Cardiomyopathy is a fundamental platform on which modern cardiology is based. Modern advanced imaging techniques not only allow more rigorous assessment, including determination of cause and of remodeling of several cardiovascular diseases, but also earlier disease detection. Basic diagnostic considerations that include clinical history and physical examination, laboratory testing, and electrocardiography do not always provide adequate information, whereas endomyocardial biopsy, often regarded as the gold standard for tissue diagnosis of cardiomyopathy, is fraught with sampling error and patient risk. These diagnostic difficulties have thus led to the increasing importance of different imaging modalities in the assessment of cardiomyopathies. The focus of modern imaging techniques is to characterize accurately the anatomic and functional status of the cardiac chambers and attempt to establish the cause of the cardiac disorder. The ability to quantify these parameters precisely with imaging techniques helps in accurate functional assessment and risk stratification and guides therapeutic decisions. We present the current state-of-the-art imaging of cardiomyopathies with special emphasis on the presentation of novel imaging techniques that might become useful in the near future for easier and more accurate diagnosis.

Modem Imaging Techniques in Cardiomyopathies

M. Fuad Jan, A. Jamil Tajik

Abstract: Modern advanced imaging techniques have allowed increasingly more rigorous assessment of the cardiac structure and function of several types of cardiomyopathies. In contemporary cardiology practice, echocardiography and cardiac magnetic resonance imaging are widely used to provide a basic framework in the evaluation and management of cardiomyopathies. Echocardiography is the quintessential imaging technique owing to its unique ability to provide real-time images of the beating heart with good temporal resolution, combined with its noninvasive nature, cost-effectiveness, availability, and portability. Cardiac magnetic resonance imaging provides data that are both complementary and uniquely distinct, thus allowing for insights into the disease process that until recently were not possible. The new catchphrase in the evaluation of cardiomyopathies is multimodality imaging, which is purported to be the efficient integration of various methods of cardiovascular imaging to improve the ability to diagnose, guide therapy, or predict outcomes. It usually involves an integrated approach to the use of echocardiography and cardiac magnetic resonance imaging for the assessment of cardiomyopathies, and, on occasion, single-photon emission computed tomography and such specialized techniques as pyrophosphate scanning.

Key Words: cardiomyopathies ■ echocardiography ■ magnetic resonance imaging

Cardiac imaging is a fundamental platform on which modern cardiology is based. Modern advanced imaging techniques not only allow more rigorous assessment, including determination of cause and of remodeling of several cardiovascular diseases, but also earlier disease detection. Basic diagnostic considerations that include clinical history and physical examination, laboratory testing, and electrocardiography do not always provide adequate information, whereas endomyocardial biopsy, often regarded as the gold standard for tissue diagnosis of cardiomyopathy, is fraught with sampling error and patient risk. These diagnostic difficulties have thus led to the

From Aurora Cardiovascular Services, Aurora Sinai/Aurora St. Luke’s Medical Centers, Milwaukee, WI.
Correspondence to A. Jamil Tajik, MD, Cardiac Specialty Center, Aurora St. Luke’s Medical Center, 2801 W. Kinnickinnic River Pkwy, Ste. 840, Milwaukee, WI 53215, E-mail publishing14@aurora.org
© 2017 American Heart Association, Inc.
Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.117.309600
Echocardiography

Because of its unique ability to provide real-time images of the beating heart combined with its noninvasive nature, images with high spatiotemporal resolution, cost-effectiveness, availability, and portability, echocardiography is the customary initial diagnostic imaging modality of choice in patients with known or suspected cardiomyopathy. It is invaluable in the assessment of cardiac structure and function, providing an excellent assessment of chamber size, wall thickness, ejection fraction (EF), diastolic function, valvular function, intracardiac and pulmonary artery pressure estimations, stroke volume and cardiac output, and wall motion abnormalities.

Echocardiography has made dramatic strides from the first use of unidimensional M mode echocardiography in 1958 to today’s complex real-time 3-dimensional echocardiography (3DE) and myocardial deformation imaging. In fact, the most recent echocardiographic guidelines from the American Society of Echocardiography emphasize the advantages of 3DE because it does not rely on geometric assumptions and recommend that 3DE measurements be used when available and feasible.7

In addition to having an immense influence on the diagnosis of cardiomyopathies, echocardiography improves our understanding of the underlying pathobiology. Echocardiography has been identified as being among the top advances in cardiovascular medicine in the 20th century8 and continues to improve, taking advantage of technological advances in computer processing and engineering.

