A rational approach for the treatment of acute heart failure: current strategies and future options

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Purpose of review

Acute decompensated heart failure represents a major, growing health problem in the developed world. However, until recently, relatively little research has been performed in this field to provide a basis for rational treatment strategies. The purpose of this review is to discuss the current approach and the potential future strategies for treatment of patients with acute decompensated heart failure.

Recent findings

Recent data have confirmed the heterogeneous nature of patients admitted with acute decompensated heart failure, and the limitations of the current therapeutic regimens with diuretics, intravenous vasodilators (*ie,* nitroglycerin, nitroprusside), and intravenous inotropes (*ie,* dobutamine, milrinone). A new vasodilator, nesiritide, has been demonstrated to improve hemodynamics and symptoms at 3 hours compared with nitroglycerin, and has been added to the therapeutic armamentarium in the United States. However, none of these agents has been shown to influence patient outcomes favorably. Given the high readmission rates, morbidity, and mortality of acute decompensated heart failure, other newer approaches, such as antagonists to a number of neurohumoral targets (*ie,* endothelin [tezosentan], vasopressin [conivaptan, tolvaptan], and adenosine) and non-cAMP-mediated inotropy (*ie,* levosimendan), are currently under investigation and showing promise.

Summary

Acute decompensated heart failure presents a challenging therapeutic problem for clinicians. Although they readily correct the hemodynamic abnormalities, current treatment strategies have significant limitations and have not been shown to improve morbidity or mortality. A number of new agents are under investigation with the goal of improving patient outcomes.

Keywords

acute decompensated heart failure, vasodilators, inotropes, hemodynamics, patient outcomes

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Introduction

Heart failure afflicts more than 10 million patients in the United States and western Europe alone, representing one of the most important health problems in these countries, and acute decompensated heart failure (ADHF) is a leading cause for hospital admission [1•,2,3••]. Despite the prominence of this disorder, there had been limited research on defining who these patients are, what their outcomes may be, and how current therapies influence these outcomes. Although guidelines abound for chronic congestive heart failure (CHF), they remain conspicuously silent regarding ADHF. In the absence of such research, the formulation of a rational diagnostic and treatment process is daunting. However, recent studies have provided important new information that can guide the development of a rational approach to this growing population. The purpose of this review is to describe the current diagnostic and treatment approaches to ADHF patients and to discuss potential future strategies.

What constitutes a "rational" approach to acute decompensated heart failure?

A rational approach to the diagnosis and treatment of acute heart failure must adequately address the different goals of each process, be supported by clinical research, and be reasonable to implement. Although experience can guide the definition of the goals and pragmatism can guide the practicality of the approach, only the clinical studies can provide any semblance of rationality to the art of patient care. Thus, this review focuses on the scientific basis for a contemporary approach to the patient with ADHF.

How should patients be diagnosed with acute decompensated heart failure?

The diagnostic process has the goals of first establishing the presence of heart failure (as opposed to other etiologies of the presenting symptoms; for example, chronic obstructive pulmonary disease exacerbation as the cause of dyspnea), establishing the potential, hopefully reversible and/or treatable, underlying precipitant of the decompensation (*eg*, recent consumption of extra salty chips), and perhaps to assist with the appropriate implementation and selection of therapies. The cornerstone of diagnosis remains the history and physical examination.

As with all of medicine, a carefully and completely elicited history is essential. The history should have a special emphasis on prior cardiac problems, the evolution of the presenting and associated symptoms (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, cough, bloating, anorexia, chest discomfort or other anginal equivalents, dizziness, sleep disturbances, and etc.) and signs that the patient can note (peripheral edema, increase in abdominal girth, increase in weight, cool extremities, etc.), detailed investigations of potential precipitants (dietary indiscretion, noncompliance with medicines, initiation of new medicine, etc.), and related comorbidities (chronic obstructive pulmonary disease, renal disease, diabetes, etc.). Of particular note is the recently appreciated role that the use of nonsteroidal antiinflammatory drugs can play in precipitating heart failure. In patients without a history of heart failure, nonsteroidal antiinflammatory drug use almost doubles the risk of a hospitalization for decompensated heart failure [4•], and in those with a history of heart failure, there was almost a 10-fold increase in the risk of hospitalization [5].

