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as useful in Europe, although the usefulness is disputable. Variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HFrEF, patients from southwest Europe have a lower incidence of ischemic cardiomy opathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of HF, disparate effects are noted across populations. As a recent example, in TOPCAT, the drug spironolactone was effective when used in the U.S. population, whereas patients recruited from Russia and con tiguous territories showed no difference. Whether this represents population differences or trial conduct disparity remains a serious question. ADHF patients in Eastern Europe tend to be younger, with higher EFs and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascular ization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline char acteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification. ■ ■FURTHER READING Anker SD et al: Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 385:1451, 2021. Borlaug BA: The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 11:507, 2014. Braunwald E: Heart failure. JACC Heart Fail 1:1, 2013. Heidenreich PA et al: 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 145:e895, 2022. Hein AM et al: Medical management of heart failure with reduced ejection fraction in patients with advanced renal disease. JACC Heart Fail 7:371, 2019. Hollenberg SM et al: 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized with Heart Failure: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 74:1966, 2019. Hussein AA, Wilkoff BL: Cardiac implantable electronic device therapy in heart failure. Circ Res 124:1584, 2019. Kittleson MM et al: 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 81:1835, 2023. Kusumoto FM et al: HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. Circu lation 130:94, 2014. McMurray JJ et al: Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371:993, 2014. McMurray JJV et al:

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Joseph Loscalzo

Classification of

Cardiomyopathy The term cardiomyopathy describes primary disease of the heart muscle itself, originally excluding myocardial dysfunction resulting from other cardiovascular disease. Common usage, however, often includes diagnoses of ischemic cardiomyopathy, valvular cardiomyopa thy, and hypertensive cardiomyopathy. The traditional morphologic classification defines the three major phenotypes of hypertrophic car diomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM) (Table 266-1). Left ventricular wall thickness is increased (≥13–15 mm depending on context) and ejection fraction is normal or high with HCM. DCM is defined when the left ventricular ejection fraction (LVEF) is ≤0.50, but most clinical presentations are with LVEF ≤0.40. RCMs typically pres ent with mildly decreased ejection fraction and variably increased wall thickness and are often defined less by morphology than by evidence of abnormal diastolic physiology on echocardiography or invasive hemodynamic measurement. Although these phenotypes are helpful to guide initial evalua tion of clinical disease, the phenotypes increasingly overlap over time as there is increasing recognition that DCMs can respond to recommended therapies with “reverse remodeling” to higher ejec tion fraction and smaller ventricles, while HCM evolves in ~5% of patients to a reduced ejection fraction (HCM-rEF) with more restric tive physiology. A fourth evolving phenotype with predominantly genetic causes is arrhythmogenic right ventricular cardiomyopathy (ARVC), originally termed arrhythmogenic right ventricular dysplasia, characterized by life-threatening arrhythmias and abnormal right ventricular structure and function, with variable expression in the left ventricle. As new phenotype-genotype connections are revealed, the terminology continues to evolve, as arrhythmogenic right ven tricular dysplasia may also be termed ACM-RV (arrhythmogenic cardiomyopathy–right ventricle predominant), in line with ACM-LV, in which the arrhythmias and structural changes are predominantly in the left ventricle. If the ACM terminology is expanded to include acquired disease, the granulomatous disease of sarcoidosis and the protozoal myocarditis of Chagas’ disease can both cause phenotypes with cardiomyopathy and ventricular arrhythmias that qualify as ACM-RV

and ACM-LV. Reliance upon phenotypic presentation is diminishing as more is learned about the underlying causes of cardiomyopathy. The cata log is rapidly growing of pathogenic genetic variants that can lead to heritable cardiomyopathies, which new imaging techniques can now sometimes identify prior to clinical disease. Expanding knowledge of immune response pathways reveals how some aspects of myocardi tis may also be inherited and how they contribute to infectious and noninfectious inflammation that can cause clinical myocarditis and cardiomyopathy. Diagnosis and outcomes of clinical cardiomyopathies are further complicated by the frequent two-hit models where the clinical expression of a genetic predisposition to cardiomyopathy may

TABLE 266-1 Classification of Cardiomyopathies CARDIOMYOPATHY (CM) PHENOTYPE DIAGNOSTIC CRITERIA OTHER MORPHOLOGY COMMON CHALLENGES IN DIAGNOSIS Hypertrophic cardiomyopathy (HCM) Mid-range LVEF includes rare transition to HCM with LV systolic dysfunction (LVEF <0.50) Septal thickness in men ≥15 mm,