Modern echocardiographic techniques utilized in the diagnostic evaluation of cardiomyopathies include

- Two-dimensional echocardiography (2DE)
- Color Doppler
- Spectral Doppler
- Tissue Doppler imaging (TDI)
- 2D strain; vector velocity imaging
- Torsion
- Contrast
- 3DE

Echocardiography is key to the diagnostic evaluation of cardiomyopathies and includes a comprehensive 2D imaging of the cardiac structure with 3D imaging for quantification of left ventricular (LV) volumes and LVEF. Comprehensive hemodynamic assessment and evaluation of valves is undertaken with tissue, color, pulsed-wave, and continuous-wave Doppler imaging. Newer measurements based on 2D speckle-tracking and tissue velocity imaging allow for more sophisticated assessment of ventricular function and synchrony,9 whereas strain and torsion echocardiography (newer imaging techniques) provide accurate and reliable quantitative assessment of myocardial mechanics.

Two-Dimensional Echocardiography

LV Assessment: Size, Morphology, and Function

Visual presentation of high-resolution images in real time has led to the routine use of 2DE to quantify cardiac chamber size and function. Indeed, visual estimation of EF is widely used, and it has been shown that the eye of an experienced observer is comparable to the measurement made using a trackball to define the LV boundaries.10 Regional myocardial function is assessed on the basis of the wall thickening and endocardial motion of the myocardial segment (a 17-segment model being the standard practice in modern echocardiography).7

Quantification of LV volumes and systolic function by 2DE provides valuable diagnostic, prognostic, and therapeutic information. LVEF is measured and derived from 2DE assessment using LV volume. The method recommended for this measurement is the Simpson biplane method with a manual digitalization of the endocardial boundaries, ideally from the apical 4-chamber and the apical 2-chamber views.11 This approach provides the most recognized measure of LV systolic function and is predictive of net adverse cardiovascular events (heart failure [HF], arrhythmias, and death).12,13 LVEF derived from 2DE correlates well with LVEF derived by cardiac magnetic resonance (CMR) imaging although echocardiographic LV volumes tend to be underestimated owing to limitations of geometric assumptions and of image quality.14,15

Serial 2DE Follow-Up Also Enables Evaluation of Disease Progression or Regression

Although appropriate frequency of serial imaging in cardiomyopathies is patient specific and may be subject to debate, repeat imaging usually is performed with a change in clinical status and to assess response to therapy. Echocardiography provides great reproducibility on serial measurements of LV volumes. Recent analysis shows that patients with HF and recovered EF may be clinically distinct from those with persistently preserved or reduced LVEF with lower mortality, less frequent hospitalizations, and fewer composite end points.16

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DE</td>
<td>Two-dimensional echocardiography</td>
</tr>
<tr>
<td>3DE</td>
<td>Three-dimensional echocardiography</td>
</tr>
<tr>
<td>AHCMP</td>
<td>Apical hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>ARVD/C</td>
<td>Arrhythmogenic right ventricular dysplasia/cardioamyopathy</td>
</tr>
<tr>
<td>CCT</td>
<td>Cardiac computed tomography</td>
</tr>
<tr>
<td>CMR</td>
<td>Cardiac magnetic resonance</td>
</tr>
<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>HCM</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrium/left atrial</td>
</tr>
<tr>
<td>LGE</td>
<td>Late gadolinium enhancement</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle/left ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVNC</td>
<td>Left ventricular noncompaction</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>NICM</td>
<td>Nonischemic cardiomyopathies</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>RCM</td>
<td>Restrictive cardiomyopathy</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle/right ventricular</td>
</tr>
<tr>
<td>SAM</td>
<td>Systolic anterior motion</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
</tr>
<tr>
<td>TDI</td>
<td>Tissue Doppler imaging</td>
</tr>
<tr>
<td>TTC</td>
<td>Takotsubo cardiomyopathy</td>
</tr>
</tbody>
</table>
Dilated Cardiomyopathy