Many articles bemoan the decline of the physical examination in medicine. In heart failure, this loss of clinical skills has dramatic consequences. In approaching the patient with ADHF, one may be guided by the words of Oliver Wendell Holmes, Jr.: "First, strike for the jugular and let the rest go." An assessment of volume status through the detection of elevated jugular venous pressure, abdominal–jugular reflux, rales, peripheral or sacral edema, in conjunction with a clinical determination of the perfusion status of the patient (hypotension, cool extremities, etc.) is essential to establishing the presence of heart failure, guiding therapy [6], and even providing prognostic information [7•]. Elevated jugular venous pressure and elevated S3 are extremely useful clinical signs and are independently associated with an increased risk of progression of heart failure [8]. Nonetheless, reliance on these historic and physical examination findings, especially in the emergency setting, can underestimate the presence of heart failure and the severity of the underlying hemodynamic abnormalities.

Natriuretic peptides for diagnosis

There are many diagnostic tests that are important in establishing the diagnosis and guiding the therapy of heart failure, including serum chemistries, CK-MB/ troponin, chest radiography, electrocardiography, and echocardiography. There has been increasing evidence that biochemical markers of myocardial necrosis, such as troponins, also have prognostic value [9]. Recently, assays for B-type natriuretic peptide (BNP) have been developed that hold considerable promise in assisting with the diagnosis of heart failure. In response to increased ventricular pressure and stretch, the ventricles synthesize pro-BNP, which is cleaved into the inactive N-terminal brain natriuretic peptide (nt-BNP) peptide and the biologically active BNP protein. Consequently, measures of both these markers of BNP production have been developed, and the clinical applications of these tests have been reviewed extensively [10•,11]. The largest study of this diagnostic test, the Breathing Not Properly study, has been reported repeatedly [12,13,14••,15••]. This study of 1586 patients presenting to the emergency department with dyspnea demonstrated that, using a cutoff of 100 pg/mL, the test had a diagnostic accuracy of 83%, a sensitivity of 90%, and a specificity of 76%, compared with the "gold standard" diagnostic categorization of two cardiologists. Another study compared measuring BNP versus nt-BNP in the patients presenting with acute shortness of breath, and found both the BNP and nt-BNP tests to compare favorably with well-validated laboratory assays [16•]. Although specificity appeared to be higher with nt-BNP assays, sensitivity was greater with BNP assays. The BNP assay may therefore be more useful in excluding heart failure whereas nt-BNP assays have slightly better specificity and positive predictive value, also correlating with prognosis [17].

Although these BNP assays have a role in the diagnosis of acute heart failure, there remain some important caveats. First and foremost, there is no evidence to demonstrate that these assays can supplant clinical decision making and, as with any diagnostic test, should only be used in the context of the totality of the patient's presentation. Second, normal ranges for these assays have yet to be clearly established and may be affected by age, gender, renal function, and drug use (especially diuretics and β-blockers). It is important to note that values may be elevated in patients with right heart failure resulting from severe lung disease or pulmonary embolism and in patients with known systolic dysfunction who present with dyspnea unrelated to heart failure. Third, there has been no definitive demonstration that knowing the BNP will change clinical practice or favorably influence clinical outcomes of the patients, although a recent study suggests that BNP testing for the diagnosis of dyspnea may provide these benefits. In the BASEL study [18••], 452 patients presenting to the emergency department with dyspnea were randomized to a diagnostic strategy

including measurement of BNP or to a standard assessment strategy. Patients in the BNP-guided group were hospitalized less frequently, were admitted to the intensive care unit less frequently, had a significantly decreased length of stay, and incurred lower hospitalization costs. More important, there appeared to be no difference in 30-day rates of rehospitalization or mortality. However, many treating physicians will probably treat the uncertain, intermediate cases presenting with dyspnea as both a chronic obstructive pulmonary disease exacerbation and heart failure, especially with an intermediate BNP level. Thus, BNP testing has the potential to add to the diagnosis of ADHF when used in conjunction with other historical, physical examination, and laboratory findings. An additional role for BNP as a screening test and prognostic tool is supported by a recent report from the Framingham Offspring Study, which demonstrated that BNP levels in the "normal" range still have considerable prognostic significance [19•].

