Heart Failure in the Elderly

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Abstract

Heart failure is common in the elderly population. Approximately 6 to 10 percent of the population 65 years or older have heart failure. Heart failure is the most common reason for hospitalization in elderly patients. Etiology of heart failure is often multifactorial in the elderly. The common causes of heart failure include ischemic heart disease, valvular heart disease, hypertensive heart disease, and cardiomyopathy. Exacerbation of heart failure in the elderly is often accompanied by precipitating factors which include arrhythmia, renal failure, anemia, infection, adverse effect of drugs and noncompliance with medication and/or diet. Diagnosis of heart failure may be difficult in the elderly because symptoms of heart failure are often atypical or even absent. Heart failure with preserved systolic function is common in the elderly because aging has a greater impact on diastolic function. It is important to recognize that very old patients with heart failure are underrepresented in clinical trials.
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Key words: heart failure, elderly, diastolic dysfunction

Introduction

Heart failure (HF) is the pathophysiological state in which the heart is unable to pump blood at a rate sufficient to meet metabolic demands or can do so only from an elevated filling pressure.

HF is common in the elderly population. Approximately 6 to 10 percent of the population 65 years or older have HF (1). In the Framingham study, the prevalence of HF was shown to rise progressively with age, from 1 percent of persons in their 50s to 10 percent of persons in their 80s (2, 3) (see Fig. 1). HF is the most common reason for hospitalization in elderly patients (2, 3). Approximately 80 percent of all HF admissions occur in patients older than 65.

Etiology of HF in the Elderly

HF is a clinical syndrome and can be caused by virtually any form of heart disease. The distribution of causes of HF depends on what kind of patients with HF are selected.

In the population-based study conducted in Framingham, MA, USA, the common causes of HF were ischemic heart disease (54%), hypertensive heart disease (24%), and valvular heart disease (16%) (3). In a hospital-based study done in Fukuoka, Japan, the frequent causes of HF were ischemic heart disease (35%), valvular heart disease (28%), hypertensive heart disease (20%), and cardiomyopathy (19%) (4) (see Fig. 2). Differences in patient selection and/or racial variation may explain these results.

Distribution of causes of HF in the elderly in Japan is thought to be similar to that in Fukuoka study since the mean age of patients was 69 years and 70 percent of the patients were >65 years of age, although it was not designed to specifically examine the elderly. Also, the etiology of HF in the elderly is often multifactorial as shown in the Fukuoka study.

Ischemic heart disease

Ischemic heart disease is the most common cause of HF in the elderly. The severity and extent of coronary atherosclerosis increases with age, presumably as a result of prolonged exposure to coronary risk factors. Elderly patients more frequently have multivessel disease and lower ejection fraction than do younger patients (5). Non-Q wave myocardial infarction is relatively common in the old population.

In the elderly, silent myocardial ischemia (presence of coronary artery disease without symptoms) is common. Myocardial infarction may not be recognized by some of the elderly patients due to lack of chest discomfort. It may be discovered only on subsequent routine ECG (unrecognized myocardial infarction). The prevalence of unrecognized myocardial infarction increases with age. In one study, unrecognized myocardial infarction was more than 5% prevalent in the group aged 75 to 79 years compared to nearly none in the youngest age group (6). Common initial presentation of myocardial infarction in the elderly is shortness of breath and easy fatiguability without symptom of chest pain.
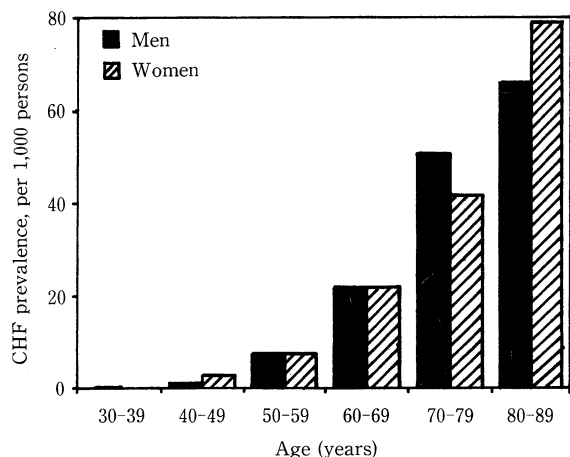
Figure 1. Prevalance rates of heart failure among Framingham heart study subjects, by gender and age (3).
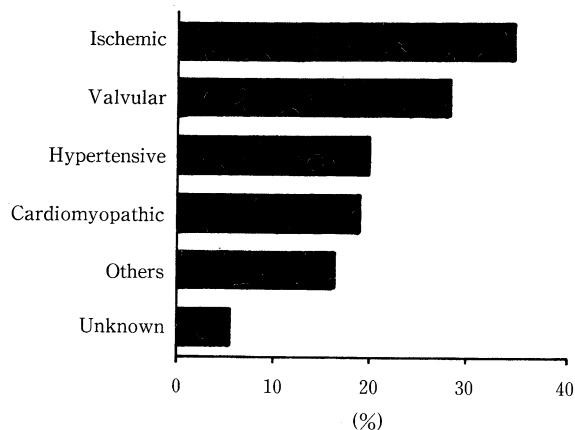

