Diagnostic and Prognostic Testing in Heart Failure

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KEYWORDS

• Biomarkers • Echocardiography • Cardiac MRI • Cardiac imaging
• Risk stratification

KEY POINTS

- Diagnostic testing in heart failure involves the use of biomarkers, echocardiography, and advanced imaging techniques, such as cardiac MRI, to classify the type of heart failure and etiology of the disease.
- Prognostic testing plays a critical role in assessing the long-term outcomes of patients with heart failure by evaluating biomarkers, imaging parameters, and functional capacity.
- Certain heart failure presentations may require additional testing to determine the etiology of cardiomyopathy and prognosis, including genetic testing and advanced imaging techniques.
- Accurate diagnostic and prognostic assessments are essential for improving patient management and outcomes.

Heart failure (HF) is a complex clinical syndrome characterized by impaired cardiac function that leads to inadequate circulation and systemic congestion, selected etiologies of heart failure listed in **Box 1**. Accurate diagnosis and prognosis are crucial for optimizing treatment strategies and improving patient outcomes. Diagnostic testing in HF involves a combination of biomarkers, imaging modalities such as echocardiography and cardiac MRI, genetic testing, and invasive hemodynamic measurements to determine the underlying etiology and severity of dysfunction. These diagnostic tests also carry important prognostic information which can help with predicting disease progression, the risk of adverse events, and guide therapeutic decisions. Advances in diagnostic and prognostic methodologies continue to enhance the precision of HF management, aiding in early intervention and personalized treatment approaches.

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Abbreviations	
6MWT	6-minute walk test
ACC	American College of Cardiology
ACM	arrhythmogenic cardiomyopathy
AHA	American Heart Association
ARNi	angiotensin receptor-neprilysin inhibitors
ATTR	transthyretin amyloidosis
ATTRwt	wild-type ATTR
BNP	B-Type natriuretic peptide
CCTA	cardiac CT angiography
CMR	cardiac magnetic resonance
CT	computed tomography
DCM	dilated cardiomyopathy
ECV	extracellular volume
FDG	fluorodeoxyglucose
HCM	hypertrophic cardiomyopathy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
hs-CRP	high-sensitivity C-reactive protein
LGE	late gadolinium enhancement
LVEDP	left ventricular end-diastolic pressure
LVIDD	left ventricular internal diameter at end diastole
MACE	major adverse cardiac events
MIBG	metaiodobenzylguanidine
NCCM	noncompaction cardiomyopathy
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PASP	pulmonary artery systolic pressure
RCM	restrictive cardiomyopathy
RHC	right heart catheterization
RV	right ventricular
SGLT2	sodium-glucose cotransporter 2
SI_{QPS}	sphericity index
SPECT	single photon emission computed tomography
sST2	soluble ST2

BIOMARKERS

Biomarkers have shown significant diagnostic and prognostic value in HF management, with B-Type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic eptide (NT-proBNP) being the most widely used and validated. However, there is an evolving role for others, including cardiac troponins (cTnI and cTnT), soluble ST2 (sST2), and galectin 3.

B-Type Natriuretic Peptide and N-Terminal Pro-B-Type Natriuretic Peptide

ProBNP, a prohormone of BNP and NT-proBNP, is released by myocardium in response to volume overload and increased filling pressures. These hormones act as peripheral vasodilators and diuretics through increased natriuresis of the kidneys.[1] BNP and NT-proBNP have proven to be useful biomarkers in HF, particularly, for the diagnosis and management of HF with reduced ejection fraction (HFrEF).[2] BNP and NT-proBNP are used clinically in ruling out acute HF given their high sensitivity.[3]

The Breathing Not Properly Multinational Study, a 2002 prospective trial of 1586 patients, showed the clinical utility of BNP; levels above 100 pg/mL had a sensitivity of 90% and specificity of 73% for acute HF in patients presenting with acute dyspnea.

Box 1
Etieologies of heart failure listed by primary chamber affected

Isolated LV dilation/dysfunction
- Ischemic cardiomyopathy
- Hypertensive cardiomyopathy
- Familal cardiomyopathy
- Alcohol cardiomyopathy (can also cause Biventricular dysfunction)
- Viral cardiomyopathy
- Mitral or aortic regurgitation.