Invasive hemodynamic monitoring

The use of invasive pulmonary artery (PA) pressure catheter monitoring has been variously viewed as a necessity in the appropriate management of heart failure patients to a potentially dangerous procedure with limited usefulness. Both of these extremes can be partially supported by evidence, but the truth most likely is to be found in the cast range of clinical practice between these points. The American College of Cardiology/American Heart Association Task Force recommendations provide few guidelines on the use of hemodynamic monitoring in heart failure [20]. The SUPPORT trial examined the 30-day survival of 5735 critically ill patients who were treated with or without PA catheters [21] and suggested that PA catheter placement was associated with increased mortality and use of resources. However this study was not randomized and most patients had etiologies other than CHF, with the CHF patients comprising 11% of the study group. Another recent multicenter study of 676 patients with shock, primarily resulting from sepsis, acute respiratory distress syndrome, or both, randomized patients to receive either a PA catheter or not, and found that early use of the PA catheters did not adversely affect mortality or morbidity [22•]. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (or ESCAPE) trial is a multicenter, randomized trial designed to test the long-term safety and efficacy of treatment guided by invasive hemodynamic monitoring and clinical assessment versus that guided by clinical assessment alone in patients hospitalized with New York Heart Association class IV heart failure [23]. Until the results of the ESCAPE trial shed more light on this controversial issue, "routine" PA catheter placement for management of ADHF cannot be recommended. In our clinical practice, PA catheter placement is considered a diagnostic tool to distinguish between cardiogenic versus noncardiogenic compromise and to guide therapy in patients with persistently severe symptoms or cardiogenic shock.

What are the contemporary characteristics of patients with acute decompensated heart failure?

Despite being one of the leading causes for hospitalization, there has been limited characterization of patients admitted for ADHF. Two recent reports are providing important information on these patients. The EuroHeart Failure Survey [3••,24••] screened consecutive discharges or deaths during 2000 to 2001 from medical wards at 115 hospitals in 24 European and Mediterranean countries over a 6-week period, and screened 46,788 discharges to enroll 11,327 patients with suspected or confirmed heart failure. Approximately half the patients were women, but there were notable gender differences in these patients. Although 51% of the women were older than 75 years only 30% of the men were elderly, and more men (51%) had decreased systolic function with an ejection fraction less than 40% than women (28%). Conversely, 45% of the women had normal left ventricular systolic function compared with 22% of the men. A new diagnosis of atrial fibrillation was evident in 13% of the patients whereas 20% had a comorbidity of diabetes mellitus. This survey will be a tremendous resource in the coming years to provide more insight into the characteristics of these patients.

The Acute Decompensated Heart Failure National Registry (ADHERE) is another tremendous resource for understanding these patients. ADHERE is an industry-sponsored (Scios, Inc., Fremont, CA, USA) registry enrolling patients during October 2001 to the present discharged from 263 hospitals with a primary or secondary diagnosis of heart failure. Medical history, management, treatments, and health outcomes were collected on these patients without individual identifiers and, consequently, a single patient could be entered more than once. The most recently available data from the second quarter of 2003 [25••] includes information on 58,919 discharges from July 1, 2002, to June 30, 2003, and shows findings remarkably consistent with the EuroHeart Failure survey. The median age was 75.3 years and 52% of the patients were women; almost 60% of the patients who had ejection fractions evaluated before admission had an ejection fraction less than 40% or had moderate-to-severe dysfunction, whereas only 46% of patients having ejection fraction evaluated during the admission had such evidence of systolic dysfunction. One difference from EuroHeart, which has been noted in other contexts presumably as a result of increasing obesity, is the higher prevalence of diabetes mellitus in the United States-based ADHERE patients (44%). Atrial fibrillation was reported in 31% of the patients. Almost 90% of the patients presented with dyspnea and 32% with fatigue,

whereas 67% of the patients had rales and 65% had peripheral edema on physical examination. As discussed later, ADHERE can provide important insight not only into who these patients are, but also how they are treated and what are their outcomes.

What is wrong with the current treatment of acute decompensated heart failure?

