Section 4: Evaluation of Patients for Ventricular Dysfunction and Heart Failure

Overview

Patients undergoing evaluation for ventricular dysfunction and heart failure (HF) fall into 3 general groups: (1) patients at risk of developing HF, (2) patients suspected of having HF based on signs and symptoms or incidental evidence of abnormal cardiac structure or function, and (3) patients with established symptomatic HF.

Patients at Risk for HF. Patients identified to be at risk for HF require aggressive management of modifiable risk factors as outlined in Section 3 of this guideline. Patients with risk factors may have undetected abnormalities of cardiac structure or function. In addition to risk factor reduction, these patients require careful assessment for the presence of symptoms of HF and, depending on their underlying risk, may warrant noninvasive evaluation of cardiac structure and function.

Patients Suspected of Having HF. The evaluation of patients suspected of having HF focuses on interpretation of signs and symptoms that have led to the consideration of this diagnosis. Careful history and physical examination, combined with evaluation of cardiac structure and function, should be undertaken to determine the cause of symptoms and to evaluate the degree of underlying cardiac pathology.

Patients With Established HF. The evaluation of patients with an established diagnosis of HF is undertaken to identify the etiology, assess symptom nature and severity, determine functional impairment, and establish a prognosis. Follow-up of patients with HF or cardiac dysfunction involves continuing reassessment of symptoms, functional capacity, prognosis, and therapeutic effectiveness.

Evaluation of Patients at Risk

Recommendations

4.1 Evaluation for clinical manifestations of HF with a routine history and physical examination is recommended in patients with the medical conditions or test findings listed in Table 4.1. (Strength of Evidence = B)

4.2 Assessment of Cardiac Structure and Function. Echocardiography with Doppler is recommended to determine cardiac structure and function in asymptomatic patients with the disorders or findings listed in Table 4.2. (Strength of Evidence = B)

Table 4.1. Indications for Evaluation of Clinical Manifestations of HF

Conditions	Hypertension
	Diabetes
	Obesity
	CAD (eg, after MI, revascularization)
	Peripheral arterial disease or cerebrovascular disease
	Valvular heart disease
	Family history of cardiomyopathy in a first-degree relative
	History of exposure to cardiac toxins
	Sleep-disordered breathing
Test Findings	Sustained arrhythmias
	Abnormal ECG (eg, LVH, left bundle branch block, pathologic Q waves)
	Cardiomegaly on chest X-ray

Table 4.2. Assess Cardiac Structure and Function in Patients with the Following Disorders or Findings

Coronary artery disease (eg, after MI, revascularization)
Valvular heart disease
Family history of cardiomyopathy in a first-degree relative
Atrial fibrillation or flutter
Electrocardiographic evidence of LVH, left bundle branch block, or pathologic Q waves
Complex ventricular arrhythmia
Cardiomegaly

Background

Identification of Risk Factors. Identification of risk factors, predisposing conditions, and markers that confer increased risk for developing HF is an important part of the routine medical evaluation.[1] A number of conditions predispose to the development of HF,[2–12] and persuasive evidence exists that treatment of these risk factors decreases the likelihood of subsequent HF (see Guideline Section 3 for more details on risk factor modification and HF prevention). Although risk factors vary in the degree to which they are modifiable, detection of any risk factor identifies a patient in whom aggressive risk factor modification and more careful follow-up are warranted.

Method of Evaluation. Patients at risk for developing cardiac dysfunction should undergo careful history and physical examination to detect evidence of clinical HF and to uncover other conditions that predispose to HF. Appropriate therapies should be introduced to reduce the likelihood that left ventricular (LV) dysfunction will develop. Selected groups of high-risk patients and patients with signs and symptoms of HF should undergo echocardiographic examination to assess cardiac structure and function.[13] This initial examination may identify patients with cardiac dysfunction with or without symptomatic HF. These patients should undergo evaluation and treatment as defined in this guideline.

Echocardiography. The presence of certain risk factors makes the likelihood of underlying ventricular remodeling and dysfunction sufficiently likely to warrant diagnostic echocardiography (Table 4.2).

Characterization of cardiac structure and function is critical for proper diagnosis, estimation of prognosis, and therapeutic decision-making. Contributions of cardiac dysfunction to the HF syndrome extend beyond the traditional view of simply quantifying LV systolic function (or left ventricular ejection fraction, LVEF), since the capacity and the efficiency of the LV also dictates the adequacy of stroke volume. This may explain why approximately 50% of patients with symptoms and signs of HF have a preserved LVEF.[14-17] Therefore, echocardiographic and Doppler assessment should include analysis of chamber sizes, valve function, LV mass and wall thickness, parameters of LV systolic and diastolic function, right ventricular (RV) systolic function, the presence of pulmonary hypertension, and the presence of pericardial disease. In patients whose echocardiographic imaging is unsatisfactory or when the degree of LVEF influences therapeutic decision making, other techniques such as radionuclide ventriculography, cardiac magnetic resonance imaging, or computed tomography may be used.

Recommendation

4.3 Routine determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) concentration as part of a screening evaluation for structural heart disease in asymptomatic patients is not recommended. (Strength of Evidence = B)

Background

Interest is high in developing markers of cardiac dysfunction that can be used to screen patients at risk for HF. Although initial data suggest that determination of BNP or NT-proBNP levels may be useful in this regard, data are insufficient to make a specific recommendation concerning their use for screening in a routine manner. The positive predictive value for these tests in a low-prevalence and asymptomatic population for the purpose of detecting cardiac dysfunction varies among studies, and the possibility of false positive results has significant cost-effectiveness implications.[18-23]

BNP is released by the heart in response to increased ventricular filling pressures, but may also be increased in the plasma as a result of ongoing myocardial dysfunction or hypertrophy. A low plasma BNP or NT-proBNP concentration has a high negative predictive value for cardiac dysfunction in patients presenting to the emergency room with dyspnea, and it may therefore be used to exclude HF as a cause of dyspnea with a relatively high degree of certainty.[24,25]

Evaluation of Patients Suspected of Having Heart Failure

Recommendation

4.4 Symptoms Consistent with HF. The symptoms listed in Table 4.3 suggest the diagnosis of HF. It is recommended that each of these symptoms be elicited in all patients in whom the diagnosis of HF is being considered. (Strength of Evidence = B)

Background

Symptoms. Thorough detection and evaluation of symptoms is critical in the assessment of patients suspected of having HF. The most common symptoms are dyspnea and fatigue from fluid retention, the inability to adequately augment cardiac output and oxygen delivery during exertion, or peripheral factors such as abnormal respiratory and skeletal muscle structure and function. These often manifest as exercise intolerance or a reduction in the intensity of usual activities. Signs of HF relate to manifestations of fluid retention. Dyspnea is typically noted during activity but may be severe enough to be present at rest. Dyspnea may be intermittent even when present at rest or manifest as periodic breathing (e.g., Cheynes-Stokes respiration).[26] Patients whose cardiac dysfunction evolves chronically may reduce their activity to minimize symptoms.[27] Comparing current activity level with exercise tolerance in the past may be helpful in detecting a decline in functional capacity. A patient's functional capacity should be judged with allowance for age and level of conditioning. Congestion may take many forms. Orthopnea and paroxysmal nocturnal dyspnea are symptoms of elevated left heart filling pressures that are more specific to underlying central congestion. These patients may or may not have visible edema. Peripheral edema occurs in the presence of elevated right-sided filling pressures, together with impaired renal handling of sodium and water. Significant volume overload typically is associated with substantial functional incapacity, yet patients may present with fatigue or exercise intolerance and manifest no signs of fluid retention. Symptoms may occur in isolation or not be classically related to physical signs. Nocturnal symptoms may predominate, whereas daytime symptoms, such as dyspnea on exertion, may be absent.