Figure 2. Causes of heart failure in Fukuoka, Japan. Patients could have more than one cause of heart failure. Numbers denote the percentage of patients to the total number of study patients (4).

Hypertensive heart disease

Hypertensive heart disease is a common cause of HF in old patients with a long-standing history of hypertension. Isolated diastolic dysfunction which often accompanies with hypertensive heart disease can cause HF in the presence of preserved systolic function. Left ventricular dilatation and systolic dysfunction may occur at the advanced stage of hypertensive heart disease, if wall stress remains high because of inadequate hypertrophy.

Valvular heart disease

Aortic stenosis is the most common valvular disease that requires surgery in the elderly. The most frequent cause of aortic stenosis in the elderly is degenerative calcification of the tricuspid aortic valve that accounts for almost half of the patients with aortic stenosis who are 70 years of age or older. In contrast, in patients younger than 70 years, calcification of congenital bicuspid aortic valves accounts for half of the cases (7). Mitral regurgitation due to mitral valve prolapse or ruptured chordae tendinae is also common in the elderly.

Although rare, isolated severe tricuspid regurgitation can be at times a cause of HF in the elderly (8). This usually occurs in elderly patients with long history of atrial fibrillation (AF) and is characterized by severe right-sided heart failure with preserved left ventricular systolic function. The tricuspid annulus is markedly dilated without organic leaflet lesion in this condition. AF is known to cause annular dilatation of tricuspid valve and significant tricuspid regurgitation (9). Tricuspid regurgitation begets farther annular dilatation and then becomes more severe. This vicious circle may be responsible for this disease.

Cardiomyopathy

Both dilated and hypertrophic cardiomyopathies occur in the elderly. Dilated cardiomyopathy can cause HF in the elderly just as in younger patients. Hypertrophic cardiomy-

opathy is being diagnosed increasingly in elderly patients. In patients with hypertrophic cardiomyopathy, cardiac hypertrophy is usually evident by the end of the accelerated adolescence growth period. However, expression of hypertrophy may often be delayed until middle age or old age in patients caused by cardiac myosin-binding protein C gene mutations (10, 11). Although the prognosis of elderly patients with hypertrophic cardiomyopathy is favorable, HF due to progressive left ventricular dilation and systolic dysfunction does occur in a small number of patients (so-called, "dilated phase hypertrophic cardiomyopathy"). In our experience, 4 out of 14 hypertrophic cardiomyopathy patients caused by cardiac myosin-binding protein C gene mutations progressed to the dilated phase later in their lives and they deteriorated clinically (12).