Isolated RV dilation/dysfunction
- Pulmonary hypertension
- Arrhythmogenic RV cardiomyopathy
- Congenital shunts
- Acute RV pressure overload

Biventricular dilation
- Nonischemic cardiomyopathies
- Chemo-induced cardiomyopathies
- Infiltrative cardiomyopathies

Left atrial dilation
- Mitral valve disease
- HFpEF
- Atrial fibrillation

Right atrial dilation
- Tricuspid regurgitation
- Pulmonary hypertension
- Atrial septal defect

Similarly, the PRIDE study from 2005 showed that levels of NT-proBNP above 300 pg/mL had a sensitivity of 99% and specificity of 68% for diagnosing acute heart failure.[4,5]

According to the 2022 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines, the use of BNP/NT-proBNP is recommended as a class IA recommendation for the initial diagnosis of HF.[6] However, the use of natriuretic peptide-guided therapy for HF has had mixed results when studied and remains a class IIA recommendation.[7,8] The OPTIMIZE-HF trial identified a predictive benefit when BNP levels were obtained prior to discharge, with the expectation that this was the patient's *dry* BNP. This analysis showed that higher levels of BNP at discharge were associated with increased 1 year readmission rate and mortality.[9]

The GUIDE-IT trial (2017) showed that NT-proBNP-guided heart failure treatment, with a goal of less than 1000 pg/mL, did not improve hospitalization for cardiovascular mortality in chronic HFrEF. The PARADIGM-HF and PRIMA II trials examined patients with acute decompensated HF and used direct treatment to reduce NT-proBNP levels by at least 30%; while the PRIMA II trial showed no difference, the PARADIGM trial showed improved outcomes.[10,11] The results of the latter were likely due to the incorporation of angiotensin receptor-neprilysin inhibitors (ARNi) into treatment regimens.

It is important to note that most of these trials were performed before the widespread use of newer HF treatment agents, including ARNi and sodium-glucose cotransporter 2 (SGLT2) inhibitors. The use of ARNi has become common in the treatment of HF, and one mechanism of action is the inhibition of neprilysin, which is the enzyme responsible for the degradation of BNP.[12,13] For this reason, BNP is less useful in patients taking ARNis, especially for those initiating therapy with ARNi. The

PROVE-HF trials identified that, while BNP levels with certain dose increased, NT-proBNP levels, especially at lower doses, decreased with ARNI treatment.[14] When used with other clinical data BNP/NT-ProBNP can provide useful diagnostic information and can be used to tailor management of HF.

Cardiac Troponins

Cardiac troponins (cTnI and cTnT) are highly sensitive and specific markers of myocardial injury and can be useful in the prognosis of HF. While classically used in the diagnosis of acute coronary syndrome, elevated troponin levels are also observed in patients with HF. As per the ACC/AHA, it is a class IA recommendation to obtain troponins to rule out myocardial infarction as a cause of acute HF.[6] In chronic HF, elevated troponin levels correlate with increased in-hospital mortality.[15] A more significant association was found when further stratified for both BNP and troponin; BNP levels greater than or equal to 840 pg/mL with elevated troponin demonstrated an odds ratio of 2.09 for in-hospital mortality.[16,17]

Other Biomarkers

sST2, Galectin 3, and high-sensitivity C-reactive protein (hs-CRP) are other biomarkers that have shown some evidence of prognostic utility in HF. Elevated sST2 levels indicate myocardial fibrosis and remodeling, with levels above 35 ng/mL linked to higher mortality risk but improved outcomes with appropriate treatment of HF.[18,19] Galectin-3, involved in inflammation and fibrosis, has shown independent prognostic value in chronic HF, particularly in patients with HF with preserved ejection fraction (HFpEF).[20,21] hs-CRP, a marker of systemic inflammation, also adds prognostic value by indicating higher risk of cardiovascular events and mortality in patients with HF[22] (**Table 1**).

These biomarkers—BNP/NT-proBNP, cardiac troponins, sST2, galectin-3, and hs-CRP—each provide unique and complementary information about different aspects of HF pathophysiology. Outside of BNP/NT-ProBNP and troponin, more studies are needed to help justify the use of the other biomarkers in clinical practice. However, it might be beneficial to identify the appropriate clinical scenario to use these biomarkers in selecting treatment strategies (eg, BNP for acute diagnosis, NT-ProBNP for response to ARNi, and sST2 to identify if CRT will be beneficial).

Imaging modalities in diagnosis and prognosis of heart failure

Imaging modalities play a crucial role in the diagnosis, prognosis, and management of HF. Using these imaging modalities described below by themselves or in combination can give us insights into cardiac structure, function, and hemodynamics, enabling more accurate and timely interventions. **Table 2** below lists imaging modalities and their use in HF.