Less Common Presenting Symptoms. Patients may report nocturnal wheezing or cough, which can reflect fluid overload. In patients receiving angiotensin-converting enzyme (ACE) inhibitors, worsening cough should not be assumed to be drug-related, because it may be a manifestation of increasing left heart filling pressures (Section 7). Patients

Table 4.3. Symptoms Suggesting the Diagnosis of HF

Symptoms	Dyspnea at rest or on exertion
	Reduction in exercise capacity
	Orthopnea
	Paroxysmal nocturnal dyspnea (PND) or nocturnal cough
	Edema
	Ascites or scrotal edema
Less specific presentations of HF	Early satiety, nausea and vomiting, abdominal discomfort
	Wheezing or cough
	Unexplained fatigue
	Confusion/delirium
	Depression/weakness (especially in the elderly)

with severely decompensated cardiac failure may present with gastrointestinal symptoms representative of hepatic congestion or visceral edema, including early satiety, nausea, vomiting, and right upper quadrant pain.

Recommendation

4.5   Physical Examination. It is recommended that patients suspected of having HF undergo careful physical examination with determination of vital signs and careful evaluation for signs shown in Table 4.4. (Strength of Evidence = B)

Table 4.4. Signs to Evaluate in Patients Suspected of Having HF

Cardiac Abnormality	Sign
Elevated cardiac filling pressures and fluid overload	Elevated jugular venous pressure
	S3 gallop
	Rales
	Hepatojugular reflux
	Ascites
	Edema
Cardiac enlargement	Laterally displaced or prominent apical impulse
	Murmurs suggesting valvular dysfunction
Reduced cardiac output	Narrow pulse pressure
	Cool extremities
	Tachycardia with pulsus alternans
Arrhythmia	Irregular pulse suggestive of atrial fibrillation or frequent ectopy

Background

Elevation of the jugular venous pressure, hepatic enlargement or tenderness or pulsatility, and lower extremity edema are manifestations of elevated right heart filling pressures, associated with impaired renal sodium and water clearance.[28−31] They also can be due to hepatic or renal dysfunction, various hypo-oncotic states, as well as venous thromboembolism. If due to cardiac disorders, these findings may be accompanied by a loud pulmonic closure sound, RV heave, and a RV S3 (lower left sternal border) consistent with pulmonary hypertension. A prominent laterally displaced apical impulse is indicative of LV enlargement. Increased left heart filling pressure is suggested by rales, diminished breath sounds, wheezing, and an apical S3 gallop.[29]

Recommendation

4.6   It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of having HF, especially when the diagnosis is not certain. (Strength of Evidence = A)

Background

Two forms of natriuretic peptide, BNP and NT-proBNP, have been studied extensively as aids to establish the diagnosis, estimate prognosis, and monitor the response to therapy of patients with acute HF.[23,24,32,33]

Measurement of these peptides has been proposed in cases of acute dyspnea where the diagnosis of HF is uncertain, as evident from large, multicenter investigations.[23,24,33] The diagnostic accuracy of BNP, using a cutoff value of 100 pg/mL, was 83% relative to the assessment made by the independent cardiologists, whereas the negative predictive value of BNP for HF when levels were < 50 pg/mL was 96%. As expected, measurement of BNP/NT-proBNP appeared to be most useful in patients with an intermediate probability of HF. Plasma NT-Pro BNP cut points of > 450 pg/mL for patients younger than 50 years of age, > 900 pg/mL for patients age 50-74 years of age, and > 1800 pg/mL for patients 75 years or older were equally sensitive and specific for diagnosing HF; with < 300 pg/mL providing 98% negative predictive value for ruling out HF.[23,33]

BNP was found to be predictive of HF when LV function was depressed or preserved, but cannot reliably distinguish between the two.[34] In patients with HF associated with preserved LVEF, the BNP cutoff value of 100 pg/mL still had a sensitivity of 86% and a negative predictive value of 96%.

BNP and NT-proBNP levels increase with age, more so in older women or in those with underlying renal insufficiency, in which case the same cutoff ranges may not provide the same degree of specificity for the diagnosis of HF, especially in elderly women with dyspnea.[35] However, BNP and NT-proBNP levels should be interpreted with some caution in patients with morbid obesity as they may have lower than expected plasma BNP/NT-proBNP levels.[36−38]

Recommendation

4.7   Differential Diagnosis. The differential diagnoses in Table 4.5 should be considered as alternative explanations for signs and symptoms consistent with HF. (Strength of Evidence = B)

Table 4.5. Differential Diagnosis for HF Symptoms and Signs

Myocardial ischemia
Pulmonary disease (pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary embolus, primary pulmonary hypertension)
Sleep-disordered breathing
Obesity
Deconditioning
Malnutrition
Anemia
Hepatic failure
Chronic kidney disease
Hypoalbuminemia
Venous stasis
Depression
Anxiety and hyperventilation syndromes
Hyper or hypo-thyroidism

Background

A number of signs and symptoms of HF are nonspecific, particularly shortness of breath, which may reflect

underlying pulmonary disease or physical deconditioning.[26] Recognizing this lack of specificity is particularly important in a general practice setting where patients often present with noncardiac causes of shortness of breath or edema. In patients with dyspnea who do not present with clear signs of HF, the possibility of a pulmonary pathology, including pulmonary embolism, should be considered and evaluated. Spirometry, chest computed tomography, ventilation-perfusion lung scan, or pulmonary angiography should be performed as clinically indicated. It is important to recognize that sleep apnea and HF frequently coexist.[39−42] In patients with fatigue who are without clear signs of HF, physical deconditioning, sleep apnea, hypothyroidism, and depression should be considered as potential causes. Edema may be due to calcium channel blockers, other drugs (e.g. thiazolidinediones, non steroidal anti-inflammatory drugs [NSAIDs], pregabalin), hypoalbuminemia, or venous stasis.