Although precise, national data are unavailable, most patients presenting with ADHF will be treated with oxygen and possibly morphine to assist with pulmonary venous dilation and symptom relief. In addition, patients without signs of cardiogenic shock or symptomatic hypotension who have evidence of volume overload will receive diuretics, often intravenous furosemide. In ADHERE, 14% of the patients received intravenous morphine, 88% of patients received diuretic therapy during their hospitalization (compared with 87% in the EuroHeart Failure survey [24••]), 76% received diuretics within the emergency department, and 84% of the patients given intravenous diuretics received furosemide. In fact, 64% of the patients were treated with intravenous diuretics alone. The reliance on intravenous diuretics is reflective of a number of factors. First, most patients present with evidence of volume overload, as demonstrated by the presenting signs and symptoms described earlier. In fact, excessive salt intake alone represented 22% of the precipitants of heart failure exacerbations in one study [26]. Second, diuretics provide rapid symptomatic relief. A frequently used technique among heart failure specialists is to use continuous intravenous infusions of furosemide to facilitate this process [27]. Third, they are easily used and well tolerated, avoiding many of the complexities of intravenous infusions and the related side effects of vasodilators and inotropes. However, this predominant diuretic-based approach has significant limitations. A number of reports have linked diuretic use to increased mortality [28,29] and, although some of this relation may be accounted for by the increased severity of illness of these patients, it is also well-known that intensive diuretic treatment can cause deleterious activation of neurohormones and can precipitate cardiac arrhythmias. Moreover, in the setting of progressive renal dysfunction or acute renal failure there is evidence that loop diuretics will not be effective and may be harmful [30•].

Is there evidence that the current treatment strategies are less than ideal? In the EuroHeart Failure Survey population [3••], the median duration of index hospitalization was 11 days, 6.9% of patients died during the index hospitalization, 24% of the patients were readmitted within 12 weeks of discharge, and a total of 13.5% died between admission and 12 weeks of follow-up. In ADHERE [25••], there was a 4.0% in-hospital mortality, a 4.3-day median length of hospital stay, and 23% of the patients had already been admitted at least once for heart failure in the last 6 months. These dismal morbidity and mortality measures suggest that there are serious limitations to our current treatment strategies.

The goals of treatment may be viewed in three phases. Initially, the immediate goals are to restore oxygenation, organ perfusion, and total body fluid balance. Once these goals are addressed, intermediate goals become important, such as minimizing end-organ damage, reducing hospitalization duration, especially in intensive care settings, and initiating beneficial chronic medical therapies. As discharge nears, long-term goals of reducing readmission to the hospital and improving long-term survival are more evident. Obviously, these therapeutic goals are interdependent, but they provide a framework with which to interpret the existing clinical research in this field. Patients have rapid symptomatic improvement with unrestricted use of current standard therapies, as demonstrated in recent trials, but no therapy to date has demonstrated improvements in long-term symptoms, morbidity, or mortality. These criteria are how both current and future therapies should be judged.

How do current intravenous therapies meet these treatment goals?
Intravenous inotropic agents
Intravenous inotropes including dobutamine and milrinone may be used in patients with ADHF who manifest signs of inadequate perfusion and in patients who do not respond to diuretics and vasodilators. Intravenous inotropic therapy usually produces symptomatic and hemodynamic improvement in the short term, but there is growing evidence that they may lead to increased morbidity and mortality.

In the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (or OPTIME-CHF), the trial investigators randomized 951 patients with exacerbation of chronic CHF not requiring inotropic support to 48-hour intravenous treatment with milrinone or placebo [31,32••]. The milrinone group was associated with both a higher incidence of worsening of heart failure, symptomatic hypotension requiring intervention, and new atrial arrhythmias. Although there was no difference in the primary or main secondary end points, there was a nonsignificant increase in the number of deaths in hospital and after 60 days in the milrinone group.

The use of dobutamine in heart failure will also need to be studied further given the results of OPTIME-CHF. There have been few studies that have assessed the effect of dobutamine on patient outcomes versus placebo, although at least two new therapies that were compared with dobutamine demonstrated improved survival [33,34]. Trials with intermittent dobutamine have suggested harm [35], but some of them remain unpublished.

