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Role of Neurohormonal Modulators in Heart Failure with Relatively Preserved Systolic Function

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Cardiovascular disease remains the leading cause of mortality in the developed world and is responsible for nearly 1 million deaths per year in the United States [1]. Although the age-adjusted rates of death secondary to coronary artery disease (CAD) and stroke have decreased by approximately 50% in the last 10 years, there has been a large increase in the prevalence of heart failure (HF) [2,3].

It is estimated that 5 million Americans suffer from HF, and roughly 550,000 new cases are diagnosed annually [1]. HF was responsible for nearly 1 million hospital admissions in 2001 and is the most common discharge diagnosis in patients over 65 years of age. Furthermore, it is the primary cause of readmission within 60 days of discharge [1,4]. Approximately 330,000 patients die each year from HF, and the 1-year mortality rate of newly diagnosed patients approximates 20%. The total direct and indirect cost of managing this disease is expected to exceed $25 billion for 2004 [1].

Several echocardiographic cross-sectional studies have found that 40% to 71% of patients who have HF have relatively preserved systolic functions, a condition referred to as *diastolic heart failure* (DHF) [5–15]. In the last 15 years, several hospital-based studies have found that approximately 40% of patients admitted with worsening HF had DHF [16,17]. The most recently published database of patients who have HF found that approximately 40% of patients had an ejection fraction (EF) greater than 0.40 [18]. Although there are abundant data to guide the treatment of HF and systolic dysfunction (systolic heart failure, or SHF), evidence-based data are lacking in the management of DHF. This article examines the role of neurohormonal modulators in the management of DHF.

Definition and diagnosis

Definition

HF is a clinical syndrome that results from any functional or structural cardiac disorder that impairs the ability of the ventricles to fill with or eject blood. Symptoms include fatigue, poor exercise tolerance, dyspnea (exertional or resting), and signs and radiographic evidence of pulmonary and systemic congestion [19]. Standardized criteria for the diagnosis of HF have been described, such as those from the Framingham study [20]. Other tools, such as echocardiography and measurement of B-natriuretic peptide (BNP), also are used for diagnosis. BNP is a neurohormone secreted by the ventricles in response to muscle stretch caused by volume or pressure overload. Although it is a valuable marker of HF, it cannot be used to distinguish SHF from DHF [21,22] because patients often have components of both [23]. DHF is caused by diastolic dysfunction or, more specifically, abnormalities in active relaxation or passive stiffness of the left ventricle that result in

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abnormal left ventricular (LV) filling and elevated filling pressures [24,25].

Diagnosis

The Working Group of the European Society of Cardiology first published diagnostic criteria for DHF in 1998. It suggested that DHF could be diagnosed if (1) the patient had HF symptoms, (2) there was evidence of a normal left ventricular ejection fraction (LVEF), and (3) there was evidence of abnormal LV diastolic stiffness, relaxation, or filling [26]. Vasan and Levy [27] modified these criteria and proposed categorizing DHF diagnosis as definite, probable, and possible. All patients were required to have signs and symptoms of HF as well as an LVEF greater than 0.50. Diagnosis of definite and probable DHF required LVEF to be measured within 72 hours of the HF event. Furthermore, diagnosis of definite DHF required evidence of diastolic dysfunction measured by catheterization.

Gandhi and colleagues [28] found that, among patients hospitalized for acute pulmonary edema, there was no significant difference in LVEF between the time of presentation and 72 hours later after compensation was achieved. This proved to be true in the presence of SHF and DHF and indicated that a measurement of systolic function during an acute setting may not be necessary to establish the diagnosis of DHF. Moreover, a study by Smith and colleagues [17] demonstrated that outcomes were similar in patients who had DHF whose LVEFs were examined on index admission or 6 to 12 months previously. Therefore, as long as no intervening event had occurred, DHF can be diagnosed using an LVEF greater than 0.50 within 6 to 12 months before the initial presentation of HF [17,25]. Piccini and colleagues [21] also stated that DHF can be diagnosed without a measurement of diastolic function if the patient has (1) HF symptoms, (2) LVEF greater than 0.50, and (3) no significant valvular or pericardial disease. Clinically, SHF and DHF often coexist, and their managements are similar.

A comparison of the clinical characteristics of patients who have diastolic heart failure and systolic heart failure

Patients who have DHF and SHF have differing clinical characteristics. In a recent hospital-based study examining the differences between patients who have HF, 55% of women with HF had relatively preserved systolic functions compared with 29% of men. Patients who had DHF also tended to be older than their counterparts with SHF (71 years versus 67 years of age) [29]. The Acute Decompensated Heart Failure National Registry (ADHERE), the largest HF registry, also found that patients who had DHF were older (74.2 versus 69.9 years of age) and more likely to be women (62% versus 39%) than patients who had SHF [18]. These data are consistent with prior studies that showed that women comprise 70% to 75% of patients who have DHF, and such patients have a mean age of 70 to 75 years [30–32].

Patients who have SHF and DHF also differ in their associated comorbidities. The ADHERE registry documented that a higher percentage of patients who have DHF are diabetic (46% versus 42%) and have atrial fibrillation (AF) (21% versus 17%) when compared with patients who have SHF, but CAD was more frequent in patients who have SHF (61% versus 47%) [18].

Lenzen and colleagues [29] found generally similar results (Table 1). Patients who had DHF had a higher prevalence of AF (25% versus 23%), hypertension (59% versus 50%), renal insufficiency (69% versus 59%), and history of stroke (28% versus 26%) than patients who had SHF. Although diabetes mellitus and ischemic heart disease were prevalent in both populations, they were more so in patients who had SHF.

Treatment differences, which have been studied, are quite striking. Patients who have DHF are less likely to receive angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor–blockers (ARBs), β-blockers, digoxin, or diuretics than are patients who have SHF. They are, however, more likely to receive calcium-channel blockers [29–32].

Prognosis

Unfortunately, prognosis is poor for patients who have either SHF or DHF. Among hospitalized patients, mortality is similar between the two groups. It is almost certain that any difference favoring DHF becomes insignificant 3 to 6 months after hospital discharge [17,33–35]. Community-based studies showed similar mortality rates between the two groups in patients more than 65 years of age. In patients less than 65 years of age, however, DHF carries a lower 1-year mortality rate than SHF (7%–9% versus 12%–19%, respectively) [36–40].

Mortality seems to be related to age and the degree of accompanying CAD. The DIG trial found that the 3-year mortality for DHF was as low as 9% in patients less than 50 years of age but as high as 39% in patients more than 80 years of age [41]. The