CHAPTER e31

Cardiac Manifestations of Systemic Disease

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The common systemic disorders that have associated cardiac manifestations are summarized in Table e31-1.

DIABETES MELLITUS

(See also Chap. 344) Diabetes mellitus, both insulin- and non-insulin-dependent, is an independent risk factor for coronary artery disease (CAD; Chap. 241) and accounts for 14–50% of new cases of cardiovascular disease. Furthermore, CAD is the most common cause of death in adults with diabetes mellitus. In the diabetic population the incidence of CAD relates to the duration of diabetes and the level of glycemic control, and its pathogenesis involves endothelial dysfunction, increased lipoprotein peroxidation, increased inflammation, a prothrombotic state, and associated metabolic abnormalities.

Diabetic patients are more likely to have a myocardial infarction, have a greater burden of CAD, have larger infarct size, and have more postinfarct complications, including heart failure, shock, and death, than are nondiabetics. Importantly, diabetic patients are more likely to have atypical ischemic symptoms; nausea, dyspnea, pulmonary edema, arrhythmias, heart block, or syncope may be their anginal equivalent. Additionally, "silent ischemia," resulting from autonomic nervous system dysfunction, is more common in diabetic patients, accounting for up to 90% of their ischemic episodes. Thus, one must have a low threshold for suspecting CAD in diabetic patients. The treatment of diabetic patients with CAD must include aggressive risk factor management (Chap. 344). Pharmacologic therapy and revascularization are similar in diabetic patients and nondiabetics except that diabetic patients have higher morbidity and mortality rates associated with revascularization, have an increased risk of restenosis after percutaneous coronary intervention (PCI), and probably have improved survival when treated with surgical bypass compared with PCI for multivessel CAD.

Patients with diabetes mellitus also may have abnormal left ventricular systolic and diastolic function, reflecting concomitant epicardial CAD and/or hypertension, coronary microvascular disease, endothelial dysfunction, ventricular hypertrophy, and autonomic dysfunction. A restrictive cardiomyopathy may be present with abnormal myocardial relaxation and elevated ventricular filling pressures. Histologically, interstitial fibrosis is seen, and intramural arteries may demonstrate intimal thickening, hyaline deposition, and inflammatory changes. Diabetic patients have an increased risk of developing clinical heart failure, which probably contributes to their excessive cardiovascular morbidity and mortality rates. There is some evidence that insulin therapy may ameliorate diabetes-related myocardial dysfunction.

TABLE e31-1 Common Systemic Disorders and Their Associated Cardiac Manifestations

Systemic Disorder	Common Cardiac Manifestations	Chapter
Diabetes mellitus	CAD, atypical angina, CMP, systolic or diastolic CHF	344
Protein-calorie malnutrition	Dilated CMP, CHF	75
Thiamine deficiency	High-output failure, dilated CMP	74
Hyperhomocysteinemia	Premature atherosclerosis	74
Obesity	CMP, systolic or diastolic CHF	77
Hyperthyroidism	Palpitations, SVT, atrial fibrillation, hypertension	341
Hypothyroidism	Hypotension, bradycardia, dilated CMP, CHF, pericardial effusion	341
Malignant carcinoid	Tricuspid and pulmonary valve disease, right heart failure	350
Pheochromocytoma	Hypertension, palpitations, CHF	343
Acromegaly	Systolic or diastolic heart failure	339
Rheumatoid arthritis	Pericarditis, pericardial effusions, coronary arteritis, myocarditis, valvulitis	321
Seronegative arthropathies	Aortitis, aortic and mitral insufficiency, conduction abnormalities	325
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, myocarditis, arterial and venous thrombosis	319
HIV	Myocarditis, dilated CMP, pericardial effusion	189
Amyloidosis	CHF, restrictive CMP, valvular regurgitation, pericardial effusion	112
Sarcoidosis	CHF, dilated or restrictive CMP, ventricular arrhythmias, heart block	329
Hemochromatosis	CHF, arrhythmias, heart block	357
Marfan syndrome	Aortic aneurysm and dissection, aortic insufficiency, mitral valve prolapse	363
Ehlers-Danlos syndrome	Aortic and coronary aneurysms, mitral and tricuspid valve prolapse	363

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CMP, cardiomyopathy; SVT, supraventricular tachycardia.