Retrospective data from the Flolan International Randomized Survival Trial showed an increased risk of clinical events for patients treated with dobutamine with 70% of the patients on dobutamine dying, compared with 37% in those without dobutamine [36]. Even after adjusting for baseline differences, the use of dobutamine remained an independent predictor of death. Furthermore, dobutamine is well-known to increase the incidence of arrhythmias [37,38], and even the use of non-intravenous sympathomimetics for pulmonary conditions have been noted to increase arrhythmias [39].

Unfortunately, despite these potential adverse effects of the currently available inotropes, there remain some patients with ADHF with few other options. There is clearly an unmet need for an intravenous inotrope with a mechanism of action independent of cAMP activation and demonstrated ability not to affect adversely morbidity or mortality.

Intravenous vasodilators

Vasodilators are the mainstay of therapy for ADHF in Europe. In fact, 32% of patients admitted with ADHF received nitrates during their index hospitalization [24••]. Although there is some evidence that physicians in the United States have not used nitrates nearly as frequently and prefer inotropes [40], these data may represent a selection bias of academic heart transplant centers. Although only 10% of patients in ADHERE received intravenous nitroglycerin (compared with 15% receiving inotropes), almost half received nitrates of some type during the hospitalization, although there was no reported use of nitroprusside [25••]. Both nitroglycerin and nitroprusside act by increasing cGMP in the vascular smooth muscle cell with resultant vasodilation. There is little doubt that nitroglycerin is a very effective intravenous medication for the treatment of ADHF [41], although its use is limited by the need to titrate the dose as a result of the rapid development of tachyphylaxis and frequent, marked underdosing, as well as inexperience with effectively using the drug in the context of heart failure, as opposed to angina. There are no outcome trials with nitroglycerin versus placebo, and given the low cost and ready availability of nitroglycerin, it is unlikely that any studies will be performed. However, in the Vasodilation in the Management of Acute Congestive Heart Failure trial [42] (discussed later), 6-month mortality was certainly not higher in patients treated with nitroglycerin (20.8%) compared with nesiritide (25.1%), suggesting that it is unlikely to have a major adverse effect.

Another intravenous vasodilator that is extremely efficacious [43], although infrequently used, is nitroprusside. This agent is readily titrated and very effective in reducing left ventricular filling pressures and systemic vascular resistance. Although there are concerns about thiocyanate toxicity, especially in the context of hepatic or renal hypoperfusion/dysfunction, these concerns are probably less relevant for short-term administration. Additional concerns include precipitation of hypotension and potential exacerbation of ischemia, as well as the requirement in many centers for invasive blood pressure monitoring. We think that this agent is underused and has been demonstrated to be very effective even in patients with heart failure and critical aortic stenosis [44•]. In addition, there is even evidence that short-term tailored therapy with nitroprusside and diuretics resulted in a marked decrease in neurohormonal activation with improvements in hemodynamics [45]. However, the difficulties in the administration of nitroprusside and the absence of any outcome data will most likely continue to preclude its widespread use.

Nesiritide

Nesiritide is identical to human BNP and has multiple biologic and pharmacologic effects. Like the vasodilators discussed earlier, nesiritide acts by increasing cGMP with the primary effect of causing vasodilation and resultant decreases in left ventricular filling pressures. Despite being called a "natriuretic" peptide, nesiritide has not been associated with major diuresis in clinical trials, although it may potentiate the effect of concomitant diuretics, slightly reducing the total diuretic dose required. In multiple clinical trials, nesiritide has been demonstrated to be efficacious in decreasing pulmonary capillary wedge pressure and improving patients' symptoms [40,42,46].

In a tour de force of trial design, the Vasodilation in the Management of Acute Congestive Heart Failure trial investigators compared the use of nesiritide, nitroglycerin, or placebo in addition to standard therapy in 489 patients with ADHF [42]. Patients were stratified on the basis of the investigator's decision to use invasive monitoring with PA catheterization. The coprimary end points were the change in the pulmonary capillary wedge pressure and the subject's dyspnea evaluation after 3 hours of infusion. When added to standard care, nesiritide produced a more rapid and greater improvement in hemodynamics than nitroglycerin titration or standard care alone, and these effects were sustained for at least 24 hours. Nesiritide produced a significant improvement in dyspnea at 3 hours compared with placebo, but not compared with nitroglycerin, and there were no significant differences at 24 hours between nesiritide and nitroglycerin. As noted earlier, there was no significant difference in 6-month mortality rates in patients receiving nesiritide compared with nitroglycerin (25.1% and 20.8% respectively, $P = 0.32$), and the 30-day rehospitalization rates were similar in the two groups.