The phenotype of dilated cardiomyopathy (DCM) is defined principally by cardiac enlargement and impaired systolic function, both of which are detected reliably by echocardiography (Figure 1). Echocardiography usually reveals that the LV is dilated in DCM (Figure 1), has normal wall thickness, has increased mass, and has decreased systolic function with reduced LVEF, stroke volume, and cardiac output. The commonly accepted criteria for LV dilation in adults include an LV internal diastolic dimension of >2.7 cm/m² of body surface area. LV volume is best calculated using the biplane method of disks summation technique; in laboratories with experience in 3DE, 3D measurement and reporting of LV volumes is recommended, wherever it is available.

Hypertrophic Cardiomyopathy

Two-dimensional echocardiography is an essential part of the evaluation of all patients with established or suspected hypertrophic cardiomyopathy (HCM) and is now the gold standard for establishing its morphological and hemodynamic characteristics. The presence of a localized or generalized thick ventricle (>15 mm; average, 20–22 mm) in the absence of hypertension or other factors likely to cause pressure overload or an infiltrative state is the initial clue to the presence of HCM.

Figure 1. Dilated cardiomyopathy. Apical 4-chamber view recorded in diastole in a patient with idiopathic dilated cardiomyopathy. Note the marked dilation of the left ventricle (LV). In this example, dilation of both the right and left atria (RA and LA, respectively) is also observed with a trace pericardial effusion noted as well (arrows). RV indicates right ventricle.

Figure 2. Hypertrophic cardiomyopathy (HCM). This figure demonstrates septal morphology in a patient with HCM. A, Parasternal long-axis view in diastole recorded in a young patient with HCM. Note the massive asymmetrical hypertrophy of the ventricular septum (4.3 cm, black arrow) compared with the posterior wall (1.1 cm, white arrow). The convexity of the septum is best described as reverse-curve septum (convexity toward LV cavity). B, Short-axis view of the same patient. Again note the marked hypertrophy of the mid and inferior ventricular septum (black arrow) with no hypertrophy of the true posterior wall (white arrow). Note the hypertrophic anterolateral papillary muscles.

The most common pattern of hypertrophy involves the anterior or interventricular septum, less common is hypertrophy of the anterolateral wall and inferior septum (Figures 2 and 3), and involvement of the posterior wall. However, the phenotypic involvement in HCM is varied, and various morphologies may be present. Sigmoidal HCM (hypertrophy localized to the basal and middle septum) and reverse-curve HCM (hypertrophy of the entire septum) represent the 2 most prevalent anatomic subtypes of HCM.

Two-dimensional echocardiography also allows the recognition of apical HCM (ApHCM), an uncommon, yet unique phenotypic variant of HCM in which hypertrophy is localized to the LV apex with or without midsegment involvement and with or without the formation of an apical aneurysm. Involvement of the LV apex (with or without an apical aneurysm) is the sine qua non of ApHCM, and thickness of the LV apical wall of >15 mm is considered a diagnostic hallmark. However, because the apex is normally the thinnest part of the LV, a lower threshold (13–15 mm) may be used to diagnose ApHCM when the clinical picture and other characteristics (electrocardiography, family history, gene typing, CMR imaging, Doppler interrogation, etc.) also lend themselves to the diagnosis of ApHCM.

A thick ventricle on echocardiography should not necessarily be identified with HCM, and a differential diagnosis should always be generated. This may involve, but is not restricted to (1) hypertension, (2) valvular aortic stenosis, (3) chronic kidney disease (especially dialysis dependent), (4) amyloidosis (Figure 4), (5) athlete’s heart, (6) metabolic disease, for example, Hurler and Hunter syndromes, (7) infiltrative cardiomyopathy, for example, Anderson–Fabry disease, Pompe disease, Danon disease, or (8) syndromic HCM, for example, Noonan syndrome, Friedreich’s ataxia, or LEOPARD syndrome, which are discussed in other articles in the Compendium.

In addition to the characteristic morphological appearance of the LV, 2DE is helpful in defining the site of obstruction in HCM, as determined by visualizing the area of the systolic anterior motion (SAM)–septal contact. Although LV outflow tract obstruction in classic HCM is known to occur at the most
basal portion of the septum, the obstruction may also extend into the LV from SAM of the chordal apparatus (chordal SAM). Midventricular obstruction in which a hypertrophied papillary muscle abuts the interventricular septum can also be identified.

**Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**

Two-dimensional echocardiography usually is the first-line imaging modality used in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), which is characterized by fibrofatty replacement of the right ventricular (RV) myocardium (RV outflow tract, the base of the RV, and the RV apex—triangle of dysplasia) leading to RV failure and arrhythmias.\(^{21,22}\) 2DE serves as an ideal screening tool for the assessment of RV size and function in patients with possible ARVD/C and also is of great value in the serial evaluation of disease progression in patients with established ARVD/C. Because the RV may be enlarged and therefore not completely visualized on standard imaging planes, additional off-axis images are routinely obtained when ARVD/C is suspected to ensure that all parts of the RV free wall are well visualized. This is especially important in detection of localized RV aneurysms, given the patchy nature of this disease.

Echocardiography typically shows RV dilation. In the 2010 task force criteria, a major criterion for ARVD/C is fulfilled when there is RV outflow tract dilation on the parasternal long-axis (≥32 mm) or short-axis (≥36 mm) view, along with localized akinesia, dyskinesia, or aneurysms. The presence of a wall motion abnormality with only mild dilation (≥29 to <32 mm for parasternal long axis and ≥32 to <36 mm for parasternal short axis) is a minor criterion. For both major and minor criteria, however, a segmental wall motion abnormality needs to be present (regional akinesia or dyskinesia). Because RV dilation is not specific to ARVD/C and has been reported as a physiological adaptation to high-intensity exercise,\(^{23}\) the diagnosis of ARVD/C in highly trained athletes can be challenging.\(^{24}\) In addition to RV enlargement, several morphological abnormalities including trabecular prominence (thickened, hypertrophied trabeculae that occupy a significant amount of the RV cavity at end diastole), derangement, and focal aneurysms or sacculations are noted on 2DE in individuals with ARVD/C.

Global RV function also is affected in ARVD/C, and although challenging to estimate on 2DE, finding RV volume and function by conventional 2DE is attempted by calculating the RV fractional area change from the apical 4-chamber view. Thus, in the 2010 task force criteria, the presence of severe RV dysfunction (RV fractional area change ≤33%) combined with a localized wall motion abnormality constitutes a major diagnostic criterion, whereas mild RV dysfunction (RV fractional area change >33%–≤40%) constitutes a minor criterion.

**Restrictive Cardiomyopathy**

This includes a group of conditions with distinct morphological and hemodynamic characteristics of a nondilated (or minimally dilated) LV with typically normal wall thickness and markedly dilated atria (Figure 5).\(^{24}\) The ventricular walls are rigid, resulting in severe diastolic dysfunction and restrictive filling with elevated filling pressures and a generally normal LVEF. Most cases are secondary to an identifiable disease, but some cases have no clear cause (idiopathic restrictive cardiomyopathy [RCM]). The diverse causes that usually lead to RCM are characterized by intrinsic abnormalities of the myocyte and the intercellular matrix (interstitial infiltration and fibrosis) that result in impaired LV relaxation and increased LV stiffness with abnormal LV diastolic filling, usually in the absence of LV dilation. The most common of these include (1) amyloidosis, (2) Anderson–Fabry disease, (3) Danon/Pompe/PRKAG2, (4) Friedreich’s ataxia, (5) hemochromatosis, (6) endomyocardial fibrosis, (7) hypereosinophilic syndrome, (8) post-irradiation, and (9) drug induced (eg, chloroquine, hydroxychloroquine).

Early in the course of these conditions, echocardiography typically reveals the nonspecific morphological alterations that characterize the RCM phenotype, that is, thickened LV walls, normal or mildly increased RV wall thickness, and, usually, a preserved LVEF.
Cardiac amyloidosis (Figure 4) is a prototypical RCM that arises from the aggregation of insoluble deposits of misfolded proteins,25 which is classically displayed as apple-green birefringence under polarized light microscopy with Congo Red staining. The findings of cardiac amyloidosis (stiff heart syndrome) include increased wall thickness (≥15 mm) with a normal or small LV cavity, normal or decreased LVEF, restrictive filling pattern, valvular regurgitation, and dilated atria; occasional dynamic LV outflow obstruction may coexist and might be confused with HCM.26 In addition, 2DE may demonstrate pericardial effusion and thickened RV walls and cardiac valves. Some of the latter cases may present as severe mitral regurgitation (MR).27 Occasionally the amyloid deposits may show a granular sparkling because of increased granular myocardial echogenicity.