Senile cardiac amyloidosis

Cardiac amyloidosis should be suspected in elderly patients with HF and a hypertrophied left ventricle. Amyloidosis is classified according to protein identity of the deposited amyloid (13). The most common form of cardiac amyloidosis is AL amyloidosis (formerly called primary amyloidosis). In AL amyloidosis, the amyloid protein is composed of monoclonal immunoglobulin light chain. Plasma cell dyscrasia is responsible for the excess light chain production. Patients with AL amyloidosis have a poor prognosis with a median survival of 5.4 months when presented with HF.

Senile amyloidosis is not uncommon among elderly patients with cardiac amyloidosis, although the exact incidence is not known. In senile amyloidosis, amyloid deposit consists of transthyretin, a transport protein for thyroxine and retinol-binding protein. Patients with senile cardiac amyloidosis have a better prognosis with the actuarial median survival of 5 years compared to those with AL amyloidosis. These pa-

tients should not be treated with chemotherapy because there is no tumor cell and chemotherapy will only do harm (14). Therefore, it is very important to recognize the type of amyloidosis by performing immunohistochemical staining.

Congenital heart disease

Atrial septal defect (ASD) is the most common congenital lesion in adults. While the patients with an ASD are often asymptomatic until adulthood, most patients with significant shunt flow will become symptomatic by the age of 40 (15). Right ventricular failure can be the presenting symptom in older patients. Atrial arrhythmias increases with age and precipitates HF (16, 17). In one study, for example, the incidence of atrial fibrillation or atrial flutter prior to surgery was 1 percent for those aged 18 to 40, 30 percent for those aged 40 to 60, and 80 percent in those over the age of 60 (16).

Precipitating Factors of HF in the Elderly

Exacerbation of HF in patients with underlying heart disease is often accompanied by some of the following precipitating factors. Identification of these precipitating factors of HF is very important because an episode of HF can often be terminated by treating a specific precipitating factor and may even be prevented by avoiding them.

Arrhythmia

Both tachyarrhythmia and bradyarrhythmia can precipitate HF.

The most common tachyarrhythmia in elderly population is atrial fibrillation (AF). The prevalence of AF was 9 percent in those 80 years of age compared to 0.1 percent among adults younger than 55 years of age (18). Thus, AF is primarily a disease of older subjects. Loss of atrial booster pump function with AF impairs ventricular filling and loweres cardiac output. This loss of atrial contraction is particularly deleterious in elderly patients with a less compliant left ventricle. In addition, uncontrolled rapid ventricular responses with AF reduce the time available for ventricular filling. This exacerbates diastolic dysfunction and raises atrial pressure, thus precipitating HF.

The incidence of bradyarrhythmia, such as sick sinus syndrome and AV block, also increases with age. This is probably due to age-associated fibrosis and sclerosis of the conduction system. Marked bradycardia in a patient with underlying heart disease depresses cardiac output, because stroke volume may already be maximum and cannot rise farther to maintain cardiac output.

Renal failure

Renal function deteriorates as people get old. Recent studies showed that renal dysfunction is an independent and important predictor of all-cause mortality in patients with HF (19, 20). As renal failure impairs the ability of patients with heart failure to excrete sodium and fluid, volume overload

will develop and thus exacerbate HF symptoms. Therefore, renal failure is an important precipitating factor of HF in the elderly.

Anemia

Anemia is often encountered in elderly patients with HF. Chronic anemia is associated with high cardiac output when hemoglobin is less than 8 gm/dl. Decreased blood viscosity and a reduced arteriolar tone resulted from tissue hypoxia contribute to reduced systemic vascular resistance which cause an high-output status. Development of high-cardiac output status in the presence of underlying heart disease often precipitates HF because preload reserve is already limited and left ventricular end-diastolic pressure will increase. Anemia also can exacerbate myocardial dysfunction in the presence of coronary heart disease due to myocardial ischemia caused by reduced oxygen delivery. Severe anemia in patients with HF should be corrected.

Infection

Systemic infection can precipitate HF. The mechanism responsible for worsening HF is increased total body oxygen consumption due to fever. Patients with HF are particularly susceptible to respiratory tract infection, presumably because of diminished ability of congested lungs to expel respiratory secretions.