Other studies of the effect of nesiritide on outcomes have been completed. A post hoc analysis of a subset of patients from a study [40] comparing standard care

therapy to nesiritide was performed [33] and demonstrated that readmissions for CHF, as well as all-cause readmissions, were lower in the two nesiritide groups (8% and 11%) compared with those patients selected to receive dobutamine (20%). Six-month mortality was also lower in the low-dose nesiritide group. The strength of this study's conclusions may be limited by its open-label design, nonrandomized selection of therapies used in the standard care group, and the small number of patients and events in each subgroup. Additionally, the dobutamine group had a higher incidence of previous myocardial infarction and ischemia compared with the nesiritide group. However, the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy trial was randomized and demonstrated that nesiritide was not proarrhythmic when compared with dobutamine [37].

Thus, nesiritide is generally well tolerated and, in the studies listed here, it has demonstrated fewer side effects compared with nitroglycerin [42] and an improved safety profile compared with dobutamine with fewer arrhythmias and better outcomes [33,37,38,47]. However, symptomatic hypotension can be prolonged (mean duration, 2.2 hours [42]), so it should be avoided by appropriate patient selection. Nesiritide is indicated for the ADHF patient who presents with signs of congestion without signs of inadequate perfusion. It should not be used in patients who are overdiuresed, hypotensive, or present with other signs of inadequate perfusion. In addition, patients with aortic stenosis, hypertrophic cardiomyopathy, or cardiogenic shock are not candidates for nesiritide therapy.

What potential therapies may be available for the acute decompensated heart failure patient in the future?

The need for new therapies for ADHF should be clear from the foregoing discussion. Fortunately, there are a number of very promising therapies and therapeutic approaches being developed [48].

Calcium sensitizers

Levosimendan is a calcium-sensitizing agent that produces increased inotropy in a cAMP-independent fashion, by increasing the sensitivity of troponin-C to intracellular ionized calcium, as well as peripheral vasodilation though the vascular K-ATPase channels. Multiple studies have already demonstrated that levosimendan is a very effective positive inotrope [34,49,50], producing significant increases in stroke volume and cardiac index, and decreases in pulmonary capillary wedge pressure, right atrial pressures, pulmonary arterial pressures, and mean arterial pressures. This beneficial hemodynamic effect is maintained during a 48-hour infusion and for at least 24-hours after discontinuation of a 24-hour infusion [51••], most likely because of the active

long-lived metabolite OR-1896. In addition, levosimendan appeared to improve symptoms of dyspnea and fatigue, compared with placebo [50], although confounded by the presence of hemodynamic monitoring. As noted earlier, the current positive inotropes are effective, so the true question is whether levosimendan will be as efficacious and safer than the current inotropes.

In the Levosimendan Infusion versus Dobutamine (or LIDO) trial, 203 low-output heart failure patients were randomized to intravenous dobutamine or levosimendan [34]. Treatment with levosimendan was found to improve hemodynamic performance more effectively than dobutamine (primary hemodynamic end point achieved in 28% of patients *vs* 15% patients; P = 0.022). More important, the levosimendan group also had significantly lower 6-month mortality than the dobutamine group (*26% vs 38%*; P = 0.029). Although this difference may be driven more by the adverse effect of dobutamine than the positive effect of levosimendan, and the strength of the conclusions are limited by the absence of a placebo control and the small sample size and events, another trial in 504 postmyocardial infarction patients with left ventricular dysfunction (RUSSLAN) also suggested a reduced 6-month mortality with levosimendan compared with placebo [52]. The results of LIDO and the other smaller clinical trials are supportive of the hypothesis that levosimendan is an effective and safe inotrope. To test this hypothesis further, the ongoing REVIVE study, a prospective, randomized, multicenter study is designed to evaluate short-term and long-term outcomes in patients admitted for acute heart failure who are treated with a 24-hour infusion of levosimendan compared with placebo when added to standard therapy.