**Other Cardiomyopathies**

**LV Noncompaction Cardiomyopathy**

Two-dimensional echocardiography is usually the first-choice imaging technique that brings forth the diagnosis of LV noncompaction (LVNC), a genetic cardiomyopathy3,28 (Figure 6).

Echocardiographic criteria include30

- The presence of prominent LV trabeculations, predominantly in the apical and midventricular areas of both the inferior and lateral walls.

- Two-layered appearance of the myocardium with a thin, compacted outer (epicardial) band and a thicker, noncompacted inner (endocardial) layer. The thicknesses of the compacted and noncompacted sections of the myocardium are best measured in short-axis views at end-diastole.

- Multiple deep intertrabecular recesses communicating with the ventricular cavity, as visualized on color Doppler imaging.

- Systolic thickness of compacted myocardium <8 mm.31

A dedicated echocardiographic approach to diagnosing LVNC includes an evaluation of the sizes of the trabeculations (noncompacted myocardium) in relation to compacted wall thicknesses in multiple imaging windows and at different ventricular levels during different phases of the cardiac cycle, while diligently searching for identification of the bilayered myocardium (compacted and noncompacted) in the short-axis views at the mid and apical levels and in the apical 4-chamber and apical long-axis views.29

The extreme variability of the LV trabecular anatomy and the lack of consensus about uniformly accepted standards of diagnosis influence both epidemiology and interpretation of imaging data.32 Thus, the prevalence of hypertrabeculation and LVNC is increasingly reported in large echocardiographic series33 and carries the risk of forcing a morphological marker in rigid numbers/ranges, being aware that the individual variability of the trabecular anatomy is vast. False-positives are best avoided with a meticulous technique with critical attention to obtaining short-axis images perpendicular to the ventricular long-axis view and avoiding oblique and tangential views (noncircular LV cavity appearance) for measurement of noncompacted and compacted layers. It also should be noted that the noncompacted myocardial layer is not always uniformly and evenly distributed along the apex and that the noncompacted layer location may be regional, with the apicolateral wall segment having the greatest predilection for noncompacted myocardium.29

**Takotsubo Cardiomyopathy**

Takotsubo cardiomyopathy (TTC), which is often triggered by both psychological and physiological stress, is characterized by transient LV dysfunction (LV at end-systole resembling a Japanese octopus fishing pot) in >1 coronary artery territory and remains an important differential diagnosis of acute coronary syndrome.34

In the acute phase of TTC, 2DE usually identifies the characteristic LV phenotype and its different morphological patterns according to the localization of wall motion abnormalities—circumferential, apical, midventricular, or basal distribution. In classic TTC, the apical segments are akinetic/dyskinetic (defined as apical ballooning); in contrast, the basal segments often are hyperkinetic. In midventricular TTC, akinesia is seen in the midventricular segments, mild hypokinesia, or normal contraction in the apical segments and hypercontractility in the base. Inverted TTC is characterized by 2 forms: apical sparing, with preserved apical function and severe hypokinesia of the remaining walls and basal or reverse TTC, with hypokinesia confined to the basal segments. In the acute phase, LVEF typically is reduced and recovers with resolution of myocardial stunning (mean time range to recovery, 7–37 d [average, 18 d], with the degree of LVEF reduction varying according to the severity of myocardial impairment,
higher lateral annular velocities, an average E/e’ ratio >14 is indicative of high filling pressures. 43,44 For estimation of LV filling pressures in cardiomyopathies, the E/e’ ratio is among the most reproducible echocardiographic parameters. The ability of this ratio to predict filling pressure has been demonstrated in patients with cardiomyopathies. 45,46 Assessment of LV filling pressures is important in patients with cardiomyopathies as it can successfully follow up patients at intervals and guide medical treatment. 47

**Tissue Doppler Imaging**

Tissue Doppler imaging (TDI) detects lower-velocity, higher-amplitude signals that arise from myocardial motion in contrast to high-frequency, low-amplitude signals from fast-moving red blood cells (Figure 8). This allows for a sensitive, robust, and reliable measurement of myocardial contraction velocity without relying on 2D imaging. 48,49 TDI, which measures absolute tissue velocity and can be performed in pulsed and color modes, allows measurement of regional tissue velocities, providing a means to quantify regional myocardial mechanics. Pulsed-wave TDI measures peak myocardial velocities and is well suited to the measurement of long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views.