Pulmonary embolism

Elderly patients with HF are at high risk of developing pulmonary embolism, particularly when confined to bed. Pulmonary embolism can exacerbate HF by increasing the hemodynamic burden on the right ventricle and worsening hypoxemia.

Non-compliance with medication and/or diet

A common cause of decompensation in a previously compensated elderly patient with HF is non-compliance with medication and/or diet (21). Inappropriate reduction of therapy, in forms of dietary sodium and fluid restriction or pharmacological therapy, precipitate HF. Nowadays patients with HF take a complex medication regimen and have difficulties in adhering to it. Education of the patient and family is necessary to prevent this problem.

Adverse effect of drugs

Drugs with negative inotropic action such as beta blockers and calcium antagonists can aggravate HF. More importantly, non-steroidal anti-inflammatory drugs (NSAIDs) exacerbate preexisting HF. They are often prescribed for the elderly because of arthralgia. In a report of elderly patients with heart disease, there was a 10-fold increased risk of exacerbating HF of sufficient severity to require hospitalization in patients with recent NSAIDs use, compared to those without such use; the risk was related to the dose of NSAIDs consumed within the week prior to hospitalization (22). NSAIDs use blunts the renal effects of diuretics among pa-

Table 1. Mean Age of Patients in Large Heart Failure Trials

Trial	Drug	Mean age	Exclusion criteria
V-HeFT I	hydralazine, ISDN	58	<75
V-HeFT II	enalapril	61	<75
CONSENSUS	enalapril	70	none
SOLVED-Treatment	enalapril	61	<80
ELITE-II	losartan	71	60>
Val-HeFT	valsartan	63	none
DIG	digoxin	63	none
US carvedilol trial	carvedilol	58	none
MERIT-HF	metoprolol CR	64	<80
CIBIS II	bisoprolol	61	<80
COPERNICUS	carvedilol	63	none
RALES	spironolactone	65	none

tients with HF, thereby resulting in an enhanced risk of exacerbating HF. One study of over 10,000 elderly patients found that the concurrent use of NSAIDs and diuretics was associated with a two-fold increased risk of hospitalization for HF, compared to the use of diuretics alone (23).

Diagnosis of HF in the Elderly

Diagnosis of HF may be difficult in the elderly. Symptoms of HF are often atypical or even absent in the elderly. Many older patients may not have dyspnea on exertion because of their sedentary lifestyle. Nonspecific complaints of generalized weakness, anorexia and fatigue often predominate. Some studies have reported that HF is the most frequent precipitating cause of delirium in older patients (24).

On the other hand, older patients with typical symptoms of HF are misdiagnosed with other diseases. For example, a dry cough or mild shortness of breath may be mistakenly attributed to chronic pulmonary disease. Easy fatiguability and generalized weakness may be wrongly thought merely to reflect changes associated with aging.

Given the difficulties in making a diagnosis of HF in the elderly, the possibility of using a blood test to make a diagnosis of HF is appealing. Elevated plasma levels of brain natriuretic peptide (BNP) has been shown to be a reliable indicator of HF or LV dysfunction (25). Maisel et al showed that BNP value of >100 pg/ ml was useful in establishing or excluding the diagnosis of HF in patients with acute dyspnea (26). However, this may not apply to the elderly population. In recent population-based cohort study, Redfield et al reported that BNP increased significantly with age, especially in women (27). For example, the 95th percentile range of BNP in healthy women aged >75 was 155 pg/ml in that study. Diagnosis of HF based on the BNP value needs caution in the elderly.

Treatment of HF in the Elderly

Principles of treatment of HF in the elderly is the same as those in younger patients. First of all, identification of the underlying etiology and precipitating factors of HF is essential. Then, treatment aimed at retarding or reversing the underlying conditions that predispose to the development of HF should be employed to the degree possible.

Several large-scale, randomized clinical trials have shown that various class of medications reduce the risk of death in patients with HF. Mean age of patients enrolled in these large HF trials is listed on Table 1. Patients enrolled in those trials are much younger than patients with HF in the real world. In addition, patients over 80 years of age are poorly represented in these trials (28). Although these drugs are increasingly being used in older patients with HF, the efficacy of therapies remains uncertain in the very old. Future clinical trials should adequately include the elderly population that carry the burden of the disease.