Endothelin antagonists

The utility of neurohormonal blockade for chronic heart failure has been well established, but recently more attention has been directed to the potential of acute blockade of deleterious neurohormones. Endothelin-1 (ET-1) is the major ET isopeptide produced in the human cardiovascular system and kidney and has many effects pertinent to the pathophysiology of ADHF: (1) it is the most potent known vasoconstrictor of the coronary and peripheral arteries, (2) ET-1 is both directly and indirectly (ischemia) proarrhythmic, (3) ET-1 increases and potentiates the activity of other neurohormones (such as aldosterone, epinephrine, and angiotensin), (4) it stimulates the release of inflammatory cytokines, (5) it is a mediator of acute ischemic renal injury, and (6) ET-1 increases vascular permeability [53]. In patients with ADHF, ET concentrations have been shown to be highly predictive of arrhythmias [54] and one of the strongest predictors of death [55]. Thus, it appeared that not only would an ET receptor antagonist be beneficial as a vasodilator, but also by favorably reducing end-organ damage and improving outcomes as a neurohormonal antagonist. Tezosentan is

a dual (ET-A/B), intravenously administered ET receptor antagonist that was specifically designed for the treatment of ADHF. In animal models of acute and chronic heart failure resulting from myocardial infarction, acute administration of tezosentan decreased pulmonary edema and improved survival [56]. Based on this study and others, and a compelling scientific rationale, tezosentan was studied in two pivotal and two ancillary clinical trials, known collectively as the Randomized Intravenous Tezosentan (RITZ) trials.

The first pivotal trial reported was RITZ-2, which enrolled 292 ADHF patients with low cardiac output and high filling pressures who were randomized to tezosentan in two doses (50 mg/hour and 100 mg/hour) and placebo, in addition to standard therapy [57••]. Tezosentan significantly increased cardiac index at 6 hours and decreased PCWP, while improving dyspnea in patients in 24 hours when compared with placebo. In addition, there was a trend toward decreasing the time to worsening of heart failure (P = 0.06). The beneficial hemodynamic effects and improved patient outcomes are very encouraging. In an attempt to reduce the bias introduced by hemodynamic monitoring that was evident in other trials into the symptom assessments, RITZ-1 tested the clinical efficacy of tezosentan by dyspnea assessment in 669 noncatheterized ADHF patients [58]. In RITZ-1, investigators found no significant difference in the 24-hour dyspnea assessment in tezosentan-treated patients compared with the patients treated with placebo in addition to standard therapy. Of note, patients in the RITZ-1 trial had a much lower event rate and seemed less symptomatic than those in RITZ-2, and the high dose of tezosentan resulted in significant side effects, suggesting that an adverse risk-to-benefit ratio at this dose may have contributed to the absence of a treatment effect. Two other studies with tezosentan (RITZ-4, which evaluated the safety of tezosentan in the setting of ADHF complicated by the acute coronary syndrome [59•], and RITZ-5, which examined the safety of tezosentan in fulminant pulmonary edema [60]) demonstrated that tezosentan was relatively safe in these populations, but confirmed that the dose was too high. Efficacy and safety data from the RITZ program and a recent dose-finding study have suggested that the optimal dosing of tezosentan is lower than the 50-mg/hour dose used. The Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study is the largest, ongoing, prospective, randomized trial in ADHF patients and will test the efficacy of a 1-mg/hour dose of tezosentan versus placebo in improving patient outcomes.

Vasopressin antagonists

Arginine vasopressin is a neurohormone produced by the central nervous system in response to changes in serum osmolality, severe hypovolemia, or hypotension. There are at least two types of vasopressin receptors (V_1 and V_2), with the V_{1a} receptor mediating vasopressin-induced vasoconstriction and the V_2 receptors mediating water resorption in the kidneys. Thus, vasopressin stimulation results in vasoconstriction and fluid retention, both of which can worsen ADHF. In heart failure, vasopressin levels have been shown to be markedly elevated and may be associated with adverse cardiovascular outcomes [61,62]. Two main strategies for vasopressin antagonists have evolved, based on the receptor pharmacology. Conivaptan is a V_{1a} and V_2 receptor antagonist and it was acutely administered to 142 stable NYHA class III/IV CHF patients [63]. The conivaptan-treated patients had significantly decreased PCWP and right atrial pressure, as well as an increase in urine output, but no change in cardiac index or other hemodynamic variables. Other trials in ADHF patients are planned.