TDI is used for the assessment of both systolic and diastolic function in patients with cardiomyopathies. The peak systolic myocardial velocity, reflective of longitudinal myocardial fiber shortening, is used to measure LV systolic function 50,51 and is even useful for detecting prehypertrophic HCM in genotype-positive and phenotype-negative individuals (subclinical LV systolic dysfunction). 52 Furthermore, systolic TDI velocity has demonstrated prognostic value for morbidity and mortality 53,54 and is an independent predictor of advanced LV diastolic dysfunction. 54

In a typical spectral display, the TDI-derived parameters used routinely in clinical echocardiography include
- myocardial systolic velocity—a positive waveform
- mitral annular early diastolic velocity (e’)—corresponding to early filling
- atrial contraction (a’)
- LV filling pressure (E/e’).
Thus, careful use of spectral and tissue Doppler echocardiography enables it to be a noninvasive representative of cardiac hemodynamics in cardiomyopathies—the so-called echo hemodynamics—plays a central role in hemodynamic assessment of HCM and its variants. HCM patients with SAM and mitral-septal contact have a typical shape on continuous-wave Doppler tracings. The Doppler tracing reveals an inflection point early in systole where the tracing changes from convex-to-the-left to concave-to-the-left (a point that generally occurs between a velocity of 1 and 2.5 m/s) and continues until peak velocity, the so-called dagger-shaped profile. This early systolic inflection point correlates temporally with the time of mitral-septal contact and beginning of the pressure gradient across the LV outflow tract. Dynamic obstruction may be absent in the basal resting state, and thus provocation with the Valsalva maneuver, inhalation of amyl nitrite, or exercise/patent ventricular contraction can unmask labile or latent obstruction. In midventricular hypertrophy with midcavity obstruction and apical pouch, blood may become trapped in the apex, leading to its own unique Doppler characteristics. Blood trapped by a narrowed neck may not emerge until the onset of diastole, beginning with the isovolumic relaxation phase, when it flows into the body of the LV. Such flow is termed paradoxical because it courses toward the mitral valve in diastole and is a sign of a concealed apical chamber.

Myocardial systolic velocity investigates the longitudinal contraction of the LV by the average peak systolic velocity of the mitral annulus using 2 positions, septal and lateral, from the apical 4-chamber view. The first percentile-based study with regard to both systolic and diastolic TDI parameters defined a large reference limit for the mean velocity for normal subjects aged 35 to 75 years (6.8–12.2 cm/s). Many patients with cardiomyopathy and a normal EF might have systolic and diastolic HF. In this setting, tissue velocity measures have demonstrated incremental and superior prognostic ability compared with standard echocardiographic measures, including EF.

In HCM, systolic velocities are attenuated despite a preserved or supranormal EF, even in myocardial segments that do not demonstrate overt hypertrophy. TDI also may help in the differentiation of various conditions resulting in LV hypertrophy, with demonstrable differences in TDI velocities between conditions of physiological hypertrophy (athlete’s heart) and pathological hypertrophy. Mean systolic annular motion <9 cm/s is a variable, which is useful in differentiating pathological LV hypertrophy (HCM/hypertensive LV hypertrophy) from physiological LV hypertrophy (diagnostic accuracy, 92%).

**Mitrail Valve (Structure, Function, Regurgitation)**

MR is seen frequently in DCM and HCM and is an important determinant of symptoms and outcome as well as of progressive ventricular remodeling. Careful assessment of mitral valve structure and function is of paramount importance in both cardiomyopathies. Specific attention should be directed toward elucidating the mechanism of MR and its accurate quantification. The distinction between a failing LV caused by severe MR and severe MR causing LV failure has important management implications. Even when MR is not severe, obtaining the spectral Doppler jet can provide important information about LV systolic function. The rate at which velocity increases is analogous to the measurement of LV dP/dt (normally >1200 mm Hg/s), a pre-ejection phase index of LV contractility that is especially useful in MR because LV function may be overestimated by the LVEF.