Systolic heart failure is usually managed by diuretics, angiotensin-converting enzyme inhibitors, digitalis and beta-blockers. Japanese Circulation Society issued a guideline for the treatment of HF (29). Recommendation of therapy for HF according to the severity of symptoms is shown in Fig. 3. The management of diastolic heart failure is discussed later.

When using these drugs, it is important for physicians to take into consideration that the therapeutic range is narrow in treating elderly patients with HF. Elderly patients may have diminished responses to these medications compared with younger patients and may experience a higher risk of adverse effects attributable to treatment (30, 31).

As for the non-pharmacological aspects of management of HF, some multidisciplinary HF programs have been successful in decreasing the rate of rehospitalization and associated morbidity in elderly patients (32).

Problem of Diastolic HF in the Elderly (33)

Approximately 20 to 40 percent of patients with HF have preserved left ventricular systolic function and are believed to have impaired ventricular relaxation as the primary
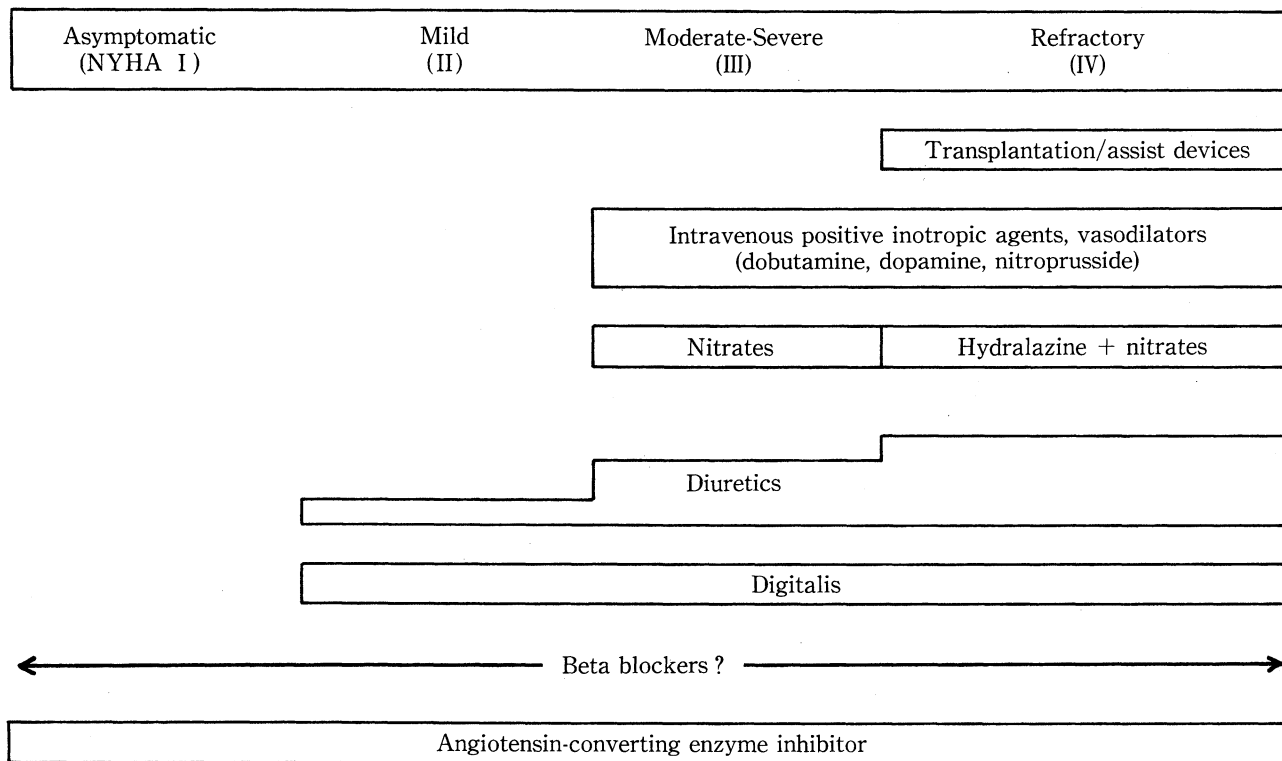
Severity of heart failure