Recommendations

4.8 It is recommended that patients with a diagnosis of HF undergo evaluation as outlined in Table 4.6. (Strength of Evidence = C)

Table 4.6. Initial Evaluation of Patients With a Diagnosis of HF

Assess clinical severity of HF by history and physical examination
Assess cardiac structure and function
Determine the etiology of HF, with particular attention to reversible causes
Evaluate for coronary disease and myocardial ischemia
Evaluate the risk of life-threatening arrhythmia
Identify any exacerbating factors for HF
Identify comorbidities which influence therapy
Identify barriers to adherence

4.9 Symptoms. In addition to symptoms characteristic of HF (dyspnea, fatigue, decreased exercise tolerance, fluid retention), evaluation of the following symptoms should be considered in the diagnosis of HF:
- **Angina**
- **Symptoms suggestive of embolic events**
- **Symptoms suggestive of sleep-disordered breathing**
- **Symptoms suggestive of arrhythmias, including palpitations**
- **Symptoms of possible cerebral hypoperfusion, including syncope, presyncope, or lightheadedness (Strength of Evidence = B)**

4.10 Functional Capacity/Activity Level. It is recommended that the severity of clinical disease and functional limitation be evaluated and recorded and the ability to perform typical daily activities be determined. This evaluation may be graded by metrics such as New York Heart Association (NYHA) functional class (Table 4.7) (Strength of Evidence = A) or by the 6-minute walk test. (Strength of Evidence = C)

Table 4.7. Criteria for NYHA Functional Classification in Patients With HF

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitations, or dyspnea.
Class III	IIIA: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. IIIB: Marked limitation of physical activity. Comfortable at rest, but minimal exertion causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency present at rest. If any physical activity is undertaken, discomfort is increased.

4.11 Volume Status. The degree of volume excess is a key consideration during treatment. It is recommended that it be routinely assessed by determining:
- **Presence of paroxysmal nocturnal dyspnea or orthopnea**
- **Presence of dyspnea on exertion**
- **Daily weights and vital signs with assessment for orthostatic changes**
- **Presence and degree of rales, S3 gallop, jugular venous pressure elevation, hepatic enlargement and tenderness, positive hepatojugular reflux, edema, and ascites (Strength of Evidence = B)**

Background

Characteristic Symptoms. The presence or absence and severity of characteristic symptoms of HF, including those related to exercise tolerance and fluid overload, should be documented in all patients undergoing initial evaluation.

Comorbidities. Symptoms of comorbidities commonly associated with HF should be sought. These include angina,[43] symptoms of sleep-disordered breathing, presyncope, or syncope.

Physical Examination. The physical examination should focus on the detection and etiology of structural heart disease, current volume status, and the severity of HF, as a guide to initiating therapy and a baseline to gauge the effect of that therapy. Height and weight should be recorded. Supine and upright vital signs should be taken to assess for orthostasis. Presence of an S3 gallop and elevation of jugular venous pressure are invaluable specific markers of elevated cardiac filling pressures. A positive Kussmaul can be a flag for restrictive disease or significant HF.

Murmurs such as those of aortic stenosis or mitral regurgitation may provide clues to the etiology of LV dysfunction. Murmurs of tricuspid regurgitation and mitral regurgitation vary depending on the degree of pulmonary or systemic pressure, respectively, volume overload, ventricular dilatation, and failure of leaflet coaptation or elevated pulmonary pressures.

The physical examination has limitations. Pulmonary rales are an insensitive indicator of elevation in pulmonary

venous pressure, unless they occur abruptly.[27] Overt pulmonary edema rarely occurs where left heart filling pressure is chronically elevated, as the pulmonary vasculature adapts with increased lymphatic drainage. Ascites is common in patients with advanced HF (with contributing right HF), but it may be difficult to appreciate on physical examination. Although abdominal complaints can be misleading, history often is a better indicator of excess abdominal fluid than physical examination. Hepatojugular reflux is a sensitive indicator of volume expansion and may be demonstrated in states of RV dysfunction.[31]

Functional Assessment. Determination of baseline exercise and functional limitation is important during the initial evaluation of patients with established HF. Decisions regarding hospitalization and response to medications and other interventions are aided by estimation of the degree of limitation present at the first evaluation.

A number of strategies can be employed to assist in these estimates, including 6-minute walk test distance.[44] One common, time-tested, and simple metric is the NYHA functional classification, which is shown in Table 4.7. [45] Although NYHA class is subjective, numerous longitudinal studies have shown the prognostic power of this determination, and serial evaluation is helpful to gauge response to therapy. Therapeutic recommendations often are directed toward patients within particular NYHA classes, based on use of this indicator as an entry criterion for clinical trials. Success of therapy may be indicated by improvement of at least 1 functional class.[46−49]

Recommendations

4.12 Standard Laboratory Tests. It is recommended that the following laboratory tests be obtained routinely in patients being evaluated for HF: serum electrolytes, blood urea nitrogen, creatinine, glucose, calcium, magnesium, fasting lipid profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), complete blood count, serum albumin, uric acid, liver function tests, urinalysis, and thyroid function. (Strength of Evidence = B)

4.13 Electrocardiogram (ECG). It is recommended that all patients with HF have an ECG performed to:
- **assess cardiac rhythm and conduction (in some cases, using Holter monitoring or event monitors)**
- **assess electrical dyssynchrony (wide QRS or bundle branch block), especially when LVEF <35%**
- **detect LV hypertrophy or other chamber enlargement**
- **detect evidence of myocardial infarction (MI) or ischemia**
- **assess QTc interval, especially with drugs that prolong QT intervals (Strength of Evidence = B)**

4.14 Chest X-Ray. It is recommended that all patients with HF have a postero-anterior and lateral chest X-ray examination for determination of heart size, evidence of fluid overload, detection of pulmonary and other diseases, and appropriate placement of implanted cardiac devices. (Strength of Evidence = B)

4.15 Additional Laboratory Tests. It is recommended that patients with no apparent etiology of HF or no specific clinical features suggesting unusual etiologies undergo additional directed blood and laboratory studies to determine the cause of HF. (Strength of Evidence = B)

Background: Initial Diagnostic Testing

Electrocardiogram and Chest X-Ray. The electrocardiogram (ECG) provides important information on acute ischemia, prior MI, conduction abnormalities, arrhythmias, and ventricular hypertrophy.[50] A chest radiograph may show evidence for cardiac chamber enlargement, increased pulmonary venous pressure, interstitial or alveolar edema, pleural effusions, valvular or pericardial calcification, or coexisting lung disease.

Laboratory Evaluation. The complete blood count may show anemia.[51,52] Hyponatremia, from free water retention, may reflect elevated serum vasopressin levels and activation of the renin-angiotensin system.[53,54] Hyponatremia, which has been associated with poor prognosis,[55,56] may also result from excessive diuresis, but more often indicates severe HF with excess total body salt and water. Elevated serum creatinine may not only reflect important underlying renal impairment but may also represent a prerenal state from reduced cardiac output, venous congestion, intraabdominal hypertension or excessive diuresis.[57−59] Renal dysfunction is associated with a worse prognosis.[60−63] Prerenal azotemia is usually associated with a disproportionate increase in blood urea nitrogen. If creatinine is disproportionately elevated, it generally indicates intrinsic renal disease. Hypoalbuminemia contributes to low plasma oncotic pressure and edema formation. An abnormal urinary sediment may suggest glomerular disease or infection, and proteinuria may play a role in low oncotic pressure and edema formation. Hyper- or hypothyroidism can precipitate or aggravate ventricular dysfunction and clinical HF and may be clinically occult in the elderly. A lipid profile is valuable in patients with significant risk factors for or a documented history of coronary artery disease.