Echocardiography

Echocardiography is the most widely available and cost-effective imaging modality for HF and allows us to gather important information regarding etiology, anatomy, and hemodynamics. Important echocardiographic features include chamber size, left ventricle (LV) wall thickness, systolic and diastolic function, regional wall motion abnormalities, the presence of a pericardial effusion, and valvular function. Based on clinical history and echocardiogram findings, diagnosis, prognosis, and etiologies of HF can be identified.

Chamber sizes can quickly identify the extent of patient's cardiomyopathy. Left ventricular internal diameter at end diastole (LVIDD) greater than 61 mm for women and greater than 68 mm for men show advanced cardiac remodeling and carries a poor

Table 1
Heart failure biomarkers and their diagnostic and prognostic utility

Biomarker	Study	Year	Findings	Utility
BNP	BNP Multinational Study	2002	BNP levels above 100 pg/mL had a sensitivity of 90% and specificity of 76% for diagnosing HF	Diagnosis of HF
NT-proBNP	PRIDE	2005	Levels above 300 pg/mL had a sensitivity of 99% and specificity of 68% for diagnosing acute HF	Diagnosis of acute HF
BNP	OPTIMIZE-HF	2007	BNP levels prior to discharge serve as a marker for 1 year mortality and risk of readmission	Predictive benefit for mortality and readmission
cTnI and cTnT	ADHERE	2011	Elevated troponin levels associated with increased in-hospital mortality and longer hospital stays	Prognostic value in HF
hs-CRP	Val-HeFT	2001	hs-CRP levels independently associated with mortality and morbidity in HF	Prognostic value in HF
sST2	PRIDE	2005	sST2 levels higher in patients with acute HF, providing incremental prognostic value	Diagnosis and prognosis of HF
Galectin-3	COACH	2014	Galectin-3 levels provided prognostic information beyond NT-proBNP	Prognostic value in HF

Table 2
Imaging modalities and their use in heart failure

Modality	Purpose	Key Trials	Guidelines
SPECT	Assess myocardial ischemia and viability	STICH	ACC/AHA
Cardiac PET	Assess myocardial ischemia, viability, microvascular dysfunction	PAREPET, STICH	ACC/AHA, American Society of Nuclear Cardiology
CPET	Assess functional capacity, prognostic markers	HF-ACTION	ESC, AHA/ACC/HFSA
CCTA	Exclude CAD, assess coronary calcification	PROMISE	—
6MWT	Measure functional capacity	None specified	AHA
Cardiac MRI	Differentiating HF phenotypes	MR-INFORM	ACC/AHA/HFSA, ESC
Echocardiography	Assess Function, progression, and prognosis.	—	ACC/AHA/HFSA, ESC
Cardiac Catheterization	Assist in ruling out CAD. Asses chamber pressures.	—	ACC/AHA/HFSA, ESC

prognosis of patient's with HFrEF.[23] **Table 3** lists these and other echocardiographic parameters used in prognostication of HF.

Analysis from the SOLVD and the Val-Heft trial identify that left ventricular mass (mass >298 g) and left ventricular function (LVEF) less than 35% are independent risk factor of cardiovascular mortality and portends a higher risk of sudden cardiac death.[24,25] A LV sphericity index (SI_{QPS}) quantifies the shape of the LV and can also be used for prognosis. An SI_{QPS} greater than 0.65 indicates a more spherical and less elliptical LV shape, and has been shown to be an accurate predictor for major adverse cardiac events (MACE).[26] LVAI correlates with diastolic dysfunction and has been shown to be a predictor of cardiac mortality.[27] Left atrial strain can be used to assess the function of the left atrium and a value of 23% or less has been shown to be an independent predictor of worse outcomes in HFpEF.

In acute on chronic HF, measurements such pulmonary artery systolic pressure (PASP) can help identify severe disease and dictate management, and is indicative of concomitant pulmonary hypertension. PASP greater than 40 mm Hg has been shown to be associated with increased risk of readmission and mortality.[28,29] In HF with the right ventricular (RV) failure, we can look at the ratio of tricuspid annular plane systolic excursion/PASP. When this ratio is less than 0.36 mm/mm Hg there is uncoupling of the right atrium and ventricular due to severe remodeling and leading to end stand disease.[30,31]

Global longitudinal strain (GLS) is an essential tool for early diagnosis and prognosis in HF. A strain of −18% or lower indicates normal LV strain. GLS can detect cardiac dysfunction earlier than traditional measures and is recommended by the 2022 AHA/ACC/HFSA Guidelines for patients with suspected HFpEF. GLS has greater prognostic value than LVEF, with studies showing each 1% decrease in GLS is associated with a 5% increased risk of death over 5 years. In acute HF, GLS is superior in predicting outcomes, and in hypertrophic cardiomyopathy, reduced GLS can signify early cardiac involvement.[32,33] **Fig. 1** below from Zito C, et al. shows strain patterns that can help in diagnosis of various cardiomyopathies[34]

