SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

Identifying the best practices for advanced heart failure: Defining, debating, deciding

Selected topics presented by: KIRK F. ADAMS, Jr., MD, LYNN WARNER STEVENSON, MD, ILEANA L. PINA, MD, BARRY M. MASSIE, MD, MICHAEL S. CUFFE, MD, MARIA R. CONSTANZO, MD, ROBERT M. CALIFF, MD

Satellite symposia and minicourses presented in conjunction with the 47th Annual Scientific Session of the American College of Cardiology

Atlanta, Georgia, March 29-April 1, 1998

Reported and discussed by:
GORDON MOE, MD

Congestive heart failure (CHF) is a common clinical condition associated with significant morbidity and mortality.[1] Patients with advanced heart failure (AHF) are among the most critically ill patients. Recurrent hospital admissions, which characterize the clinical course of these patients, likely account for a substantial portion of healthcare costs. Accordingly, understanding the definition and the therapeutic strategies of AHF is important. The symposium addressed current therapeutic options of patients with AHF with a discussion of the pros and cons of invasive hemodynamic monitoring, the first randomized clinical trial on patients with exacerbation of CHF, and end-of-life decision-making factors that confront these critically ill patients.

Definition of advanced heart failure

A proposed working definition of AHF is based on the understanding of the underlying circulatory failure, high risk of adverse outcomes, and clinical characteristics. Based on this classification, the major criteria for diagnosis of AHF include the presence of New York Heart Association (NYHA) functional classes III or IV disease; or peak VO_2 (<14 mL/kg/min), or a six-minute walk (<200m) and a left ventricular ejection fraction <30%. Minor criteria that are considered "suggestive" but not required include conventional triple therapy for ≥3 months, plasma norepinephrine level >900 pg/mL, hyponatremia, pulmonary hypertension, and elevated plasma pro-endothelin-1 levels.

Management of acute decompensation

When a patient with NYHA class III-IV symptoms who is already on triple therapy presents for clinical assessment, the patient may be classified according to the presence or absence of fluid overload (wet versus dry) and presence or absence of hypoperfusion (cold versus warm).[2] Indications for invasive hemodynamic monitoring include uncertainty of fluid status, presence of concomitant disease such as severe lung disease, and suspicion of an abnormal right atrial and pulmonary capillary wedge pressure (PCWP) relationship. The goal is to aggressively lower cardiac filling pressures within 24 hours using IV diuretics and IV inotropes. By this time, oral therapy has been adjusted and might include higher doses of angiotensin-converting enzyme (ACE) inhibition or addition of hydralazine or beta-blockers. Patients can be discharged from hospital once stable body weight and stable drug regimens can be maintained for at least 24 hours.

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Table 1: Predictive value (%) of clinical and radiographic signs of congestion in identifying patients with pulmonary capillary wedge pressure >20 mm Hg

	Predictive Value	
	Positive	Negative
Clinical		
Orthopnea	61	37
Edema	79	46
Rales	87	61
High JVP	85	62
S3 gallop	66	44
Roentgenogram		
Cardiomegaly	61	*
Redistribution	75	52
Interstitial edema	78	53
Pleural effusion	76	47

JVP=jugular venous pressure.
*cardiomegaly was absent in only three patients.

Adapted from Chakko, et al[3]

Should therapy be hemodynamically-guided?

A number of studies demonstrate a poor correlation among clinical, radiographic, and hemodynamic evaluations.[3] In particular, the absence of radiographic or physical signs of congestion does not ensure normal PCWP values. The predictive values of some of these parameters are shown in table 1.

On the other hand, the rationale for tailored therapy may be based on three assumptions: short-term hemodynamic effects can guide drug selection; short-term hemodynamic effects can guide dose determination; and changes in cardiac filling pressures and cardiac index are useful endpoints when selecting and titrating drugs. These assumptions are untested and drugs with modest or adverse short-term hemodynamic effects, such as ACE inhibitors and beta-blockers, turn out to be the agents of most benefit over the long term. On the other hand, drugs with potent hemodynamic effects – such as oral phosphodiesterase inhibitors, flosequinan, epoprostenol, and vesnarinone – all turned out to have harmful effects over the long term.[4-6] Furthermore, dose titration based on hemodynamic measurements might lead to a choice of a less beneficial or even harmful agent and, invariably, to high-dose therapy. Thus, treatment should be dictated by clinical presentation. In this instance, patients with clinical evidence of volume overload would require aggressive diuresis accompanied by ACE inhibition. Patients with clinical evidence of low output can be treated with digitalis, ACE inhibitors, hydralazine, and intravenous inotropes if their condition remains unresponsive.

Rationale and status of the OPTIME study

Decompensated CHF is the major reason for hospital admission in patients aged >65 years. Intravenous inotropic therapy is sometimes employed as long-term continuous infusions, out-patient intermittent infusions, or intermittent "bailout" therapy. Enthusiasm for this form of therapy has been tempered somewhat by an earlier report[7] of an adverse effect of intravenous dobutamine on survival.

A recent randomized trial[8] comparing outpatient intermittent milrinone and dobutamine in patients with severe CHF suggests that milrinone therapy is more effective in improving functional class and is associated with a better 6-month outcome. The Outcomes of Prospective Trial of IV Milrinone for Exacerbation of Chronic Heart Failure (OPTIME) study is a prospective, multicenter, double-blind trial designed to test the hypothesis that a treatment strategy for exacerbated CHF that includes early inotrope support with IV milrinone will improve patient outcomes. Patients with exacerbation of chronic CHF are randomized to 48 hours infusion of milrinone (0.5 µg/kg/min, no loading dose) or to placebo. At the same time, concurrent therapy with agents such as ACE inhibitors and diuretics is optimized. The key endpoints are length of stay in hospital, and clinical status at 30 and 60 days, with attention to readmission and emergency-room visits. Study enrollment started in July 1997. At the time of this presentation, 200 patients had been enrolled by 80 investigators in the USA. The expected completion date is late 1998. OPTIME will be the first large-scale trial to investigate acute decompensation of CHF and to explore its outcomes.

