

## Pharmacotherapy of systolic heart failure

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Systolic heart failure is defined as heart failure due to left ventricular systolic dysfunction. It represents a major admission diagnosis, and carries a high rate of mortality and morbidity. Ischemic heart disease and systemic hypertension are the two most common causes of systolic heart failure. Moreover, lack of compliance with diet and/or drug therapy represents the most common cause of heart failure decompensations and hospital readmissions. The pharmacotherapy of systolic heart failure aims toward reduction of

both mortality and morbidity. This includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, spironolactone, digitalis, and others. Moreover, a new modality of adjunctive therapy was recently introduced for severe heart failure i.e. cardiac resynchronization therapy.

*Key words:* heart failure, systolic dysfunction, ACEI

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Heart failure has emerged as a major health challenge increasing in prevalence as age adjusted rates of myocardial infarction and stroke decline. Affecting 4 to 5 million people in the United States of America with more than 2 million hospitalizations each year, heart failure alone accounts for 2-3% of the US national health care budget.<sup>1</sup> Moreover, once clinical heart failure manifests, the 6 year mortality rate approaches 80% in men and 65% in women.<sup>2</sup>

Recent advances in our understanding of the pathophysiology of heart failure and new developments in the therapy of this disorder have greatly expanded the information base on which to make decisions. We elected to limit this review to adults who present with heart failure associated with left ventricular systolic dysfunction. This decision is based on the fact

that the great majority of heart failure patients have left ventricular systolic dysfunction, and the greatest advances in our understanding and treatment of heart failure are associated with this entity.

The review will cover two clinical categories:

1. Acute heart failure
2. Chronic heart failure

It is important in the course of managing patients with heart failure to reveal the precipitating factors for the decompensation<sup>3</sup> (Table 1). In order to understand the day to day phy-

**Table 1. Precipitating factors for heart failure decompensation**

| Precipitant   | n (101) |
|---|---------|
| Lack of compliance:                                     | 64      |
| With diet   | 22      |
| With drugs  | 6       |
| With diet and drugs                                     | 37      |
| Uncontrolled hypertension                               | 44      |
| Cardiac arrhythmias                                     | 29      |
| Atrial fibrillation                                     | 20      |
| Atrial flutter  | 7       |
| Multifocal atrial tachycardia                           | 7       |
| Ventricular tachycardia                                 | 1       |
| Environmental factors                                   | 19      |
| Inadequate therapy                                      | 17      |
| Chest infection   | 12      |
| Emotional stress  | 7       |
| Administration of inappropriate drugs or fluid overload | 4       |
| Myocardial infarction                                   | 6       |
| Endocrine dysfunction                                   | 1       |

sical limitation associated with different degrees of heart failure severity, a functional classification was developed by the New York Heart Association. This classification is based

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on the relation between symptoms and the amount of effort required to provoke them:<sup>4</sup>

**Class I:** No limitation (asymptomatic) at the ordinary level of activity.

**Class II:** Slight limitation of physical activity. Ordinary activity results in fatigue, palpitation, dyspnea, or angina.

**Class III:** Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activities lead to symptoms.

**Class IV:** Inability to carry on any physical activity without discomfort. Patient is symptomatic even at rest.

## Etiology

The majority of patients with heart failure secondary to left ventricular systolic dysfunction have underlying systemic hypertension or ischemic heart disease as shown from several trials.<sup>5-8</sup> The etiologies of left ventricular dysfunction are shown in Table 2.

**Table 2. Causes of left ventricular systolic dysfunction**

- Common causes
  - Underlying systemic hypertension
  - Ischemic heart disease
- Less common causes
  - Infection: Viral, bacterial, fungal, parasitic
  - Infiltrative: amyloid, hemochromatosis, sarcoidosis
  - Toxins: Heroin, cocaine, alcohol, amphetamine, adriamycin, cyclophosphamide, sulfonamide, lead, arsenic, cobalt, phosphorus, ethylene glycol
  - Nutritional deficiencies: protein, thiamine, selenium
  - Electrolyte disorders: hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia
  - Collagen vascular disorders: SLE, RA, PAN, systemic sclerosis, hypersensitivity vasculitis, Takayasu syndrome, polymyositis, Riter's syndrome
  - Endocrine and metabolic diseases: diabetes mellitus, thyroid disorders, hypoparathyroidism with hypocalcemia, pheochromocytoma, acromegaly
  - Tachycardia induced: incessant supraventricular tachyarrhythmias, atrial fibrillation with rapid ventricular response
  - Miscellaneous: hypereosinophilic syndrome, peripartum cardiomyopathy, sleep apnea syndrome, Whipple's disease, L-carnitine deficiency.

