Evaluation and Management of Chronic Heart Failure

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Introduction

Heart failure (HF) is a leading cause of hospitalization and it is associated with a poor prognosis. HF occurs when the cardiac function fails to pump a supply of blood adequate to meet the needs of metabolizing tissues. Development of HF can result in various signs and symptoms, such as dyspnea and fatigue, which may limit exercise tolerance along with fluid retention, pulmonary congestion, peripheral edema and body weight gain. As patients with HF face a very high risk of hospitalization and mortality, optimal therapies based on the results from large scale clinical trials should be selected according to an appropriate grading of the HF.

Acute and Chronic HF

Several forms of HF are known—right-sided versus left-sided, acute versus chronic, low-output versus high-output, and systolic versus diastolic. The therapeutic strategy and goal may slightly differ between acute and chronic HF. For example, the therapeutic goals in the management of acute HF are to relieve symptoms and to ameliorate the hemodynamic abnormalities: these goals are achieved by diuretics and inotropes, and sometimes, by mechanical circulatory support (LVAD, IABP and PCPS). By contrast, chronic HF patients should be treated by the appropriate applications of evidence-based, guideline-recommended medical therapies to retard progression of the disease and thereby decrease the risk of hospitalization and death.

Assessing the Causes and Severity of HF

HF is a principal complication of virtually all forms of heart disease. Among them, coronary artery disease, hypertension, and dilated cardiomyopathy are the main causes of HF in a substantial proportion. Other underlying disorders include arrhythmias, congenital heart disorders, and other myocardial and pericardial diseases.

For many years, HF was considered to be synonymous with diminished contractility of the left ventricle (LV). However, it has been increasingly recognized that a large number of HF patients, as many as 20% to 60%, have a relatively (or near) normal LV ejection fraction (LVEF).

How can we diagnose whether the symptom is due to HF when LV systolic function is preserved? Measurement of brain natriuretic peptide (BNP) and Doppler echocardiography can help estimate the severity of HF. It has recently become evident that the heart is not just a pump but is also an endocrine organ, which may play a crucial role in controlling the circulating blood volume. BNP, a member of a family

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of the natriuretic peptides, is mainly secreted from the ventricles. BNP measurements can help in diagnosis by providing information on the severity of HF and thus provide an objective guide for optimizing the treatment of HF. Doppler echocardiography is an useful noninvasive diagnostic modality that enables us to evaluate the diastolic performance of LV, by assessing the mitral valve inflow pattern, and to estimate pulmonary valve pressure, by evaluating the tricuspid valve regurgitant gradient.

**Treatment for Chronic HF**

Previous large scale clinical trials have demonstrated that several drug classes are effective in decreasing rates of hospitalization and mortality in HF patients; these include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, and aldosterone antagonists.

**ACEIs and ARBs**

Activation of the neurohumoral system, including the renin-angiotensin-aldosterone system (RAAS), may act as a compensatory mechanism against HF; however, it may also aggravate the syndrome of HF by accelerating structural changes in the heart, and by modulating body-fluid homeostasis. Many clinical trials have demonstrated that ACEIs can reduce mortality within a wide range of HF. For example, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) was one of the first double-blind, placebo controlled clinical trials to assess the efficacy of ACEIs in HF. In this study, crude mortality rate of the patients with severe HF was reduced by 40% at the end of six months in patients receiving enalapril treatment compared to placebo treatment. Many other clinical trials, such as V-HeFT II and SOLVD, have also support the proposition that ACEIs can reduce mortality of patients within a wide range of HF.

By blocking the renin-angiotensin system (RAS) at the receptor level, ARBs may provide more thorough RAS blockade than ACEIs. However, in the clinical trials where the effectiveness ACEIs and ARBs was compared (ELITE II, OPTIMAAL), these two drug classes were found to have similar efficacy, although in general, ARBs were better tolerated than ACEIs. The Candesartan in HF Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative Study has shown that ARBs decrease the risk of cardiovascular death or hospital admission for HF in patients who are ACEI-intolerant. The CHARM-Added trial has shown the possibility that the combined use of ARBs and ACEIs may lead to a further reduction in relevant cardiovascular events in patients with HF and reduced LVEF.

**Beta-Blockers**

Beta-blocking agents were previously considered to be specifically contraindicated for the HF patients owing to their intrinsic negative inotropic activity. However, recent large controlled studies, however, have shown that beta-blockers are, on the contrary, effective in reducing the rate of mortality and sudden cardiac deaths in patients within a wide range of HF, like ACEIs and ARBs. In the US Carvedilol Study, carvedilol treatment resulted in a 48% reduction in the progression of HF as compared with the placebo treatment in patients who had a LVEF $\leq 35\%$ and were receiving optimal standard therapy, including ACEIs.

Notably, in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Trial, beta-blocker therapy was also found to be effective in reducing morbidity and mortality in patients with severe HF, which was defined by the occurrence of dyspnea or fatigue at rest or on minimal exertion and a LVEF $\leq 25\%$ despite appropriate conventional therapy.

Several further clinical trials, such as CIBIS-II and MERIT-HF, have shown that other beta-blocking agents, bisoprolol and metropolol, are also effective in decreasing the hospitalization rate due to HF and in improving the functional status and survival rate of HF patients. It is worth keeping in mind, however, that beta-blockers are not always safe. They may worsen the bronchial asthma, bradycardia, hypotension, and atrio-ventricular block as well as HF symptoms. Beta-blockers should be administered at a low initial dose after 2 or 4 weeks of clinical symptoms. In-hospital initiation of beta-blockers is recommended, especially when patients are within moderate to severe HF. In-hospital initiation of beta-blockers also provides positive effects.
on long-term patient compliance and clinical outcomes.

**Aldosterone Antagonists**

Spironolactone is a competitive aldosterone receptor antagonist. Aldosterone is considered to aggravate HF by promoting the sodium retention and subsequent intravascular volume expansion, sympathetic activation, and myocardial fibrosis. The Randomized Aldactone Evaluation Study (RALES) has demonstrated that the blockade of aldosterone receptors by spironolactone in subjects receiving standard therapy significantly reduces the risk of both morbidity and death of patients with severe HF. In the RALES trial, treatment of HF patients with this “old” diuretic surprisingly resulted in a 30% reduction in the risk of death as compared with the placebo treatment. Although aldosterone receptor antagonists are such effective agents in the treatment of HF, we have to keep in mind that hyperkalemia can occur especially in older patients treated with ACEIs. Indeed, the publication of RALES was associated with an abrupt increase in hyperkalemia-associated morbidity and mortality. Gynecomastia or breast pain was reported in 10 percent of men who were treated with spironolactone. This side-effect may be weakened by Eplerenone, a next generation aldosterone receptor antagonist that is selective for aldosterone receptors. Eplerenone has also been shown to reduce the morbidity and mortality of HF patients who are already treated with ACEIs and beta-blockers; nevertheless, hyperkalemia must still be given due attention.

**Conclusions**

Recently the AHA/ACC guidelines for the diagnosis and management of CHF have been updated. These guidelines recommend that most patients with current or prior symptoms of HF should be routinely managed with a combination of three types of drugs: a diuretic, an ACEI or an ARB, and a beta-blocker. In addition, even when the patient responds favorably to the diuretic, treatment with both an ACEI and a beta-blocker should be initiated and maintained in patients who can tolerate them. Besides selecting evidence-based guideline-recommended therapies, it is advisable to be aware of the possible adverse effects of the above-mentioned drugs. Hence, successful treatment of HF demands close cooperation between general physicians and cardiologists.

**References**