CARDIAC MRI

Cardiac magnetic resonance (CMR) plays an important role in the evaluation of HF, particularly for structural, functional and myocardial tissue assessment. CMR provides comprehensive anatomic and functional assessment of the heart, including accurate left and RV ejection fractions, diastolic parameters, and valvular assessment, which are crucial for diagnosing and classifying HF. Additionally, late gadolinium enhancement (LGE), T1/T2 mapping, T2* and extracellular volume quantification can provide

Table 3
Quantitative echocardiography parameters and their heart failure prognostic implications

Parameter	Value	Prognosis
LVIDD	>61 mm (Women), >68 mm(Men)	Poor prognosis in DCM[23]
LV Mass	>298g	Higher risk of sudden cardiac death[81]
LVEF	<35%	Higher risk of sudden cardiac death[82]
SIQPS	> 0.65	Predictor for MACE[26]
LVAI	$\geq$40 mL/m^2	Predictor of cardiac mortality[83]
Left Atrial Strain	<23%	Predictor of worse outcomes in HFpEF[84]

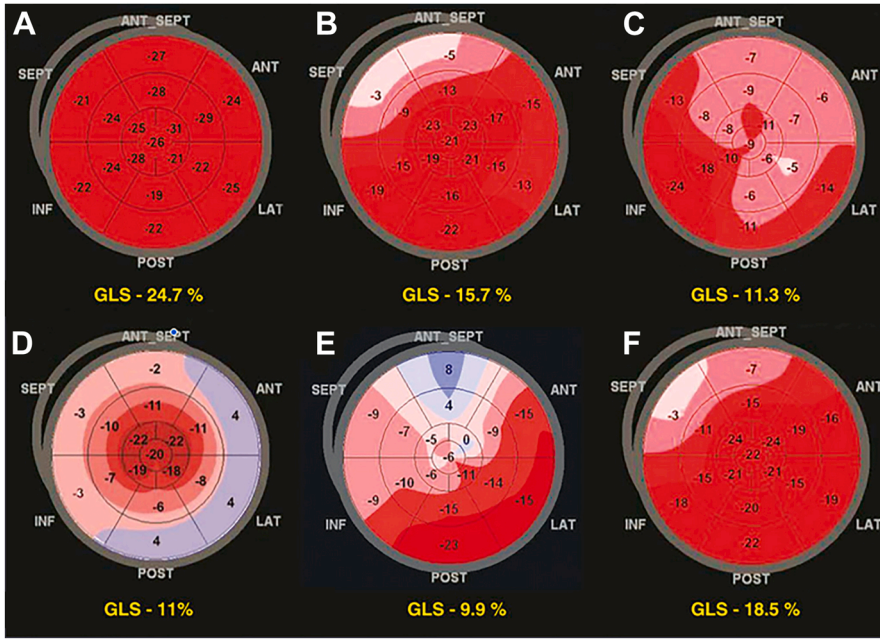

Fig. 1. Bull's eye maps of GLS depicting different patterns of LV hypertrophy: a normal subject (*A*), hypertension (*B*), hypertrophic cardiomyopathy (*C*), amyloidosis with the classical *apical-sparing* pattern (*D*), anterior myocardial infarction (*E*), and aortic stenosis with hypertrophy of basal segments (*F*). (Zito, Concetta et al., Ten Years of 2D Longitudinal Strain for Early Myocardial Dysfunction Detection: A Clinical Overview, BioMed Research International, 2018, 8979407, 14 pages, 2018. https://doi.org/10.1155/2018/8979407.)

a more detailed evaluation of myocardial tissue, identifying the presence and pattern of fibrosis, edema, or other changes that offer insights into the underlying cause of cardiomyopathy and its prognosis.[35]

CMR can help diagnosis specific etiologies of HF such as sarcoidosis, hemochromatosis, amyloidosis, and myocarditis through advanced tissue characterization. The comprehensive detailed evaluation assists in the diagnosis and prognosis of HF.