## Acute Heart Failure

Acute heart failure may present as pulmonary edema or cardiogenic shock.

### DIAGNOSTIC EVALUATION

The initial diagnostic evaluation of the patient includes:

1. Focused history and physical examination;
2. 12 lead electrocardiogram to rule out acute myocardial ischemia or injury, or significant arrhythmias;
3. Continuous ECG monitoring;
4. Blood studies: complete blood count (CBC), electrolyte, blood urea nitrogen (BUN), creatinine, and cardiac biomarkers;
5. Digital pulse oxymetry/arterial blood gas;
6. Chest radiography;
7. Transthoracic echocardiography if previously not done, or if acute valvular pathology is suspected, or tamponade, or mechanical complications of an acute myocardial infarction;
8. Coronary angiography if intervention for acute myocardial infarction is anticipated and/or to determine the cause for refractory acute pulmonary edema;
9. Placement of indwelling pulmonary or arterial catheters should be considered in the setting of deteriorating clinical course, cardio-genic shock on inotropes, if uncertainty exists regarding the volume status, or if high doses of nitrate or nitroprusside are required for stabilization.

### MANAGEMENT

The management of acute heart failure includes:

1. Oxygen therapy;
2. Sublingual nitrate;
3. Furosemide;
4. Morphine sulfate;
5. Mechanical ventilation;
6. Coronary reperfusion.

Administration of sublingual nitrate (0.4-0.6 mg, repeated every 5-10 minutes as needed) is effective in both ischemic and non-ischemic acute heart failure due to its reduction of preload and afterload, and epicardial coronary arteriodilation. If systemic blood pressure is acceptable (i.e. systolic blood pressure > 95-100 mm Hg), nitroglycerin can be given intravenously (starting dose of 0.3-0.5 microgram/Kg/minute). Sodium nitroprusside (starting dose of 0.1 microgram/Kg/minute) may be selected for patients not responding to nitrate infusion and for those whose pulmonary edema is attributed to severe mitral or aortic regurgitation or marked systemic hypertension.<sup>9</sup> The dose is

increased as needed to improve the patient's overall clinical and hemodynamic status, using systolic pressure of 90 mm Hg as the usual lower limit for dose incrementation in patients previously normotensive, and as long as adequate perfusion of vital organs is maintained.

Furosemide (20-80 mg intravenously) should be given shortly after the diagnosis of acute pulmonary edema is established given the systolic pressure is >90 mm Hg.

Morphine sulfate (3-5 mg intravenously) is effective in ameliorating many of the symptoms of acute pulmonary edema, and can be safely administered to most patients. It should be given with caution to patients with pulmonary insufficiency and those with respiratory or metabolic acidosis.

Mechanical ventilation is of value in patients with severe hypoxia that does not respond rapidly to standard therapy and in those with severe respiratory acidosis.

Coronary reperfusion therapy in acute myocardial infarction.<sup>10,11</sup>

Introduction of agents of proven value as tolerated including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), spirinalactone, digoxin, and once clinically compensated and stabilized, beta blockers.

### CARDIOGENIC SHOCK

Patients who present with acute cardiogenic shock are of particular challenge since their overall mortality rate is in excess of 85% if the shock is not due to repairable lesion or if the lesion is not repaired in an efficient and effective manner.<sup>12</sup>

The therapeutic management of patients with cardiogenic shock includes:

1. Oxygen therapy;
2. Intravenous administration of fluid boluses;
3. Dopamine infusion.

In the absence of frank intravascular volume overload, brisk intravenous administration of fluid boluses especially in the setting of acute myocardial infarction, since it is estimated that 10-15% of these patients may be significantly volume depleted.<sup>13</sup> It is also important to realize that jugular venous pressure is not a consistently reliable indicator of left heart failure, e.g. pericardial tamponade and right ventricular infarction.<sup>14</sup>

In case of severe hypotension (systolic pressure <70 mm Hg) or clinical shock, or both, occurring in the presence of overt volume overload or persisting after fluid boluses, the approach should be with moderate (4-5 microgram/Kg/min), then if necessary, increasing doses of dopamine infusion.<sup>15</sup> If hypotension or clinical shock persists despite dopamine doses >15 microgram/Kg/minute, institution of intra-aortic balloon counterpulsation should be considered for patients with potentially reversible condition or as a bridge for cardiac transplantation. If the latter is not available, nor-epinephrine can be started to increase the systolic blood pressure to acceptable levels (systolic pressure of >80 mm Hg). Patients with volume overload in near shock or with lesser degrees of systemic hypotension often respond to dobutamine infusion.