MALNUTRITION AND VITAMIN DEFICIENCY

Malnutrition

(See also Chap. 75) In patients whose intake of protein, calories, or both is severely deficient, the heart may become thin, pale, and hypokinetic with myofibrillar atrophy and interstitial edema. The systolic pressure and cardiac output fall, and the pulse pressure narrows. Generalized edema is common and relates to a variety of factors, including reduced serum oncotic pressure and myocardial dysfunction. Such profound states of protein and calorie malnutrition, termed *kwashiorkor* and *marasmus,* respectively, are most common in underdeveloped countries. However, significant nutritional heart disease also may occur in developed nations, particularly in patients with chronic diseases such as AIDS, patients with anorexia nervosa, and patients with severe cardiac failure in whom gastrointestinal hypoperfusion and venous congestion may lead to anorexia and malabsorption. Open-heart surgery poses increased risk in malnourished patients, and those patients may benefit from preoperative hyperalimentation.

Thiamine deficiency (Beriberi)

(See also Chap. 74) Generalized malnutrition often is accompanied by thiamine deficiency; however, this hypovitaminosis also may occur in the presence of an adequate protein and caloric intake, particularly in the Far East, where polished rice deficient in thiamine may be a major dietary component. In Western nations where the use of thiamine-enriched flour is widespread, clinical thiamine deficiency is limited primarily to alcoholics, food faddists, and patients receiving chemotherapy. Nonetheless, when thiamine stores are measured using the thiamine-pyrophosphate effect (TPPE), thiamine deficiency has been found in 20–90% of patients with chronic heart failure. This deficiency appears to result from both reduced dietary intake and a diuretic-induced increase in the urinary excretion of thiamine. The acute administration of thiamine to these patients increases the left ventricular ejection fraction and the excretion of salt and water.

Clinically, patients with thiamine deficiency usually have evidence of generalized malnutrition, peripheral neuropathy, glossitis, and anemia. The classic associated cardiovascular syndrome is characterized by high-output heart failure, tachycardia, and often elevated biventricular filling pressures. The major cause of the high-output state is vasomotor depression leading to reduced systemic vascular resistance, the precise mechanism of which is not understood. The cardiac examination reveals a wide pulse pressure, tachycardia, a third heart sound, and, frequently, an apical systolic murmur. The electrocardiogram (ECG) may reveal decreased voltage, a prolonged QT interval, and T-wave abnormalities. The chest x-ray generally reveals cardiomegaly and signs of congestive heart failure (CHF). The response to thiamine is often dramatic, with an increase in systemic vascular resistance, a decrease in cardiac output, clearing of pulmonary congestion, and a reduction in heart size often occurring in 12–48 h. Although the response to inotropes and diuretics may be poor before thiamine therapy, these agents may be important *after* thiamine is given, since the left ventricle may not be able to handle the increased work load presented by the return of vascular tone.

Vitamin B_6, B_{12}, and folate deficiency

(See also Chap. 74) Vitamin B_6, B_{12}, and folate are cofactors in the metabolism of homocysteine. Their deficiency probably contributes to the majority of cases of hyperhomocysteinemia, a disorder associated with increased atherosclerotic risk. Supplementation of these vitamins has reduced the incidence of hyperhomocysteinemia in the United States; however, the clinical cardiovascular benefit of normalizing elevated homocysteine levels has not been proved.

OBESITY

(See also Chap. 77) Severe obesity, especially abdominal obesity, is associated with an increase in cardiovascular morbidity and mortality rates. Although obesity itself is not considered a disease, it is associated with an increased prevalence of hypertension, glucose intolerance, and atherosclerotic CAD. In addition, obese patients have a distinct cardiovascular abnormality characterized by increased total and central blood volumes, increased cardiac output, and elevated left ventricular filling pressure. The elevated cardiac output appears to be required to support the metabolic demands of the excess adipose tissue. Left ventricular filling pressure is often at the upper limits of normal at rest and rises excessively with exercise. In part as a result of chronic volume overload, eccentric cardiac hypertrophy with cardiac dilation and ventricular dysfunction may develop. In addition, altered levels of adipokines secreted by adipose tissue may contribute to adverse myocardial remodeling via direct effects on cardiac myocytes and other cells. Pathologically, there is left and, in some cases, right ventricular hypertrophy and generalized cardiac dilation. Pulmonary congestion, peripheral edema, and exercise intolerance may all ensue; however, the recognition of these findings may be difficult in massively obese patients.

Weight reduction is the most effective therapy and results in reduction in blood volume and the return of cardiac output toward normal. However, rapid weight reduction may be dangerous, as cardiac arrhythmias and sudden death owing to electrolyte imbalance have been described. Treatment with angiotensin-converting enzyme inhibitors, sodium restriction, and diuretics may be useful to control heart failure symptoms. This form of heart disease should be distinguished from the Pickwickian syndrome (Chap. 264), which may share several of the cardiovascular features of heart disease secondary to severe obesity but, in addition, frequently has components of central apnea, hypoxemia, pulmonary hypertension, and cor pulmonale.