Determination of Etiology. Initial assignment of HF etiology should be as specific as possible. Significant differences in prognosis are commonly noted among the various etiologies of HF, and identification of specific etiologies, such as ischemic heart disease, may trigger specific directions for evaluation and treatment (Section 13). A number of common etiologies dominate the causes of HF in most practice settings. Ischemic heart disease remains a common cause, especially among patients with reduced LVEF.[43]

Background: Common Etiologic Factors

Coronary Artery Disease. Patients with evidence of a MI, coronary artery bypass graft surgery, or percutaneous angioplasty or patients who have coronary artery narrowing of greater than 70% in at least 1 artery are most likely to have an ischemic cardiomyopathy.[64] On the other hand, the mere presence of atherosclerotic coronary artery disease may not necessarily explain the underlying etiology if cardiac dysfunction is out of proportion to the degree of coronary artery disease. Patients with initially established non-ischemic cardiomyopathy can also develop progressive coronary artery disease, leading to adverse clinical outcomes, such as sudden cardiac death.

Hypertension. Population-based analyses have shown hypertension to be the most important population-attributable risk for HF.[5,65] Hypertensive or previously hypertensive patients with a non-dilated left ventricle, preserved LVEF, left atrial enlargement, and concentric LV hypertrophy are most likely to have hypertension as the principal etiology for HF. Among all hypertensive patients with HF, elevated blood pressure should be presumed to contribute to both the cardiovascular pathology and ongoing clinical manifestations of the disease.

The assignment of hypertension as an etiology, particularly of LV systolic dysfunction, has been challenged of late. Clearly, hypertension often is associated with ischemic heart disease and typically is not considered primary in these cases. Documentation of the presence of hypertension may be difficult in many cases of apparently idiopathic cardiomyopathy unless the medical history is carefully reviewed. Many patients with a history of hypertension will not be hypertensive when presenting with systolic dysfunction. Likewise, hypertension may emerge as ventricular function improves with institution of proper medical therapy. In any event, close observation for the development of hypertension is warranted during follow-up.

Alcoholic Cardiomyopathy. Careful history should be directed to determining the quantity of alcohol consumption. In the absence of a clear alternative, an alcoholic etiology is likely among patients with a dilated left ventricle and history of consuming excessive amounts of alcohol.

Valvular Disease. In patients with chronic valvular disease, physical findings may not be characteristic because of low cardiac output. This is especially true of patients with ''low gradient aortic stenosis.'' A history of known valvular or rheumatic heart disease should be sought. Detection of occult valvular disease is one reason for the importance of routine echocardiography as part of the evaluation process.

Idiopathic and Familial Dilated Cardiomyopathy. A number of patients have no apparent cause for their HF despite careful clinical evaluation. The label idiopathic cardiomyopathy represents a diagnosis of exclusion, and less common causes should be sought as indicated below. A family history of cardiomyopathy should be solicited, especially if non-ischemic cardiomyopathy is associated with conduction system disease and arrhythmias. A finding of idiopathic cardiomyopathy might warrant cardiovascular testing in first- and second-degree relatives.[66−68] Apical ballooning (''tako-tsubo'') cardiomyopathy is a transient syndrome with profound anteroapical dysfunction of unclear etiology and associated with emotional stress or high catecholamines surge. Table 4.8 lists physical and laboratory findings that can point to less common etiologies.

Table 4.8. Physical Examination Findings Related to Etiology

Physical Examination	Findings and Implications
Skin	Pigmentation: iron overload
	Lipid deposits: hyperlipidemia
	Spider angiomata: liver disease
	Easy bruisability, nail pitting, amyloidosis
	Cushingoid features: glucocorticoid excess
	Skin laxity: pseudoxanthoma elasticum
	Rash: pellagra
	Malar rash of discoid: lupus
	Sclerodactyly or skin tightening: CREST or scleroderma
Lymph nodes	Adenopathy: sarcoidosis; lymphoma
Thyroid	Modularity enlargement: hyper- or hypothyroidism
Jugular veins	Kussmaul sign: constriction or restriction
Heart rate	Resting tachycardia: a very rapid ventricular response to atrial fibrillation or persistent tachyarrhythmia may suggest a tachycardia-induced cardiomyopathy
Carotids	Delayed upstroke: aortic stenosis
	Bifid carotid contour: may suggest hypertrophic cardiomyopathy
	Carotid bruits may suggest associated atherosclerotic disease
Cardiac palpation	Hyperdynamic, laterally displaced apical impulse: LV volume overload (aortic or mitral regurgitation),an adynamic point of maximal impulse suggests a dilated cardiomyopathy. These displaced PMI findings are usually accompanied by an S3 gallop
Cardiac auscultation	Murmurs: specific valvular pathologies of aortic stenosis, aortic regurgitation, mitral stenosis and mitral regurgitation may be present indicating the potential etiology. Elevation of diastolic pressures may lessen traditional murmurs of regurgitation and low cardiac output may lessen traditional murmurs of stenosis
	Diastolic knock: pericardial disease
	Diastolic plop: thrombus or atrial myxoma
Extremities	Cyanosis: may be a manifestation of extreme low output state or right to left shunting through a congenital defect
	Bounding peripheral pulse and a Quincke's sign: suggest wide pulse pressure and may be clues to hyperthyroidism, aortic regurgitation, AV fistula
	Warm extremities and high cardiac output: beriberi, hyperthyroidism

Familial Hypertrophic Cardiomyopathy. Hypertrophic cardiomyopathy is an autosomal dominant condition with both genotypic and phenotypic variability, and patients with this condition may present with dyspnea or syncope.

Echocardiography is an effective diagnostic approach. Genetic testing is often indicated.[68]

Peripartum Cardiomyopathy. HF occurring 1 month before or within 5 months of delivery, with no prior patient history of heart disease or other etiology of cardiomyopathy, is generally labeled peripartum cardiomyopathy.

Chagas Cardiomyopathy. In patients from Latin America presenting with electrocardiographic and echocardiographic manifestations of "ischemic" cardiomyopathy, but who are found to have no significant coronary artery disease on angiography, the diagnosis of Chagas cardiomyopathy should be considered, and Trypanosoma Cruzi titers checked, if they come from an endemic region (e.g., Central or South America).

Endocrine Abnormalities. Pheochromocytoma should be considered in patients with hypertension that is particularly difficult to manage or is characterized by severe fluctuations in blood pressure. Because hypo- or hyperthyroidism can exacerbate HF and, on rare occasion, can represent the principal cause of HF, thyroid-stimulating hormone should be measured. Acromegaly is a rare, but well-recognized, finding in cardiomyopathy and may be uncovered by obtaining a history of increase in jaw, hand, or foot size, or by comparison of the patient's current features with dated photographs. Diabetes mellitus is commonly associated with the development of HF, especially in those with microvascular diseases such as retinopathy or microalbuminuria.[69] Diabetes mellitus can contribute directly to the development of HF, via its role as a risk factor for coronary artery disease, or secondary to diabetic agents such as thiazolidinediones that cause fluid retention (see Section 3 for a full discussion of the contribution of diabetes to the development of HF).