Asymptomatic (NYHA I)	Mild (II)	Moderate-Severe (III)	Refractory (IV)

Transplantation/assist devices

Intravenous positive inotropic agents, vasodilators (dobutamine, dopamine, nitroprusside)

Nitrates	Hydralazine + nitrates

Diuretics

Digitalis

← Beta blockers ? →

Angiotensin-converting enzyme inhibitor

Figure 3. Therapy for heart failure in relation to the severity of symptoms (29).

mechanism of HF (34). Heart failure associated with preserved systolic function is primarily a disease of elderly, most of whom have hypertension (35). This observation may be related to the fact that aging has a greater impact on diastolic function than on systolic performance (36). Aging is associated with decreases in the elastic properties of the heart and great vessels, which leads to an increase in systolic blood pressure and an increase in myocardial stiffness. The rate of ventricular filling decreases in part because of structural changes in the heart (due to fibrosis) and because of a decline in active relaxation (due to an increase in afterload). These deleterious effects on diastolic function are exacerbated by a decrease in beta-adrenergic receptor density and a decline in peripheral vasodilator capacity, both of which are characteristic of elderly patients. In addition, elderly patients commonly have associated disorders (such as coronary artery disease, diabetes mellitus, aortic stenosis, atrial fibrillation), which can adversely affect the diastolic properties of the heart or decrease the time available for ventricular filling.

In contrast to the treatment of HF due to systolic dysfunction, few clinical trials are available to guide the management of patients with HF due to diastolic dysfunction. In the absence of controlled clinical trials, the management of patients with diastolic dysfunction is frequently determined by a set of therapeutic principles (37). These include control of

hypertension, control of tachycardia, reduction in central blood volume, and alleviation of myocardial ischemia.

Hypertension exerts a deleterious effect on diastolic function by causing both structural and functional changes in the heart. Increases in systolic blood pressure have been shown to slow myocardial relaxation (38), and the resulting hypertrophy may adversely affect passive chamber stiffness. Physicians should make every effort to control both systolic and diastolic hypertension with effective antihypertensive therapy.

Tachycardia can shorten the time available for ventricular filling and coronary perfusion. Drugs that slow the heart rate or the ventricular response to atrial arrhythmias (eg, beta-blockers) can provide symptomatic relief in patients with diastolic dysfunction.

Circulating blood volume is a major determinant of ventricular filling pressure. So the use of diuretics may improve breathlessness in patients with diastolic as well as systolic dysfunction.

Because myocardial ischemia can impair ventricular relaxation, coronary revascularization should be considered in patients with coronary artery disease in whom symptomatic or demonstrable myocardial ischemia is believed to be exerting a deleterious effect on diastolic function.

Summary

HF is common in elderly population. The common causes of HF in the elderly are ischemic heart disease, valvular heart disease, hypertensive heart disease, and cardiomyopathy. Exacerbation of HF is often accompanied by precipitating factors in the elderly. Making a diagnosis of HF may be difficult in the elderly because symptoms of HF are often atypical. Heart failure with preserved systolic function is common in the elderly. Basic principles of HF treatment in the elderly is similar to those in the young patients.

References

1) Kupari M, Lindroos M, Iivanainen AM, et al. Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study. J Intern Med **241**: 387–394, 1997.

2) Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J **121**: 951–957, 1991.

3) Ho KK, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol **22**: 6A–13A, 1993.

4) Tsuchihashi M, Tsutsui H, Kodama K, et al. Clinical characteristics and prognosis of hospitalized patients with congestive heart failure—A study in Fukuoka, Japan—. Jpn Circ J **64**: 953–959, 2000.