Myocardial Tissue Characteristics

Late gadolinium enhancement

LGE is a CMR technique using gadolinium contrast and is particularly useful in identifying areas of myocardial fibrosis. Gadolinium contrast exhibits differential distribution between normal and abnormal myocardial tissue, with increased extracellular uptake and delayed washout in areas affected by fibrosis, necrosis, or inflammation. LGE is one of the most widely used CMR techniques and can identify the etiology of HF through the pattern of fibrosis and give prognostic information relating to the amount of fibrosis. Ischemic cardiomyopathy typically demonstrates subendocardial or transmural LGE, while nonischemic cardiomyopathies can demonstrate midmyocardial, subepicardial, diffuse, or patchy LGE, or subendocardial patterns depending on the underlying cause of the cardiomyopathy (**Fig. 2**).

The presence and extent of LGE has prognostic implications and has been shown to be an independent risk factor for adverse cardiac events in patients with advanced HF.[36] A meta-analysis involving 15,217 patients demonstrated that the presence of

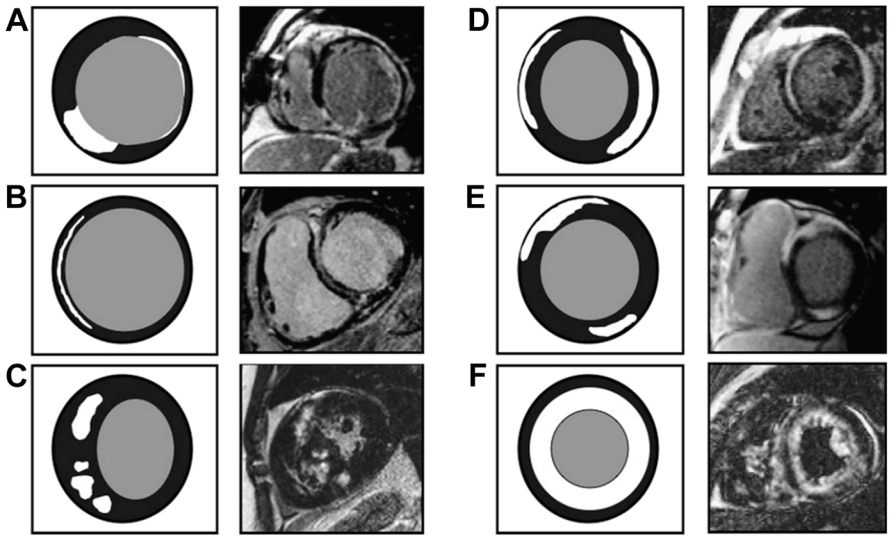

Fig. 2. Characteristic patterns of late enhancement in specific cardiomyopathies. (*A*) Ischemic cardiomyopathy: regional thinning with 50% transmural scar in lateral wall and 100% transmural scar in inferoseptal wall. (*B*) Idiopathic dilated cardiomyopathy: mid-wall late enhancement in the basal septum. (*C*) HCM: patchy late enhancement within septum. (*D*) Myocarditis: epicardial-zone late enhancement in inferolateral and anteroseptal walls. (*E*) Sarcoidosis: dense epicardial-zone late enhancement. (*F*) Amyloidosis: diffuse late enhancement progressing from subendocardium to epicardium (pattern may also be seen in uremic cardiomyopathy and post heart transplantation).[85] (James A. White, Manesh R. Patel, The Role of Cardiovascular MRI in Heart Failure and the Cardiomyopathies, Magnetic Resonance Imaging Clinics of North America, 15 (4), 2007, 541-564, https://doi.org/10.1016/j.mric.2007.08.009.)

any LGE was associated with an odds ratio of 3.99 for major ventricular arrhythmic events, 2.14 for all-cause mortality, and 2.53 for HF hospitalization.[37] Further, the extent of LGE is independently correlated with the risk of all-cause mortality, arrhythmia, and major adverse cardiac events.[38] The correlation of adverse outcomes, including all-cause mortality, major adverse cardiac events, and HF hospitalizations, has also been shown in patients with HFpEF.[39]

Given that LGE is a marker of myocardial fibrosis, its presence and extent have also been shown to predict the likelihood of LV recovery after medical therapy or revascularization. Multiple studies have shown that the absence of LGE in nonischemic cardiomyopathy increases the likelihood of reverse remodeling of the LV in response to therapy.[40,41] In patients with chronic ischemic cardiomyopathy with LV dysfunction, the presence and extent of LGE is negatively associated with the likelihood and time course of contractile improvement.[42]