Cardiotoxin Exposure. Anthracyclines and occasionally other anti-cancer agents may result in cardiomyopathy, depending on the dose received.[70,71] In rare cases, sulphur containing drugs and a number of other agents, including some antibiotics, may initiate an allergic inflammatory reaction leading to eosinophilic myocarditis and decline in heart function.[72] Dating the onset of HF to the initiation of these agents will be helpful.

Radiation Therapy. Chest radiation can affect all cardiac structures, including the pericardium, myocardium, coronary arteries and heart valves, and result in a constrictive/restrictive cardiomyopathy, valvular heart disease and/or ischemic heart disease. Ideally, evaluation and management of radiation-induced heart disease should involve a HF specialist and/or cardiac surgeon with expertise in cardio-oncology.[73]

Exposure to Illicit Drugs. The use of stimulant drugs such as cocaine and methamphetamine may lead to the development of HF.[74–77] Patients should be educated on the cardiovascular risks of using these agents.

Drugs Associated With HF Exacerbation. Some pharmacologic agents, including selected calcium channel blockers and antiarrhythmics, may depress cardiac function and increase the likelihood of HF or exacerbation of preexistent or subclinical heart dysfunction.[78,79] NSAIDs have been associated with an increased risk of HF hospitalization, and they should be recognized as a causative factor for HF exacerbation and avoided in these patients.[80] Thiazelinediones and pregabalin are also associated with fluid retention in patients with HF, and they are not recommended in patients with symptomatic HF.[81,82] Tumor necrosis factor antagonists have also been associated with new onset and/or exacerbation of existing HF.[83]

Connective Tissue Disorders. Systemic lupus erythematosus, scleroderma, and other connective tissue disorders may represent a cause of HF. Vasculitis, hypertension, systemic lupus erythematosus, pericardial involvement, and renal impairment all may contribute to the syndrome of HF. Scleroderma may be associated with myocardial fibrosis with restrictive physiology. In the presence of characteristic skin changes, arthritis, or other organ system involvement, serum antinuclear antibody and rheumatoid factor should be measured.

Toxin Exposure. Lead, arsenic, and cobalt are three toxins that may cause progressive myocardial dysfunction. A history of consumption of lead paint or drinking of well water may provide clues to this unusual cause.

Myocarditis (see also section 16). Rapidly progressive cardiomyopathy, including a rapidly deteriorating clinical condition, should raise suspicion of active myocarditis, including giant cell myocarditis, and represents an indication for consideration of endomyocardial biopsy.[84] Myocarditis may be characterized with a subclinical onset or gradual deterioration. Hepatitis C or HIV infection may be a cause of myocarditis, and there should be a low threshold for measurement of viral serology.[85–88]

Nutritional Deficiencies. Beriberi (thiamine deficiency) may appear in individuals on fad diets or those hospitalized in intensive care units receiving inadequate nutrition. Patients with protein-losing enteropathy due to right HF may develop thiamine deficiency. Selenium deficiency has been recognized as a potential etiology.

Amyloidosis. HF with preserved LVEF and minimal or no LV dilatation, coupled with increased LV and RV wall thickness by echocardiogram, despite normal or diminished QRS voltage on ECG, should raise suspicion of amyloidosis.[89] Serum and urine immunoelectrophoresis should be performed, along with measurement of serum free light chains, and confirmation with endomyocardial biopsy (and in some cases genotyping) may be warranted to determine the presence and subtype of amyloidosis involved as they may have different prognosis and management strategies. In particular, specific testing for the presence of transthyretin

deposition (familial or wild-type) may identify subtypes that are amenable to transplantation considerations. Cardiac magnetic resonance imaging (MRI) can also aid with the diagnosis and prognosis of cardiac amyloidosis.

Hemoglobinopathies. Repeated transfusions from chronic hemolytic anemia may result in iatrogenic iron overload.

High Output States. Hyperthyroidism, arteriovenous (AV) malformations (rarely), large AV fistulas used for dialysis, or sepsis may result in severe volume overload and high output failure, characterized by preserved LVEF with increased ventricular volumes. HF related to sepsis and other critical acute illnesses is usually a result of transient LV dysfunction that is often self-resolving.

Tachycardia Mediated Cardiomyopathy. Several types of tachycardias including ectopic atrial tachycardia, permanent junctional reciprocating tachycardia (PJRT) using an accessory pathway, atrial fibrillation with a rapid ventricular response, incessant idiopathic ventricular tachycardias, and frequent premature ventricular beats have been associated with the development of a reversible dilated cardiomyopathy. Although conclusive studies are lacking to determine the upper limit of heart rate that may be associated with the development of a cardiomyopathy, a general consensus is that persistent tachycardia > 110 beats per minute is required to induced cardiomyopathy. In addition, frequent premature ventricular contractions (PVCs) (20-30% of all beats or > 10,000 per 24 hour)[90,91] may also be associated with the development of cardiomyopathy.[92,93] The optimal level of rate control to prevent the development of cardiomyopathy in patients with atrial fibrillation is not known. In general, a resting ventricular response of 60 to 80 beats per minute and a ventricular response between 90-115 beats per minute during moderate exercise have been suggested.[94] The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial targeted heart rates of ≤80 bpm at rest, ≤110 bpm during a 6 minute walk test, or an average heart rate of 100 beats per minute over at least 18 hours of continuous ambulatory monitoring.[95]

Sarcoidosis. Sarcoid can mimic many things; it commonly is associated with conduction abnormalities and ventricular tachyarrhythmias. Hilar lymphadenopathy may be a clue to the diagnosis of sarcoidosis. It can be confirmed by endomyocardial biopsy, although false negatives are frequent and a negative biopsy does not exclude a diagnosis of sarcoidosis. Cardiac MRI or specialized positron emission tomography − computed tomography (PET-CT) protocols may help to determine the presence of inflammation.

Hemochromatosis. In the setting of dilated cardiomyopathy, darkened skin, and diabetes, hemochromatosis should be excluded using ferritin. In acute inflammatory states, when ferritin is elevated, other tests, such as iron, iron saturation, and total iron-binding capacity, may be considered.

Cardiac MRI may provide reliable accuracy in determining cardiac involvement of iron deposition.

Recommendations

4.16 Evaluation of myocardial ischemia is recommended in those who develop new-onset LV systolic dysfunction especially in the setting of suspected myocardial ischemia or worsening symptoms with pre-existing CAD. The choice of testing modality should depend on the clinical suspicion and underlying cardiac risk factors. Coronary angiography should be considered when pre-test probability of underlying ischemic cardiomyopathy is high and an invasive coronary intervention may be considered. (See Section 13 for specific clinical situations and Strength of Evidence)

4.17 Exercise testing for functional capacity is not recommended as part of routine evaluation in patients with HF. Specific circumstances in which maximal exercise testing with measurement of expired gases should be considered include:
- **Assessing disparity between symptomatic limitation and objective indicators of disease severity**
- **Distinguishing non HF-related causes of functional limitation, specifically cardiac versus pulmonary**
- **Considering candidacy for cardiac transplantation or mechanical circulatory support**
- **Determining the prescription for cardiac rehabilitation**
- **Addressing specific employment capabilities (Strength of Evidence = C)**

Background

Treadmill exercise testing, with or without measurement of oxygen uptake, to assess functional capacity is not routinely required in the evaluation of patients with a known diagnosis of HF. Nevertheless, there are a number of clinical circumstances in which such testing is beneficial.[96] Exertional dyspnea and exercise intolerance may be due to noncardiac causes, especially pulmonary. When there is a disparity between symptoms and objective findings of HF, exercise testing with measurement of expired gases to determine peak oxygen consumption may be useful.