5) Reynen K, Bachmann K. Coronary arteriography in elderly patients: Risk, therapeutic consequences and long-term follow-up. Coron Artery Dis **8**: 657–666, 1997.

6) Sigurdsson E, Thorgeirsson G, Sigvaldason H, et al. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris. The Reykjavik Study. Ann Intern Med **122**: 96–102, 1995.

7) Passik CS, Ackermann DM, Pluth JR, Edwards WD. Temporal changes in the causes of aortic stenosis: A surgical pathologic study of 646 cases. Mayo Clin Proc **62**: 119–123, 1987.

8) Iga K, Konishi T, Matsumura T, et al. Markedly enlarged right atrium associated with physical signs of tricuspid regurgitation: A cause of congestive heart failure in the elderly. Jpn Circ J **58**: 683–688, 1994.

9) Zhou X, Otsuji Y, Yoshifuku S, et al. Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. Circ J **66**: 913–916, 2002.

10) Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med **338**: 1248–1257, 1998.

11) Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol **38**: 315–321, 2001.

12) Doi YL, Kitaoka H, Hitomi N, et al. Clinical expression in patients with hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutation. Circulation **100**: 448–449, 1999.

13) Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med **337**: 898–909, 1997.

14) Kyle RA, Spittell PC, Gertz MA, et al. The premortem recognition of systemic senile amyloidosis with cardiac involvement. Am J Med **101**: 395–400, 1996.

15) John Sutton MG, Tajik AJ, McGoon DC. Atrial septal defect in patients ages 60 years or older: operative results and long-term postoperative follow-up. Circulation **64**: 402–409, 1981.

16) Berger F, Vogel M, Kramer A, et al. Incidence of atrial flutter/fibrillation in adults with atrial septal defect before and after surgery. Ann Thorac Surg **68**: 75–78, 1999.

17) Gatzoulis MA, Freeman MA, Siu SC, et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. N Engl J Med **340**: 839–846, 1999.

18) Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) Study. JAMA **285**: 2370–2375, 2001.

19) Mahon NG, Blackstone EH, Francis GS, et al. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol **40**: 1106–1113, 2002.

20) Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol **35**: 681–689, 2000.

21) Ghali JK, Kadakia S, Cooper R, et al. Precipitating factors leading to decompensation of heart failure. Traits among urban blacks. Arch Intern Med **148**: 2013–2016, 1988.

22) Heerdink ER, Leufkens HG, Herings RM, et al. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med **158**: 1108–1112, 1998.

23) Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Arch Intern Med **160**: 777–784, 2000.

24) Rockwood K. Acute confusion in elderly medical patients. J Am Geriatr Soc **37**: 150–154, 1989.

25) McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet **351**: 9–13, 1998.

26) Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med **347**: 161–167, 2002.

27) Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol **40**: 976–982, 2002.

28) Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med **162**: 1682–1688, 2002.

29) Matsuzaki M, Sasayama S, Aizawa Y, et al. Japanese Circulation Society guidelines for the management of chronic heart failure. Jpn Circ J **64** Suppl. IV: 1023–1079, 2000 (in Japanese).

30) ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. Circulation **97**: 2202–2212, 1998.

31) Stafford RS, Saglam D, Blumenthal D. National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure. Arch Intern Med **157**: 2460–2464, 1997.

32) Rich MW, Beckham V, Wittenberg C, et al. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med **333**: 1190–1195, 1995.

33) Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation **104**: 2996–3007, 2001.

34) Davie AP, Francis CM, Caruana L, et al. The prevalence of left ventricular diastolic filling abnormalities in patients with suspected heart failure. Eur Heart J **18**: 981–984, 1997.

35) Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. N Engl J Med **312**: 277–283, 1985.

36) Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. J Am Coll Cardiol **22**: 318–325, 1993 (published erratum appears in J Am Coll Cardiol **22**: 1272, 1993).

37) Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. J Am Coll Cardiol **22**: 49A–55A, 1993.

38) Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation **69**: 190–196, 1984.