≥13 mm in women. 13–14 mm may be diagnostic in relatives of proband with known HCM or with positive genetic test. LVEF ≥ normal, usually >0.60 LV chamber volume ≤normal. PART 6 Disorders of the Cardiovascular System Mid-range LVEF (0.40–0.50) Restrictive cardiomyopathy (RCM) Least common cardiomyopathy (CM) phenotype Functional diagnosis based on moderate-severe diastolic dysfunction and/or elevated cardiac filling pressures. Wall thickness often increased but can appear normal. LVEF usually mildly reduced, occasionally normal. Mid-range LVEF is often a transition in DCM, either deterioration from early DCM or improvement into DCM remission LV dilated cardiomyopathy (DCM) • Early: LVEF ≤0.50 and/or LVEDV >112% normal for age/sex or LVEDD >95% predicted sex/height • LVEF ≤0.40: threshold for traditionally recommended therapies for heart failure with low LVEF • Persistent LVEF ≤0.30–0.35: threshold for primary prevention ICD Arrhythmogenic CM Dominant in LV (ACM-LV) Usually DCM, occasionally RCM Morphologic criteria generally those for DCM. Ventricular tachyarrhythmias dominate without or before severely reduced LVEF and heart failure. Primary prevention ICD considered even when LVEF >0.35. Arrhythmogenic CM Dominant in RV (ACM-RV; also termed ARVC) Modified task force criteria from 2010 include combinations of major and minor criteria Ventricular arrhythmias and evidence of both ACM-RV and ACM-LV Biventricular arrhythmogenic CM Trait of LV noncompaction (LVNC) Implications determined by CM phenotype and genotype Often assessed by maximum ratio of noncompacted/compacted LV myocardium >2.3 and other criteria Abbreviations: ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction. be triggered by acquired conditions such as infections, toxic exposures, pregnancy, or tachycardia. CLINICAL PRESENTATION AND EVALUATION OF CARDIOMYOPATHY Early symptoms of cardiomyopathy often reflect exertional intolerance with breathlessness or fatigue. Arrhythmias are often presenting events of unrecognized cardiomyopathy, which can also present with embolic events related to atrial fibrillation or apical ventricular thrombi. Car diomyopathy may often present first with the syndrome of congestion, with fluid retention and elevated left heart filling pressures causing shortness of breath with minimal activity or even at rest, particularly with orthopnea. It may be accompanied by elevated right-sided filling pressures causing edema and often abdominal symptoms. The non specific historical term congestive heart failure describes the syndrome

Patterns of LV hypertrophy (LVH) in HCM: • Asymmetric septal hypertrophy • Inverse (sigmoid pattern) septal Distinction from athlete’s heart and severe chronic hypertension The storage diseases of GLA (AndersonFabry), PRKAG2, and LAMP2 (Danon’s), which can mimic HCM morphology Exclude aortic stenosis In older patients, exclude amyloidosis, which can also cause asymmetric septal thickening hypertrophy • Concentric LVH • Apical hypertrophy Usually marked atrial enlargement Although both ventricles affected, clinical right heart failure often dominates. Marked wall thickness suggests: • Amyloidosis • Inherited storage diseases • Inborn metabolic diseases Common etiologies of radiation, scleroderma-type connective tissue diseases, doxorubicin and other medications Some sarcomeric variants and storage diseases can appear with RCM as well as HCM phenotypes Although traditionally listed as restrictive, sarcoidosis more often has morphology of regional wall motion abnormalities, DCM phenotype, or right ventricular (RV) involvement with systolic dysfunction Can involve LV alone or with RV involvement either from primary cause or from secondary RV failure due to chronically elevated pulmonary artery pressures Structural heart disease such as coronary artery disease or infarction from other cause, primary valve disease Suggestive but not necessarily conclusive differences in patterns of late gadolinium enhancement between different variants Occasional ACM-LV with RCM phenotype For frequent PVCs or NSVT, may be difficult to distinguish PVC-related CM from genetic CM causing both the arrhythmias and the CM Abnormal RV function or structure Biventricular ACM often diagnosed from LGE in ventricle with less involvement Cardiac sarcoidosis can cause predominantly RV involvement with ventricular arrhythmias, RV wall motion abnormalities, aneurysms, and dilation Can occur with HCM, DCM, some dystrophies, and other syndromic presentations Can occur in normal hearts, pregnancy Increased prevalence in athletic hearts of congestion, which is common to diverse cardiac diagnoses such as congenital heart disease, primary pulmonary hypertension, and struc tural valve disease. “Congestive heart failure” should not be considered a diagnosis or an etiology of cardiomyopathy but a nonspecific syn drome requiring thorough evaluation of possible etiology/ies. Initial evaluation of possible cardiomyopathy begins with a detailed clinical history and examination seeking clues to cardiac, genetic, and systemic causes of heart disease, which help to guide subsequent evaluation (Table 266-2). Echocardiography remains the initial imaging modality to define morphology and function, with increasing use of magnetic resonance imaging to provide further information on myocardial tissue charac terization, patterns of fibrosis indicated by late gadolinium enhance ment, and T1 and T2 mapping for evidence of focal and diffuse inflammation.

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