THYROID DISEASE

(See also Chap. 341) Thyroid hormone exerts a major influence on the cardiovascular system by a number of direct and indirect mechanisms, and, not surprisingly, cardiovascular effects are prominent in both hypo- and hyperthyroidism. Thyroid hormone causes increases in total-body metabolism and oxygen consumption that indirectly increase the cardiac workload. In addition, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation (e.g., tachycardia, increased cardiac output); they are mediated at least partly by both transcriptional and nontranscriptional effects of thyroid hormone on myosin, calcium-activated ATPase, Na^+-K^+-ATPase, and myocardial β-adrenergic receptors.

Hyperthyroidism

Common cardiovascular manifestations of hyperthyroidism include palpitations, systolic hypertension, and fatigue. Sinus tachycardia is present in ~40% of hyperthyroid patients, and atrial fibrillation in ~15%. Physical examination may reveal a hyperdynamic precordium, a widened pulse pressure, increases in the intensity of the first heart sound and the pulmonic component of the second heart sound, and a third heart sound. An increased incidence of mitral valve prolapse has been described in hyperthyroid patients, in which case a midsystolic murmur may be heard at the left sternal border with or without a midsystolic click. A systolic pleuropericardial friction rub (*Means-Lerman scratch*) may be heard at the left second intercostal space during expiration and is thought to result from the hyperdynamic cardiac motion.

Elderly patients with hyperthyroidism may present with only cardiovascular manifestations of thyrotoxicosis such as sinus

tachycardia, atrial fibrillation, and hypertension, all of which may be resistant to therapy until the hyperthyroidism is controlled. Angina pectoris and CHF are unusual with hyperthyroidism unless there is coexistent heart disease; in such cases, symptoms often resolve with treatment of the hyperthyroidism.

Hypothyroidism

Cardiac manifestations of hypothyroidism include a reduction in cardiac output, stroke volume, heart rate, blood pressure, and pulse pressure. Pericardial effusions are present in about one-third of patients, rarely progress to tamponade, and probably result from increased capillary permeability. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, distant heart sounds, and pleural effusions. Although the signs and symptoms of myxedema may mimic those of CHF, in the absence of other cardiac disease, myocardial failure is uncommon. The ECG generally reveals sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T-wave abnormalities. Chest x-ray may show cardiomegaly, often with a "water bottle" configuration; pleural effusions; and, in some cases, evidence of CHF. Pathologically, the heart is pale and dilated and often demonstrates myofibrillar swelling, loss of striations, and interstitial fibrosis.

Patients with hypothyroidism frequently have elevations of cholesterol and triglycerides, resulting in premature atherosclerotic CAD. Before treatment with thyroid hormone, patients with hypothyroidism frequently do not have angina pectoris, presumably because of the low metabolic demands caused by their condition. However, angina and myocardial infarction may be precipitated during initiation of thyroid hormone replacement, especially in elderly patients with underlying heart disease. Therefore, replacement should be done with care, starting with low doses that are increased gradually.

MALIGNANT CARCINOID

(See also Chap. 350) Carcinoid tumors most often originate in the small bowel and elaborate a variety of vasoactive amines (e.g., serotonin), kinins, indoles, and prostaglandins that are believed to be responsible for the diarrhea, flushing, and labile blood pressure that characterize the carcinoid syndrome. Some 50% of patients with carcinoid syndrome have cardiac involvement, usually manifesting as abnormalities of the right-sided cardiac structures. These patients invariably have hepatic metastases that allow vasoactive substances to circumvent hepatic metabolism. Left-sided cardiac involvement is rare and indicates either pulmonary carcinoid or an intracardiac shunt. Pathologically, carcinoid lesions are fibrous plaques that consist of smooth-muscle cells embedded in a stroma of glycosaminoglycans and collagen. They occur on the cardiac valves, where they cause valvular dysfunction, as well as on the endothelium of the cardiac chambers and great vessels.

Carcinoid heart disease most often presents as tricuspid regurgitation, pulmonic stenosis, or both. In some cases a high cardiac output state may occur, presumably as a result of a decrease in systemic vascular resistance resulting from vasoactive substances released by the tumor. Treatment with somatostatin analogues (e.g., octreotide) or interferon α improves symptoms and survival in patients with carcinoid heart disease but does not appear to improve valvular abnormalities. In some severely symptomatic patients, valve replacement is indicated. Coronary artery spasm, presumably due to a circulating vasoactive substance, may occur in patients with carcinoid syndrome.