The acceptable indications for intraaortic balloon counterpulsation in heart failure patients are:<sup>16</sup>

1. Cardiogenic shock, pulmonary edema, and other acute heart failure conditions refractory to proper medical therapy in patients with potentially reversible heart failure or as a bridge to heart transplantation.
2. Acute heart failure accompanied by refractory ischemia, in preparation for cardiac revascularization.
3. Acute heart failure complicated by significant mitral regurgitation or ventricular septal rupture to obtain hemodynamic stabilization until definitive diagnostic and therapeutic measures taken.

### Chronic and Stabilized Acute Heart Failure

#### DIAGNOSTIC WORKUP

The diagnostic workup should aim to reveal the etiology of the left ventricular systolic dysfunction and heart failure decompensation, and to evaluate the possible benefits for interventional procedures. This workup includes the following, in addition to what was previously listed under acute heart failure:

1. Non invasive stress testing with an imaging modality to detect ischemia in patients without angina but with high probability of coronary artery disease who would be candidates for revascularization;

2. Non invasive testing to detect ischemia and assess myocardial viability or coronary angiogram in patients with previous myocardial infarction but with no angina who would be candidates for revascularization;
3. Coronary angiogram in patients with angina or large area of myocardial ischemia or hibernation; also in patients at high risk for coronary artery disease who are to undergo high risk noncardiac surgeries;
4. Other workup as indicated.

### THERAPY

The aim of therapy in patients with chronic systolic heart failure is to prolong event free survival, and to improve the quality of life and reduce the hospitalization rate. This is achieved by several drugs and techniques of proven efficacy.

#### *Diuretics*

This therapy should be limited to symptomatic heart failure patients. The strategy should be individualized.<sup>17</sup> An initial approach would be to utilize a thiazide diuretic in mild to moderate symptomatic patients, and then proceed to the more potent loop diuretics. Thiazide diuretics are of less value when the glomerular filtration rate is <30-40ml/minute. When diuretic resistance develops, using a combination of diuretic drugs that act in different nephron segments (thiazide diuretic as metolazone and a loop diuretic) is often effective.<sup>18</sup> Special attention should be given toward replacing the electrolytes wasted during the course of aggressive diuretic therapy.

#### *Spironolactone*

This is a potassium sparing diuretic, which acts through blocking the aldosterone receptor. It should be started at a dose of 25 mg once daily, and then advanced to 50 mg/day in the absence of renal insufficiency or hyperkalemia. This agent has been shown to significantly improve the quality of life and reduce the mortality rate in patients with symptomatic heart failure.<sup>19</sup>

#### *Digoxin*

In symptomatic heart failure patients optimized on other standard therapy, a low dose of digoxin can be started. This agent does not reduce mortality but reduces the hospitalization rate due to heart failure decompensation.<sup>20</sup>

#### *Angiotensin Converting Enzyme Inhibitors (ACEI)*

Angiotensin II is an important regulator of blood pressure and has a large number of biologic actions. It is produced from the precursor angiotensin I by ACE, and angiotensin I in turn is formed from cleavage of aniotensinogen by rennin. Angiotensin II stimulates the production of aldosterone. This system is referred to as the rennin-angiotensin system (RAS). Angiotensin is produced by several tissues including heart and the vasculature. Tissue RAS may be upregulated independently from circulating or systemic RAS. Circulating RAS is activated in decompensated heart failure and in patients on diuretics. Tissue RAS is probably activated in patients with systolic left ventricular dysfunction without overt heart failure. ACEI has combined venous and arterial vasodilatory effect, and therefore reducing preload, afterload, and wall stress without increasing the heart rate. They also augment the renal blood flow and reduce the production of aldosterone and antidiuretic hormones, thus, prompting excretion of sodium and water. ACEI have potent antihypertrophic effects on ventricular and vascular cells which is partially independent of their blood pressure reducing effect, and contribute to their role in the prevention of ventricular remodeling. ACEI have been demonstrated to reduce ischemic events in patients with left ventricular systolic dysfunction post myocardial infarction.<sup>5,21-29</sup>

ACEI have also been shown to decrease sympathetic tone and improve the parasympathetic nervous system tone, which could result in reducing electrophysiological instability in infarcted or cardiomyopathic hearts.<sup>30</sup>