T1/T2 mapping, T2*, extracellular volume

CMR sequences can further characterize myocardial tissue providing valuable insight into pathological changes, aiding in the identification of specific causes of and extent of the cardiomyopathy. T1 mapping evaluates the longitudinal relaxation time of myocardial tissue, which reflects alterations in the interstitial space and extracellular volume fraction. Elevated T1 values are associated with myocardial fibrosis, amyloidosis, and myocarditis, while reduced T1 values may indicate conditions such as Fabry disease or iron overload.[43] T2 mapping, which measures the transverse relaxation

time, is sensitive to myocardial edema and inflammation. The T2 sequence is particularly valuable in identifying inflammation during the acute phase of myocardial injury, as it highlights areas of edema and inflammatory processes that contribute to myocardial damage in various forms of HF, including myocarditis and acute ischemic events.[44] It is particularly useful in HF caused by hemochromatosis or transfusion related iron overload identifying iron deposition with magnetic field distortions and a shorter T2* signal time. Further, the degree of T2* time shortening is correlated with the degree of iron overload. T2* time below 20 milliseconds indicates significant iron deposition, while below 10 milliseconds is associated with high risk of HF and arrhythmia.[45,46] Increased extracellular volume (ECV) has been shown to correlate with multiple clinical outcomes, including increased risk of death and HF hospitalization.[47,48] The combination T1/T2 mapping, T2* and ECV offers a comprehensive myocardial tissue assessment, allowing clinicians to better understand the underlying pathophysiology, monitor disease progression, and assess disease prognosis.

Quantitative assessment

CMR is widely recognized as the *reference standard* for quantitative assessment of the heart and is superior to echocardiogram in accuracy and reproducibility for quantifying chamber size, ejection fraction, and myocardial mass, all of which are important prognostic markers in HF.[49] CMR plays a valuable role when echocardiogram images are suboptimal or further information regarding HF is required.[35] CMR allows for accurate quantification of regurgitant volumetrics in valvular disease. CMR can also identify and grade diastolic dysfunction, with strong agreement with echocardiographic measurements, and is a reliable alternative for diastolic assessment.[50,51] Lastly, myocardial strain derived from feature tracking on CMR has been shown to be a significant independent predictor of adverse outcomes in patients with chronic dilated cardiomyopathy.[52]

Cardiac stress MRI

Stress MRI is an emerging noninvasive tool that assesses myocardial ischemia, viability, and cardiac function. It demonstrates high sensitivity and specificity for functionally significant coronary artery disease and is particularly useful in patients with challenging imaging characteristic.[53] Stress MRI provides a single test comprehensive assessment that can detect CAD including microvascular disease, as well as anatomic, functional, and myocardial tissue characterization listed above.

NUCLEAR IMAGING

Nuclear myocardial perfusion imaging with single photon emission computed tomography (SPECT) is widely used for CAD. It can be utilized in diagnosing the cause of HF. Cardiac PET imaging allows us to use myocardial flow reserve, which can help differentiate the causes of HF such as epicardial disease versus microvascular dysfunction. This is particularly important in patients with HFpEF, as microvascular dysfunction has been associated with poor prognosis.[54,55]

The PAREPET study looked at 204 patients with LVEF less than 35% undergoing assessment of primary prevention ICD placement. Utilizing PET the authors quantified the uptake of a catecholamine analog throughout the myocardium as a measure of "cardiac denervation." It was found that patients with a higher burden of cardiac denervation had a higher risk of sudden cardiac death.[56]

Cardiac PET also excels in detecting cardiac sarcoidosis and amyloidosis via fluorodeoxyglucose (FDG) and technetium-pyrophosphate tracers, respectively. FDG-PET is also a valuable tool in assessing the extent of infection, such as prosthetic valve endocarditis.

Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog that is labeled with iodine-123 to quantify cardiac sympathetic innervation, which plays a prognostic role in HF. In HF, the sympathetic nervous system is often overactivated, leading to increased norepinephrine release and subsequent downregulation or dysfunction of adrenergic nerve terminals. This dysfunction can be captured by reduced MIBG uptake. The ADMIRE-HF study demonstrated that reduced MIBG uptake was associated with higher risk of HF progression, arrhythmic events, and cardiac death.[57] MIBG use has been recommended in the Japanese Circulation Society guidelines; however, a consensus has not been established in the European or North American guidelines.[58] This may be due to the need for further validation, cost, and competing risk assessment modalities.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) remains the gold standard for assessing functional capacity in HF, quantifying peak oxygen consumption (VO_2) and the VE/VCO_2 slope, both powerful prognostic markers. The HF-ACTION trial established that peak VO_2 less than or equal to14 mL/kg/min predicts higher mortality and guides transplant eligibility. A VE/VCO_2 slope greater than 35 is associated with a 3.5-fold increased risk of death, independent of LVEF. CPET also identifies exercise oscillatory breathing, a marker of autonomic dysfunction linked to poor outcomes. guidelines recommend CPET for risk stratification in advanced HF, while the 2022 AHA/ACC/HFSA guidelines emphasize its role in transplant and mechanical circulatory support candidacy.