PHEOCHROMOCYTOMA

(See also Chap. 343) In addition to causing labile or sustained hypertension, the high circulating levels of catecholamines resulting from a pheochromocytoma may cause direct myocardial injury. Focal myocardial necrosis and inflammatory cell infiltration are present in ~50% of patients who die with pheochromocytoma and may contribute to clinically significant left ventricular failure and pulmonary edema. In addition, associated hypertension results in left ventricular hypertrophy. Left ventricular dysfunction and CHF may resolve after removal of the tumor.

ACROMEGALY

(See also Chap. 339) Exposure of the heart to excessive growth hormone may cause CHF as a result of high cardiac output, diastolic dysfunction owing to ventricular hypertrophy (with increased left ventricular chamber size or wall thickness), or global systolic dysfunction. Hypertension occurs in up to one-third of patients with acromegaly and is characterized by suppression of the renin-angiotensin-aldosterone axis and increases in total-body sodium and plasma volume. Some form of cardiac disease occurs in about one-third of patients with acromegaly and is associated with a doubling of the risk of cardiac death.

RHEUMATOID ARTHRITIS AND THE COLLAGEN VASCULAR DISEASES

Rheumatoid arthritis

(See also Chap. 321) Rheumatoid arthritis may be associated with inflammatory changes in any or all cardiac structures, although pericarditis is the most common clinical entity. Pericardial effusions are found on echocardiography in 10–50% of patients with rheumatoid arthritis, particularly those with subcutaneous nodules. Nonetheless, only a small fraction of these patients have symptomatic pericarditis, and when present, it usually follows a benign course, only occasionally progressing to cardiac tamponade or constrictive pericarditis. The pericardial fluid is generally exudative, with decreased concentrations of complement and glucose and elevated cholesterol. Coronary arteritis with intimal inflammation and edema is present in ~20% of cases but only rarely results in angina pectoris or myocardial infarction. Inflammation and granuloma formation may affect the cardiac valves, most often the mitral and aortic valves, and may cause clinically significant regurgitation owing to valve deformity. Myocarditis is uncommon and rarely results in cardiac dysfunction.

Treatment is directed at the underlying rheumatoid arthritis and may include glucocorticoids. Urgent pericardiocentesis should be performed in patients with tamponade, but pericardiectomy usually is required in cases of pericardial constriction.

Seronegative arthropathies

(See also Chap. 325) The seronegative arthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthritides associated with ulcerative colitis and regional enteritis, are all strongly associated with the HLA-B27 histocompatibility antigen and may be accompanied by a pancarditis and proximal aortitis. The aortic inflammation usually is limited to the aortic root but may extend to involve the aortic valve, mitral valve, and ventricular myocardium, resulting in aortic and mitral regurgitation, conduction abnormalities, and ventricular dysfunction. One-tenth of these patients have significant aortic insufficiency, and one-third have conduction disturbances; both are more common in patients with peripheral joint involvement and long-standing disease. Treatment with aortic valve replacement and permanent pacemaker implantation may be required. Occasionally, aortic regurgitation precedes the onset of arthritis, and therefore, the diagnosis of a seronegative arthritis should be considered in young males with isolated aortic regurgitation.

Systemic lupus erythematosus (SLE)

(See also Chap. 319) A significant percentage of patients with SLE have cardiac involvement. Pericarditis is common, occurring in about two-thirds of patients, and generally follows a benign course, although rarely tamponade or constriction may result. The characteristic endocardial lesions of SLE are verrucous valvular abnormalities known as *Libman-Sacks endocarditis*. They most often are located on the left-sided cardiac valves, particularly on the ventricular surface of the posterior mitral leaflet, and are made up almost entirely of fibrin. These lesions may embolize or become infected but rarely cause hemodynamically important valvular regurgitation. Myocarditis generally parallels the activity of the disease and, although common histologically, seldom results in clinical heart failure unless associated with hypertension. Although arteritis of epicardial coronary arteries may occur, it rarely results in myocardial ischemia. There is, however, an increased incidence of coronary atherosclerosis that probably is related more to associated risk factors and glucocorticoid use than to SLE itself. Patients with the antiphospholipid antibody syndrome may have a higher incidence of cardiovascular abnormalities, including valvular regurgitation, venous and arterial thrombosis, premature stroke, myocardial infarction, pulmonary hypertension, and cardiomyopathy.

FURTHER READINGS

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