#### *Angiotensin Receptor Blockers (ARB)*

Several trials comparing ARB to placebo showed significant improvement in end points of morbidity and mortality in heart failure patients. However, ARB were not shown to be superior to ACEI. In a meta-analysis of these two classes of drugs, it was shown that both classes are equally effective as monotherapy in patients with heart failure.<sup>31,32</sup>

Combination of both agents have been shown in some trials to have added benefits as compared to each alone.<sup>33-35</sup>

*Isosorbide Dinitrate and Hydralazine*

In patients who are not tolerating ACEI or ARB, this combination could be used in cases of severe hypotension, azotemia, hyperkalemia, cough, rash, or angioneurotic edema.<sup>21,36</sup>

*Beta-Blockers*

After a myocardial insult that results in left ventricular systolic dysfunction, there is an increased activity of RAS and sympathetic tone. The sympathetic tone increase may accelerate the left ventricular remodeling, worsen myocardial function, and lower the threshold for life threatening arrhythmias.<sup>37</sup> It is possible that by reducing the harmful effects of excessive and continuous increased adrenergic drive on the myocardium, beta-blockers cause time dependent improvement in ventricular structure and function. Other likely beneficial actions include reduction in heart rate and blood pressure, inhibition of the RAS, reduction of atrial and ventricular arrhythmias, and anti-ischemic effects. Beta-blockers improve the contractility of viable but not contractile myocardial regions in patients with ischemic (hibernating myocardium), and non-ischemic cardiomyopathy.<sup>38</sup> The beneficial effects of chronic beta blockade in heart failure occurs despite an initial transient decrease in contractility.<sup>39</sup> Numerous trials have been conducted to evaluate several beta blockers in patients with different degrees of heart failure, with impaired left ventricular systolic function. All of them showed significant improvement in both mortality and morbidity. Carvedilol, a non selective B1/B2 blocker, was studied extensively showing significant reduction of mortality and morbidity across the whole spectrum of clinical heart failure patients (mild to severe).<sup>40,41</sup> Selective B1 blockad have also shown similar results. Bisoprolol and metoprolol showed improvement in end points in both ischemic and nonischemic cardiomyopathy patients.<sup>42-44</sup>

*Anticoagulation in Chronic Heart Failure*

In an analysis of major heart failure studies, the incidence of arterial thromboembolism in the largest studies was 2-2.4% per 100 patient-year. Chronic anticoagulation is therefore indicated in patients with decreased ejection fraction and atrial fibrillation, prior cardioembolic events, recent large myocardial infarction, or left ventricular thrombus. The use of chronic anticoagulation in other patients with ejection

fraction <25% is a matter of controversy but many physicians chose to anticoagulate this subset of patients in the absence of other indications.<sup>45-48</sup>

*Resynchronization (Biventricular Pacing) Therapy in Patients with Chronic Heart Failure*

This new modality of adjunctive therapy was introduced recently for patients with severe heart failure (class III and IV) and left ventricular systolic dysfunction in the presence of electrocardiographic evidence of intraventricular conduction delay (QRS >150 msec), or echocardiographic basal left ventricular dyssynchrony and optimal medical therapy. The recent studies have shown clearly a significant maintained benefit in terms of improved exercise capacity, left ventricular systolic function, reduced mitral regurgitation severity, and decreased hospitalization rate.<sup>49-51</sup>

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### CME/CPD Questions

After you have completed reading the article *Pharmacotherapy of systolic heart failure*, take the test given below. Circle T (True) or F (False) in the answer sheet (page 96) to show the correct answer to each question. Questions 11 to 20 are related to the content in this article.

11. The New York Heart Association (NYHA) classification in heart failure is based on the relation between symptoms and the radiographic finding in heart failure patients.
12. Coronary angiography is indicated in all patients presenting with acute pulmonary edema.
13. Jugular venous pressure is always a reliable indicator of intravascular volume status in patients with cardiogenic shock.
14. An appropriate indication for intra-aortic balloon counterpulsation is cardiogenic shock refractory to proper medical therapy in patients with potentially reversible heart failure.
15. Intra-aortic balloon counterpulsation pump can be safely inserted in a patient with cardiogenic shock and history of aorto-bifemoral bypass grafts.
16. All patients with systolic heart failure should be placed on diuretic therapy.
17. Beta-blockers are contraindicated in patients with chronic heart failure..
18. Angiotensin receptor blockers (ARB) are superior to angiotensin converting enzyme inhibitors (ACEI) in patients with systolic heart failure.
19. ACEI are beneficial in patients with reduced left ventricular systolic function even if asymptomatic.
20. Cardiac resynchronization therapy is an acceptable treatment modality in patients with mild heart failure (NYHA class I/II).