CARDIAC COMPUTED TOMOGRAPHY

Cardiac computed tomography angiography (CCTA) is pivotal in both HFrEF and HFpEF for excluding CAD and assessing coronary calcification. Computed tomography (CT) can often reliably and noninvasively exclude obstructive coronary disease as an etiology of HF, and according to the most recent chest pain guidelines, it is a class I indication for the evaluation of chest pain.[59]

HEART CATHETERIZATION

Left and right heart catheterization is an invasive procedure but a valuable tool for the assessment of HF. Coronary angiography via left heart catheterization is the gold standard for assessing for coronary disease and classification of the cardiomyopathy as ischemic or nonischemic. Direct pressure measurement in the LV can determine the LV end-diastolic pressure (LVEDP), which is useful for the volume status in HFrEF and HFpEF. Elevated LVEDP measurements can also help confirm HFpEF in patients with unclear diagnosis, and exercise induced elevations of LVEDP can indicate diastolic dysfunction, which is a hallmark of HFpEF.[60]

Right heart catheterization (RHC) is essential for assessing pulmonary pressure and RV function. It is especially useful for distinguishing between different types of pulmonary hypertension, which can significantly impact the management and prognosis of HF. RHC is also useful in cases of HF where the volume status or hemodynamics are uncertain, and filling pressures and cardiac output need to be determined.[61]

6-MINUTE WALK TEST

Although the 6-minute walk test (6MWT) is less prognostically robust than CPET, it provides a simple measure of functional capacity.[62] A distance of less than 300 m

correlates with the New York Heart Association class III-IV symptoms and higher hospitalization rates, although the 2018 AHA scientific statement notes that it lacks independent prognostic power compared to CPET parameters. Its role is limited to baseline functional assessment in resource-limited settings.

The 2022 ACC/AHA/HFSA guidelines endorse multimodality imaging to differentiate HF phenotypes, with nuclear/PET imaging for ischemia/viability, CT for anatomic assessment, and CPET for functional profiling. The ESC guidelines similarly prioritize CPET and advanced imaging to tailor therapy.[6] Emerging data from trials such as MR-INFORM support the superiority of stress CMR in guiding revascularization, but nuclear and PET imaging remain the cornerstone modalities for ischemia evaluation.[63] Collectively, these tools refine risk prediction, optimize therapeutic strategies, and improve outcomes in HF management.

GENETIC TESTING

Genetic testing plays an important role in determining the etiology of specific types of HF, including dilated, hypertrophic, restrictive, arrhythmogenic, and noncompaction cardiomyopathies. The ACC/AHA (Class IB) recommends genetic counseling and screening for patients with first-degree relatives with known genetic cardiomyopathy and for select patients with nonischemic cardiomyopathy to identify potential treatment for the patient and their family members.[35] Genetic testing can be considered when there is a known family history of genetic cardiomyopathy or if the patient's phenotype suggests a genetic cause. It is important to note that there is a significant overlap of phenotype per gene, and the genes often have variable penetrance, which can affect prognosis. The cardiomyopathic phenotypes and genetic testing implications for diagnosis and prognosis are discussed below.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is genetically heterogeneous, with mutations identified in over 50 genes, including those encoding cytoskeleton, mitochondria, nucleoskeleton, and calcium handling proteins. Genetic testing should be considered in patients with idiopathic DCM when no other cause can be identified, especially if there is a family history of DCM or concurrent conduction disease or ventricular arrhythmia.[64] Genetic variants are implicated in 25% to 40% of patients with a positive family history, and 10% to 25% of patients without a recognized family history.[65–67] If a genetic variant is identified, it can be useful in further genetic counseling for the patient's family and for risk stratification. Several pathogenic variants are associated with an increased risk of sudden cardiac, such as LMNA and desmosomal genes such as DSP.[68] In these patients, special consideration should be given to early ICD placement. Genetic panels often include dozens of genes implicated in DCM, but the most common and recommended for inclusion in gene panels are BAG3, DES, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNT2, TTN, and DSP.[64] When there is a known genetic mutation in a family member, targeted genetic testing for that gene can be ordered; otherwise, the full cardiomyopathy genetic panel is typically used.