Another approach to vasopressin antagonism is to block selectively the V_2 receptor, resulting in aquaresis without electrolyte imbalances or neurohormonal stimulation. Tolvaptan is a selective V_2 receptor antagonist, which caused increased urine output and decreased body weight and edema during 25 days of treatment in 254 mild chronic heart failure patients [64•]. The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (or ACTIV-CHF) study was designed to test the efficacy of tolvaptan when administered to patients hospitalized for worsening heart failure [65]. The study results were recently presented at the 2003 Scientific Sessions of the American Heart Association in Orlando, Florida, USA, by Dr. Gheoghiade. ACTIV-CHF randomized 319 patients with known CHF (ejection fraction < 40%) who required hospitalization for fluid overload to placebo and three doses of tolvaptan. The primary end point was body weight reduction at 24 hours after randomization, and all doses of tolvaptan were significant compared with placebo, although there was no difference in in-hospital mortality or worsening of heart failure. Thus, tolvaptan appeared to be effective in facilitating fluid loss without adverse sequelae in the ADHF patient with reduced systolic function. The effect of tolvaptan on mortality in patients hospitalized for heart failure is being evaluated in the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan.

Adenosine agonists

The combination of heart failure and deteriorating renal function, the cardiorenal syndrome, remains one of the most challenging problems in heart failure management. Approximately 21% of patients will have worsening of their renal function during treatment for ADHF, and these patients have longer hospitalizations and increased mortality [66,67], Unfortunately, the cardiorenal syndrome is poorly understood, and current therapies such as positive inotropes are empiric. Adenosine levels are increased significantly in heart failure patients [68] and

this elevation has been indicted as playing a role in the tubuloglomerular feedback that reduces the glomerular filtration rate (GFR) through afferent glomerular arteriole vasoconstriction. These effects are mediated by the A_1 adenosine receptor, and early studies suggested that A_1 receptor blockade would result in increased urine volume and sodium excretion, with preservation of GFR. In a study of 12 chronic heart failure patients, treatment with the A_1 selective adenosine agonist BG9719 (CVT124) did in fact increase diuresis and natriuresis while maintaining GFR [69]. In a larger study of 63 CHF patients, BG9719 (CVT124) was found to increase both urine output and GFR and, when given in addition to furosemide, improved urine output further with no deterioration in GFR [70]. The hypothesis that these agents may promote natriuresis while preserving renal function needs to be tested in further trials, but they offer promise for a vexing problem.

Conclusion

The diagnosis of ADHF will continue to evolve as currently available markers such as troponins and BNP are understood more completely and as new markers are discovered. A rational strategy would be to use diagnostic tests that would allow for accurate diagnosis of heart failure and give insight into the individualized selection of the best therapies. Unfortunately, we do not know enough about patients with ADHF to tailor therapy in such a manner, yet. The immediate treatment goal of patients with ADHF is rapid clinical and hemodynamic improvement, and our current therapies with aggressive diuretics, inotropes, and vasodilators appear to address this goal sufficiently. However, despite this rapid efficacy, the ultimate goals of preventing progressive deterioration, reducing readmission, and decreasing mortality remain largely unaddressed. Increasing the use of vasodilators and limiting the use of the currently available positive inotropes might have a favorable impact, but the great need is for a positive inotrope without the deleterious effects associated with dobutamine and milrinone. Another great need is for effective neurohormonal antagonism in the acute setting, with the hope of limiting myocardial and renal damage during the acute event. Finally, new therapies to treat the cardiorenal syndrome would allow for effective treatment of one of the most confounding management issues in heart failure. It is clear that there is a tremendous need for newer agents so that we may have a meaningful impact on the devastating morbidity and mortality engendered by ADHF.

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