Treatment of advanced heart failure

The choice of treatment for these sick patients is often empirical since an evidence-based approach is frequently not feasible. The favorable experience of the Comprehensive Heart-failure Management Program at the Ahmanson University of California suggested that patients with AHF should be referred to a heart-failure program not only for heart transplantation but also for medical management.[9]

Milrinone has been used for acute exacerbation of chronic CHF, refractory chronic CHF, CHF complicating myocardial infarction, CHF before surgical revascularization, assessment of reversibility of pulmonary hypertension and renal dysfunction, and attempt to improve right ventricular contractile function in patients with left-ventricular assist devices. Results of a previous study[7] that suggested a detrimental effect of IV inotropic therapy in CHF should be interpreted with extreme caution. In that study, the inotrope used was dobutamine and the dosage employed was exceedingly high. Currently, in some centres, use of IV milrinone involves a more sustained infusion, with the goal of relieving symptoms rather than achieving hemodynamic endpoints. When an acute hemodynamic response is not the objective, a loading dose is not always administered. Left ventricular assist devices continued to hold promise in the treatment of these patients. The ongoing Randomized Evaluation of Mechanical Assistance Therapy for Congestive Heart Failure (REMATCH) study is further addressing the impact of assist devices on quality of life, morbidity, and mortality.

Ethical dilemmas

The high mortality rate, the disability, and the multiple hospitalizations of patients with AHF create a special case of societal dilemma. The Study to Understand Prognosis and Outcomes and Risks of Treatment (SUPPORT) was a multi-institution project designed to improve the understanding of how decisions and outcomes are affected by patient preferences, family interactions, provider benefits, and disease severity. The conditions studied included acute exacerbation of chronic obstructive lung disease and CHF, chronic liver disease, colonic cancer with hepatic metastasis, and non-small-cell lung carcinoma. Phase I of SUPPORT was an observational study whereas phase II consisted of randomized intervention with advanced directives.

SUPPORT revealed some sobering findings regarding patients with AHF. Not surprisingly, AHF was the most common diagnosis. Deaths occurred in 27% of the patients within 6 months, 39% within 1 year, and 6.5% in the hospital. Seventy-five percent of patients stayed in hospital more than 5 days. Forty-four percent of patients were admitted to intensive care units, but only 17% of patients were listed DNR (do not resuscitate) – a much lower incidence than in other chronic illness – and 69% of patients requested CPR (cardiopulmonary resuscitation). Factors associated with foregoing of this decision included older age, Caucasian race, female sex, and depression.

There was a poor correlation between physicians and patients regarding the decision for or against advanced life support. Among patients who did not want CPR, 53% of their attending physicians perceived otherwise. In terms of

Table 2: Management of CHF

Evaluate symptoms
Determine etiology
Treat reversible causes

Optimal conventional therapy

- Salt restriction
- Diuretics
- ACE inhibitors
- Digoxin
- Beta-blockers

Special considerations

- Anticoagulant therapy
- Anti-arrhythmic therapy
- Other vasodilators
- Transplantation

Treatment of exacerbation

- IV inotropes (IV milrinone/dobutamine)
- Hospitalization and bed rest
- Intra-aortic balloon pump mechanical devices

quality of life, 43% reported moderate or severe pain, a slightly better proportion than the 50% over-all of patients in SUPPORT. In the randomized-control study, advanced directives had no effects on medical decision-making for DNR, admission to intensive care, and other use of resources. One in 5 families required member(s) to quit work to assist patients, and 31% of families reported loss of savings.

The key findings from SUPPORT are that patients with AHF in general want more aggressive care than do their families and care-providers, and that "no hope" is not well defined. Hence, there is no substitute for frequent, effective, and direct communication about preferences with these critically ill patients and their families.

Conclusion

CHF incidence is increasing as patients survive longer. AHF represents an end-stage of a number of cardiovascular diseases most commonly of coronary artery disease, hypertension, alcohol, viral or idiopathic etiology. Optimal medical therapy (table 2) may delay, but does not prevent, inevitable deterioration which frequently results in hospitalizations and a need for more intense therapy, including transplantation if appropriate. Because of these considerations, long-term management of CHF presents particularly difficult challenges.

References

1. Massie BM, Shah N. Evolving trends in the epidemiologic factors of heart failure: Rationale for preventive strategies and comprehensive disease management. *Am Heart J* 1997;133:703–712.
2. Stevenson WG, Stevenson LW, Middlekauff HR, et al. Improving survival for patients with advanced heart failure: A study of 737 consecutive patients. *J Am Coll Cardiol* 1995;26:1417–1423.
3. Chakko S, Woska D, Martinez H, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: Conflicting results may lead to inappropriate care. *Am J Med* 1991; 90:353–359.
4. Packer M, Carver J, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. *New Engl J Med* 1991;325: 1468–1475.
5. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997;134:44–54.
6. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *New Engl J Med* 1993;329:149–155.
7. Dies F, Krell MJ, Whitlow P, et al. Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986;74: II38.
8. Mehra MR, Turgut T, Smart FW, et al. Outpatient intermittent milrinone and dobutamine in severe heart failure: A randomized controlled clinical trial. *Circulation* 1997;96:I-711.
9. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. *J Am Coll Cardiol* 1997;30:725–732.