Hypertrophic Cardiomyopathy

Genetic testing is recommended by the AHA/ACC for patients with phenotypic hypertrophic cardiomyopathy (HCM) and is an important tool for the diagnosis and management of patients and their families. Genetic panel testing identifies implicated genetic variants in 30% to 60% of patients with HCM.[69,70] Genetic variants in HCM commonly

encode sarcomeric proteins, and genetic testing panels include at least 8 sarcomeric proteins: MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1. Disorders that may mimic HCM, including glycogen storage disease (PRKAG2), Danon disease (LAMP2), Fabry's disease (GLA), and amyloid (transthyretin), are also often tested.[64] If genetic testing reveals implicative genetic variations, genetic counseling and testing can be performed on potentially affected family members.

The prognostic implications of genetic testing in HCM are significant, as certain pathogenic variants carry a worse prognosis, including earlier disease onset and higher incidences of sudden cardiac death, arrhythmia, HF, and mortality. The MYH7 (myosin heavy chain) gene, which accounts for 40% to 45% of familial HCM, had earlier disease onset and a 2.7 fold higher risk of major adverse events.[71] The MYBPC3, which accounts for 15% to 25% of familial HCM, have higher rates of systolic dysfunction when compared to MYH7 patients.[72] Despite variations in risk, genetic testing alone should not be the sole determinant for ICD placement, and ICD placement in HCM should incorporate a comprehensive risk assessment.[64,69]

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is a relatively rare form of cardiomyopathy that is sometimes associated with genetic mutations. The main genetic causes of restrictive cardiomyopathy are genetic variants of the transthyretin protein causing hereditary amyloidosis; however, many of the genetic mutations that cause HCM can present with a restrictive phenotype. Genetic testing should be considered in patients diagnosed with amyloidosis or restrictive cardiomyopathy of unknown cause.[64] Cardiac amyloidosis often presents as RCM, and patients diagnosed with cardiac amyloidosis should be genetically tested to determine whether the protein misfolding is due to a hereditary variant (variant transthyretin amyloidosis [ATTR]) or wild-type ATTR (ATTRwt). Patients with variant ATTR generally have an earlier onset of disease, a more rapid disease prognosis, and higher mortality rates than those with ATTRwt. There are over 130-point mutations in the transthyretin gene, with some having significantly worse prognoses with earlier onset and worse mortality. For example, the V122I genotype is associated with earlier symptoms and increased mortality.[73]

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is characterized by fibrofatty replacement of the myocardium, which can affect both the RVs and LVs. Once ACM is diagnosed, patients should be offered genetic testing.[64,74] Approximately 50% to 66% of patients with ACM will have a positive genetic test, with desmosomal mutations comprising more than 50% of the positive tests, with the PKP2 variant being the most common.[75] There is significant phenotypic variability in patients with similar genetic variations. Nonetheless, early ICD therapy could be considered for phenotypic ARC with genetic mutations of high arrhythmogenic risk genetic mutations (such as FLNC, DSP, LMNA, DES, and PLN).

Noncompaction Cardiomyopathy

Noncompaction cardiomyopathy (NCCM) is characterized by prominent LV trabeculations and deep intraventricular recesses, which can impair myocardial function and cause HF. Genetic abnormalities, the most common being MYH7, MYBPC2, and TTN, are implicated in 17% to 41% of NCCM cases testing should be considered especially if there is a family history of HF.[64,76]

MULTIVARIABLE RISK MODELS

Risk models have been developed to combine patient information, biomarkers, and imaging studies to provide a comprehensive risk assessment in the short and long term. The ACC/AHA recommends using risk calculators to help guide treatment and prognosis for patients with HF.[77] The most established risk models for chronic HF include the Seattle heart failure model,[78] the heart failure survival score[79] and the meta-analysis global group in chronic heart failure risk score.[80]

SUMMARY

The integration of diagnostic and prognostic tools discussed in this article; biomarkers, imaging modalities, genetic testing, and functional assessments, has enhanced the management of HF. These tools allow a comprehensive evaluation of HF etiology, treatment, and risk stratification. The ongoing advancements in HF diagnostics and prognostics hold promise for even more precise and personalized patient care in the future.

CLINICS CARE POINTS

- Diagnosis and staging of heart failure (Stage A-D) can help identify at risk patient and slow progression.
- Diagnosis of heart failure can be made using key history, physical exam findings, biomarkers, and echocardiogram.
- Early identification of Stage C and D heartfailure patients can improve mortality and reduce hospital readmissions.
- The use of multimodality imaging such as echocardiography, cardiac MRI, nuclear stress testing, and invasive cardiac testing can aid in diagnosis and identification of etiology of heart failure.

DISCLOSURES

The authors have nothing to disclose.

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