Measurement of peak oxygen uptake may be of assistance in determining candidacy for cardiac transplantation by quantifying functional limitation and adding prognostic information.[97] There is no uniform agreement on a cutoff in peak oxygen uptake that constitutes an absolute criterion for candidacy for transplantation. A value of < 10 mL O_2 kg/min denotes severe functional incapacity and poor prognosis, whereas a value of < 14 mL O_2 kg/min indicates a patient with underlying advanced HF in whom advanced therapeutic options such as transplantation or ventricular assist devices may be considered.[98] The test should be

performed after optimizing medical therapy. Several studies suggest that measuring peak oxygen uptake may be less useful in predicting prognosis in patients on beta blockers.[99,100] It is commonly recognized that women have lower peak oxygen uptake than men. In younger individuals (<50 years of age) and women, percent of predicted peak VO_2 $\leq 50\%$, or a minute ventilation equivalent of carbon dioxide production slope (VE/VCO$_2$) of >35 are also indicators of poor prognosis and can be considerations for transplant candidacy.[98] In obese subjects a calculation of VO_2 by lean body mass may also be helpful.[98]

Common Errors in Initial Assessment

General History. Historical information should be well-documented wherever possible. For example, electrocardiographic or enzyme evidence of prior MI should be reviewed, rather than relying on the patient's description of the event. Early symptoms of HF, such as cough and rales, often are incorrectly attributed to respiratory infection. Specific evidence should be sought to confirm or refute the diagnosis.

Physical Examination. There are a number of ways in which the patient's volume status may be misjudged. Rales may be due to pulmonary disease, rather than pulmonary edema. Conversely, severe chronic volume overload may occur in the absence of pulmonary rales. Edema may be due to venous stasis disease or medications such as calcium channel blockers, rather than volume overload. Assessment of jugular venous pressure and its wave form is invaluable in the accurate assessment of volume status. However, the absence of evidence of volume overload on examination does not exclude the possibility of severe functional impairment related to HF. In addition, patients may have volume expansion and yet not manifest rales on chest examination. Cardiac murmurs may vary significantly depending upon the patient's volume status. Decreased murmur intensity may be due to elevated filling pressures or low cardiac output.

Recommendation

4.18   Routine endomyocardial biopsy is not recommended in cases of new-onset HF. Endomyocardial biopsy should be considered in patients with rapidly progressive clinical HF or ventricular dysfunction, despite appropriate medical therapy. Endomyocardial biopsy also should be considered in patients suspected of having myocardial infiltrative processes, such as sarcoidosis or amyloidosis, or in patients with malignant arrhythmias out of proportion to LV dysfunction, where sarcoidosis and giant cell myocarditis are considerations. (Strength of Evidence = C)

Background

In patients who present with rapidly progressive signs and symptoms of HF and ventricular dysfunction (often

associated with a dilated left ventricle and new ventricular arrhythmias or conduction abnormalities) and are poorly responsive to appropriate medical therapy, the diagnosis of giant cell myocarditis should be considered. Retrospective data suggest that this disease is associated with high mortality rates and that it may respond to immunosuppression.[84,101] Clinical trials performed in patients with more common forms of lymphocytic myocarditis have failed to demonstrate a clinical benefit from immunosuppressive therapy, and these patients have a high rate of spontaneous recovery.[102,103] Other clinical scenarios that may warrant considerations for endomyocardial biopsy including suspicion for eosinophilic/hypersensitivity myocarditis or drug-induced cardiomyopathy, and the confirmation of infiltrative cardiomyopathies, such as amyloidosis (systemic or transyretin) or sarcoidosis, or suspected forms of cardiomyopathies, such as glycogen storage disease.[104]

Follow-Up Evaluation

Recommendation

4.19   It is recommended that clinical evaluation at each follow-up visit include determination of the elements listed in Table 4.9. (Strength of Evidence = B).

These assessments should include the same symptoms and signs assessed during the initial evaluation. (Strength of Evidence = B)

Table 4.9. Elements to Determine at Follow-Up Visits of HF Patients

Functional capacity and activity level
Changes in body weight
Patient understanding of and adherence with dietary sodium restriction
Patient understanding of and adherence with medical regimen
History of arrhythmia, syncope, presyncope, palpitation or ICD discharge
Adherence and response to therapeutic interventions
The presence or absence of exacerbating factors for HF, including
    worsening ischemic heart disease, hypertension, and new or worsening valvular disease

Background

Volume Assessment. Determination of serial changes in volume status is a critical part of the follow-up of the patient with HF. Ongoing efforts to achieve diuresis may be underway as part of the management plan. Diuretic therapy can be difficult to adjust, and identifying the optimal maintenance dose can be challenging. States of persistent fluid overload or excessive weight loss are common. Restriction of dietary sodium intake is a key factor in optimizing fluid balance. Improved adherence to dietary sodium restriction may result in significant negative fluid balance, mandating adjustment of diuretic therapy.

Pharmacologic Therapy. The difficulty associated with maintaining an appropriate pharmacologic regimen in patients with HF is well known, even when the patient has experienced clinical benefit from specific medications. Economic factors, polypharmacy, side effects, and

misperceptions concerning the relationship of medications to specific somatic feelings all limit adherence with chronic medical regimens. Careful review of current medications may uncover lack of adherence and also detect use of over-the-counter medications that may be detrimental.

Recommendation

4.20 **In the absence of deteriorating clinical presentation, repeat measurements of ventricular volume and LVEF should be considered in these limited circumstances:**
- **When a prophylactic implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy device and defibrillator (CRT-D) placement is being considered in order to determine that LVEF criteria for device placement are still met after medical therapy (Strength of Evidence = B)**
- **When patients show substantial clinical improvement (for example, in response to beta blocker treatment or following pregnancy in patients with peripartum cardiomyopathy). Such change may denote improved prognosis, although it does not in itself mandate alteration or discontinuation of specific treatments (see Section 7). (Strength of Evidence = C)**
- **In alcohol and cardiotoxic substance abusers who have discontinued the abused substance. (Strength of Evidence = C)**
- **In patients receiving cardiotoxic chemotherapy. (Strength of Evidence = B)**

Repeat determination of LVEF is usually unnecessary in patients with previously documented LV dilatation and low LVEF who manifest worsening signs or symptoms of HF, unless the information is needed to justify a change in patient management (such as surgery or device implantation). (Strength of Evidence = C)

Background

Follow-Up Assessment of Ventricular Function. There generally is no reason for repeat echocardiography unless it is anticipated that findings will prompt a change in therapy. There is no evidence that changes in LV volume or LVEF warrant modifications in therapy with drugs such as ACE inhibitors or beta blockers. However, the substantial improvement or normalization in LV volumes and LVEF often seen with beta blocker treatment is associated with improved prognosis, and patients deserve this information. It is reasonable to consider repeat echocardiography for this purpose at least 3 or more months after initiation of beta blockade, particularly if the patient has manifested improvement in signs and symptoms of HF.

