treated contractile response may even be enhanced compared with a relatively low dose, 25 µg/kg given over 10 min. In contrast, dobutamine increased cardiac index only at a relatively high dose (15 µg/kg/min) that was accompanied by an increase in systemic afterload and no decrease in pulmonary artery pressures. Similar results in subjects treated chronically with carvedilol or metoprolol have been obtained with the PDEI enoximone versus dobutamine (M. Metra, oral communication).

Limitations of Beta-Blocking Agents in Chronic Heart Failure

As noted earlier, beta-blocking agents favorably alter the natural history of heart failure in subjects with a dilated cardiomyopathy (primary or secondary) phenotype, and mild to moderate CHF. However, based on results of MERIT HF and Beta-Blocker Evaluation Survival Trial (BEST), beta-blocking agents appear to be much less effective in more advanced HF; that is, subjects in New York Heart Association (NYHA) Class IV in both MERIT-HF and BEST derived no benefit from beta blockade in terms of reduction in mortality or hospitalizations. The most likely explanation for the lack of effect of beta blockers in more advanced heart failure is that withdrawal of adrenergic support to the severely failing heart is not helpful or can even harm a substantial group of these subjects.

Long-Term Treatment with Phosphodiesterase Inhibitors and Beta Blockers in Advanced Heart Failure

As discussed above and as outlined in Table II, combination therapy using a PDEI and a beta blocker might attenuate the adverse effects of each while preserving or enhancing each agent’s beneficial properties. In a recent study, 30 patients with severe CHF (left ventricular ejection fraction = 17.2 ± 1.2%, cardiac index = 1.6 ± 0.1 l/min/m², pulmonary capillary...
wedge pressure = 25.2 ± 1.5 mmHg) were treated with a combination of oral enoximone and oral metoprolol. Enoximone was administered at a dosage of 0.5–1.0 mg/kg three times per day. After clinical stabilization, metoprolol was administered at 6.25 mg twice per day and titrated up to a target dosage of 100–150 mg per day. The purpose of this protocol was to attempt to use the PDEI as a bridge to beta blockade in subjects intolerant to the latter or who had CHF too advanced to attempt introduction of beta-blocker treatment.43 Twenty-nine (97%) patients tolerated enoximone and 80% of patients tolerated the addition of metoprolol. The protocol required patients to remain on enoximone for 6 months, whereupon it was withdrawn. However, enoximone therapy had to be reinstated in 52% of patients as a result of deterioration following withdrawal of the PDEI. This finding suggests that the combination therapy had a beneficial effect beyond that produced by beta blockade. Results from this study demonstrated significant improvement in mean LV ejection fraction, from 17.7 ± 1.6% to 27.6 ± 3.4%; mean heart rate decreased from 101 ± 4.0 to 80.0 ± 4.0 beats/min and NYHA functional class improved from 4.0 ± 0 to 2.8 ± 0.1. Hospitalizations were reduced, and limited data on survival in this group of patients were promising.43 These data support the idea that the combination of a PDEI and a beta-blocking agent is additive for efficacy and subtractive for adverse effects. Because of these findings, a large placebo-controlled trial of enoximone and metoprolol versus placebo (the “EMPOWER” trial) is underway. In addition, the “PROBE” study—involving the use of milrinone to facilitate the initiation of oral carvedilol therapy in patients hospitalized with NYHA functional class III/IV CHF—will begin soon.

Conclusions

Beta-adrenergic receptor blocker treatment has become an important therapy for subjects with mild to moderate CHF. For decompensated patients with CHF in need of inotropic support, it is important to understand the interaction of inotropic and beta-blocker therapy. The beta-adrenergic agonists and PDEIs used as inotropes have different mechanisms to muscle contraction and selective beta-receptor down-regulation in heart failure. Circ Res 1986;59:297–309


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