In patients with previously documented ventricular dilatation and reduced LVEF, repeat measurement should be considered if the finding of further reduction in LVEF is likely to prompt additional treatment. A good example is the patient manifesting progressive signs and symptoms of HF who might be listed for cardiac transplantation if further worsening of LVEF is not prevented.

Recommendation

4.21 **It is recommended that reevaluation of electrolytes and renal function occur at least every 6 months in clinically stable patients and more frequently following changes in therapy or with evidence of change in volume status. More frequent assessment of electrolytes and renal function is recommended in patients with severe HF, those receiving high doses of diuretics, those on aldosterone antagonists, and those who are clinically unstable. (Strength of Evidence = C)**

See Section 7 for recommendations for patients on an aldosterone receptor antagonist.

Background

The approach to laboratory assessment during follow-up must be individualized. Circumstances requiring more frequent monitoring of renal function and electrolytes include severe HF, changes in volume status or worsening signs and symptoms of HF, diabetes, prescription of an aldosterone antagonist, and initiation or active adjustment of ACE inhibitors or diuretics. Moderate to severe renal dysfunction is common in patients with HF and reduced LVEF and in patients with HF and preserved LVEF, and it may be associated with hyperkalemia. Diabetics, elderly and patients with chronic renal insufficiency are at particular risk for hyperkalemia and require more frequent laboratory monitoring during follow-up.

The role of serial measurements of cardiac biomarkers remains controversial, although some studies have suggested that sequential monitoring may provide useful risk prediction,[105] even though the precise test ranges and frequencies have not yet been established.[106] The role of BNP and NT-proBNP in risk stratification has been very consistent, although the majority of studies have demonstrated the value of a single-point measurement as it relates to long-term outcomes. The STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) study demonstrated a significant reduction in HF death or HF hospitalization for patients randomized to BNP-guided therapy.[107] Other studies of biomarker-guided therapeutic management of HF have not demonstrated improved clinical outcomes associated with this approach as compared to standard clinical management, although some benefits have been found in specific subgroups such as those <75 years of age and in patients whose NT-proBNP were consistently below target levels during follow-up.[108,109] The incremental value of serial BNP testing *solely* for the purpose of risk stratification has not been established.

References

1. Francis G, Tang WH. Clinical evaluation of heart failure. In: Mann D, editor. A Companion to Braunwald's Heart Disease. Philadelphia: WB Saunders Co; 2003. p. 506−26.
2. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;51:1775−83.
3. Cheung N, Wang JJ, Rogers SL, Brancati F, Klein R, Sharrett AR, et al. Diabetic retinopathy and risk of heart failure. J Am Coll Cardiol 2008;51:1573−8.
4. Dhingra R, Sesso HD, Kenchaiah S, Gaziano JM. Differential effects of lipids on the risk of heart failure and coronary heart disease: the Physicians' Health Study. Am Heart J 2008;155:869−75.
5. Ekundayo OJ, Allman RM, Sanders PW, Aban I, Love TE, Arnett D, et al. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. Hypertension 2009;53:458−65.
6. Ingelsson E, Arnlov J, Lind L, Sundstrom J. Metabolic syndrome and risk for heart failure in middle-aged men. Heart 2006;92:1409−13.
7. Kaplan RC, McGinn AP, Pollak MN, Kuller L, Strickler HD, Rohan TE, et al. High insulinlike growth factor binding protein 1 level predicts incident congestive heart failure in the elderly. Am Heart J 2008;155:1006−12.
8. Kenchaiah S, Sesso HD, Gaziano JM. Body mass index and vigorous physical activity and the risk of heart failure among men. Circulation 2009;119:44−52.
9. Lee DS, Massaro JM, Wang TJ, Kannel WB, Benjamin EJ, Kenchaiah S, et al. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. Hypertension 2007;50:869−76.
10. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305−13.
11. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2003;138:10−6.
12. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, et al. Racial differences in incident heart failure among young adults. N Engl J Med 2009;360:1179−90.
13. Qin JX, Shiota T, Thomas JD. Determination of left ventricular volume, ejection fraction, and myocardial mass by real-time three-dimensional echocardiography. Echocardiography 2000;17:781−6.
14. Elesber AA, Redfield MM. Approach to patients with heart failure and normal ejection fraction. Mayo Clin Proc 2001;76:1047−52.
15. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768−77.
16. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456−67.
17. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251−9.
18. Hill SA, Balion CM, Santaguida P, McQueen MJ, Ismaila AS, Reichert SM, et al. Evidence for the use of B-type natriuretic peptides for screening asymptomatic populations and for diagnosis in primary care. Clin Biochem 2008;41:240−9.
19. Silver MA, Maisel A, Yancy CW, McCullough PA, Burnett JC Jr, Francis GS, et al. BNP Consensus Panel 2004: A clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail 2004;10:1−30.
20. Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: a randomized, controlled trial. J Am Coll Cardiol 2003;42:1793−800.
21. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655−63.
22. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288:1252−9.
23. Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007;116:e99−109.
24. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161−7.
25. McKie PM, Rodeheffer RJ, Cataliotti A, Martin FL, Urban LH, Mahoney DW, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide: biomarkers for mortality in a large community-based cohort free of heart failure. Hypertension 2006;47:874−80.
26. Wasserman K. Dyspnea on exertion. Is it the heart or the lungs? JAMA 1982;248:2039−43.
27. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989;261:884−8.
28. Felker GM, Cuculich PS, Gheorghiade M. The Valsalva maneuver: a bedside "biomarker" for heart failure. Am J Med 2006;119:117−22.
29. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 2001;345:574−81.
30. Perloff JK. The jugular venous pulse and third heart sound in patients with heart failure. N Engl J Med 2001;345:612−4.
31. Wiese J. The abdominojugular reflux sign. Am J Med 2000;109:59−61.
32. Januzzi JL, van KR, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330−7.
33. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948−54.
34. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, et al. Bedside B-Type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J Am Coll Cardiol 2003;41:2010−7.
35. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976−82.
36. Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43:1590−5.
37. Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, Lainchbury JG, Richards AM, Ordonez-Llanos J, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med 2007;167:400−7.
38. Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. Circulation 2007;115:1345−53.

39. Bradley TD, Floras JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation 2003;107:1671–8.

40. Bradley TD, Floras JS. Sleep apnea and heart failure: Part II: central sleep apnea. Circulation 2003;107:1822–6.

41. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–9.

42. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008;52:686–717.

43. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation 1998;97:282–9.

44. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. JAMA 1993;270:1702–7.

45. Criteria Committee of the New York heart Association. Nomenclature and criteria for diseases of the heart and great vessels. 9th ed. Boston: Little Brown and Co.; 1994.

46. Abdulla J, Pogue J, Abildstrom SZ, Kober L, Christensen E, Pfeffer MA, et al. Effect of angiotensin-converting enzyme inhibition on functional class in patients with left ventricular systolic dysfunction–a meta-analysis. Eur J Heart Fail 2006;8:90–6.

47. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.

48. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295–302.

49. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995;25:1154–61.

50. Stapleton JF, Segal JP, Harvey WP. The electrocardiogram of myocardopathy. Prog Cardiovasc Dis 1970;13:217–39.

51. Groenveld HF, Januzzi JL, Damman K, van WJ, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 2008;52:818–27.

52. Tang WH, Tong W, Jain A, Francis GS, Harris CM, Young JB. Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure. J Am Coll Cardiol 2008;51:569–76.

53. Schrier RW. Molecular mechanisms of clinical concentrating and diluting disorders. Prog Brain Res 2008;170:539–50.

54. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. Am J Med 2006;119:S47–53.

55. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Arch Intern Med 2007;167:1998–2005.

56. Gheorghiade M, Abraham WT, Albert NM, Gattis SW, Greenberg BH, O'Connor CM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 2007;28:980–8.

57. Campbell RC, Sui X, Filippatos G, Love TE, Wahle C, Sanders PW, et al. Association of chronic kidney disease with outcomes in chronic heart failure: a propensity-matched study. Nephrol Dial Transplant 2009;24:186–93.

58. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96.

59. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol 2008;51:300–6.

60. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.

61. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de ZD, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–10.

62. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD, et al. Correlates and impact on outcomes of worsening renal function in patients > or =65 years of age with heart failure. Am J Cardiol 2000;85:1110–3.

63. Mahon NG, Blackstone EH, Francis GS, Starling RC III, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol 2002;40:1106–13.

64. Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol 2009;53:13–20.

65. Lloyd-Jones D, Adams R, Carnethon M, De SG, Ferguson TB, Flegal K, et al. Heart Disease and Stroke Statistics–2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21–e181.

66. Michels VV, Moll PP, Miller FA, Tajik AJ, Chu JS, Driscoll DJ, et al. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. N Engl J Med 1992;326:77–82.

67. Ku L, Feiger J, Taylor M, Mestroni L. Cardiology patient page. Familial dilated cardiomyopathy. Circulation 2003;108. e118–e21.

68. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy–a Heart Failure Society of America practice guideline. J Card Fail 2009;15:83–97.

69. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med 2008;121:748–57.

70. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 2004;109:3122–31.

71. Ng R, Better N, Green MD. Anticancer agents and cardiotoxicity. Semin Oncol 2006;33:2–14.

72. Al Ali AM, Straatman LP, Allard MF, Ignaszewski AP. Eosinophilic myocarditis: case series and review of literature. Can J Cardiol 2006;22:1233–7.

73. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231–47.

74. Diercks DB, Fonarow GC, Kirk JD, Jois-Bilowich P, Hollander JE, Weber JE, et al. Illicit stimulant use in a United States heart failure population presenting to the emergency department (from the Acute Decompensated Heart Failure National Registry Emergency Module). Am J Cardiol 2008;102:1216–9.

75. Mehta PM, Grainger TA, Lust RM, Movahed A, Terry J, Gilliland MG, et al. Effect of cocaine on left ventricular function. Relation to increased wall stress and persistence after treatment. Circulation 1995;91:3002–9.

76. Chakko S, Myerburg RJ. Cardiac complications of cocaine abuse. Clin Cardiol 1995;18:67−72.

77. Hong R, Matsuyama E, Nur K. Cardiomyopathy associated with the smoking of crystal methamphetamine. JAMA 1991;265:1152−4.

78. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988;319:385−92.

79. Packer M, Kessler PD, Lee WH. Calcium-channel blockade in the management of severe chronic congestive heart failure: a bridge too far. Circulation 1987;75:V56−64.

80. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 1998;158:1108−12.

81. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, et al. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003. Circulation 2003; 108:2941−8.

82. Tang WH, Francis GS, Hoogwerf BJ, Young JB. Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. J Am Coll Cardiol 2003;41:1394−8.

83. Kwon HJ, Cote TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med 2003;138:807−11.

84. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis− natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med 1997;336:1860−6.

85. Barbaro G, Fisher SD, Lipshultz SE. Pathogenesis of HIV-associated cardiovascular complications. Lancet Infect Dis 2001;1:115−24.

86. Grumbach IM, Heermann K, Figulla HR. Low prevalence of hepatitis C virus antibodies and RNA in patients with myocarditis and dilated cardiomyopathy. Cardiology 1998;90:75−8.

87. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. Circulation 1998;97:1246−56.

88. Lipshultz SE. Dilated cardiomyopathy in HIV-infected patients. N Engl J Med 1998;339:1153−5.

89. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol 2007;50:2101−10.

90. Bhushan M, Asirvatham SJ. The conundrum of ventricular arrhythmia and cardiomyopathy: which abnormality came first? Curr Heart Fail Rep 2009;6:7−13.

91. Takemoto M, Yoshimura H, Ohba Y, Matsumoto Y, Yamamoto U, Mohri M, et al. Radiofrequency catheter ablation of premature ventricular complexes from right ventricular outflow tract improves left ventricular dilation and clinical status in patients without structural heart disease. J Am Coll Cardiol 2005;45:1259−65.

92. Efremidis M, Letsas KP, Sideris A, Kardaras F. Reversal of premature ventricular complex-induced cardiomyopathy following successful radiofrequency catheter ablation. Europace 2008;10:769−70.

93. Shiraishi H, Ishibashi K, Urao N, Tsukamoto M, Hyogo M, Keira N, et al. A case of cardiomyopathy induced by premature ventricular complexes. Circ J 2002;66:1065−7.

94. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace 2006;8: 651−745.

95. Van G, I, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347: 1834−1840.

96. Fleg JL, Pina IL, Balady GJ, Chaitman BR, Fletcher B, Lavie C, et al. Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. Circulation 2000;102:1591−7.

97. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778−86.

98. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates−2006. J Heart Lung Transplant 2006;25:1024−42.

99. Shakar SF, Lowes BD, Lindenfeld J, Zolty R, Simon M, Robertson AD, et al. Peak oxygen consumption and outcome in heart failure patients chronically treated with beta-blockers. J Card Fail 2004;10:15−20.

100. Pohwani AL, Murali S, Mathier MM, Tokarczyk T, Kormos RL, McNamara DM, et al. Impact of beta-blocker therapy on functional capacity criteria for heart transplant listing. J Heart Lung Transplant 2003;22:78−86.

101. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, et al. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 2008;102:1535−9.

102. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269−75.

103. Garg A, Shiau J, Guyatt G. The ineffectiveness of immunosuppressive therapy in lymphocytic myocarditis: an overview. Ann Intern Med 1998;129:317−22.

104. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation 2007;116:2216−33.

105. Masson S, Latini R, Anand IS, Barlera S, Angelici L, Vago T, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol 2008;52:997−1003.

106. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, Burnett JC Jr, et al. Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. Circulation 2007;116:249−57.

107. Jourdain P, Jondeau G, Funck F, Gueffet P, Le HA, Donal E, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. J Am Coll Cardiol 2007;9:1733−9.

108. Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. J Am Coll Cardiol 2009; 55:53−60.

109. Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301:383−92.