Color flow imaging by transthoracic echocardiography superimposes blood flow information on 2DE images in the form of a color-coded map, enabling evaluation of the velocity, direction, and coherence of blood flow. Color Doppler echocardiography can be used to qualitatively evaluate the mitral valve, including the direction and area of the regurgitant jet(s). Echocardiographic assessment usually involves evaluation of MR jet size, continuous-wave Doppler spectral intensity, pulmonary vein systolic flow reversal or blunting, and presence and size of vena contracta and proximal convergence. Quantification of the regurgitant volume and the effective regurgitant orifice area is performed by measuring the flow convergence or proximal isovelocity surface area although technical limitations exist with this method.

The usual mechanism of MR in DCM is failure of mitral valve leaflet coaptation primarily because of tethering of otherwise normal leaflets as a result of LV dilation and...
displacement of the papillary muscles and mitral annular dilation. The MR jet is usually centrally or posteriorly directed in the absence of anterior mitral valve leaflet prolapse. The true extent of the annular dilation and leaflet tenting can be measured accurately by 3DE.

Compared with DCM, from a pathophysiological standpoint, MR is a secondary phenomenon in HCM owing its origin to the eject-obstruct-leak mechanism.\textsuperscript{46} SAM of the mitral valve leads to a diminished systolic coaptation of the mitral leaflets and creates an interleaflet gap, resulting in MR. Classically, the MR jet is eccentric and directed posterolaterally (as the anterior leaflet is selectively pulled into the LV outflow tract), with maximum regurgitation occurring in mid and late systole and the severity of MR defined essentially by the severity of the LV outflow tract obstruction. However, careful 2DE can identify anatomic and functional abnormalities of the mitral valve that can accompany HCM, for example, increased mitral leaflet area or abnormal origin and insertion of the papillary muscles (papillary muscle insertion directly into the anterior leaflet without intervening chordae tendineae). Recognition of these is critical because these findings may influence subsequent treatment decisions. Thus, in patients who undergo myectomy, the surgical approach may have to be adapted and include creating a deeper myectomy trough and partial resection of papillary attachments to ensure adequate post-operative relief of obstruction.\textsuperscript{59} On 2DE, a centrally or anteriorly directed MR jet strongly suggests that the MR may not resolve with amelioration of obstruction and SAM (ie, intrinsic mitral valve disease).

**Strain Imaging**

One of the main limitations of TDI is that it engages only a single point of interest on the myocardium and is thus limited by tethering, for example, an akinetic segment of the myocardium may have a near-normal tissue velocity if it is tethered to a normally contracting segment. This problem of tethering is circumvented with strain imaging, in which the relative distance between 2 points in a myocardial segment of interest is tracked during the cardiac cycle. Applied to a single segment of the heart, systolic strain is simply the standardized change in length in a segment (tissue deformation) and strain rate describes the rate at which this deformation occurs.\textsuperscript{48,68,69}

The change in length is standardized, or divided, by the end-diastolic length:

\[
\text{Strain} = \frac{\text{end-systolic length} - \text{end-diastolic length}}{\text{end-diastolic length}} \times 100.
\]

Systolic segmental strain is thus a measure of an individual myocardial segment’s regional systolic function and falls under longitudinal (the change in length of LV in apical long-axis views), circumferential (the change in length of LV along the circumference of the myocardium in short-axis views), and radial (the change in length of LV between the endocardium and epicardium in short-axis views) categories to capture the 3D nature of cardiac contraction and relaxation. Myocardial strain provides valuable information on global and segmental myocardial mechanics. In contemporary practice, strain imaging is considered a more sensitive and reproducible measurement of altered myocardial mechanics than traditional assessments, such as LVEF and diastolic measurements using spectral Doppler.\textsuperscript{70–77}

Although strain and strain rate can be calculated by color TDI from Doppler velocity data independent of 2D image quality, modern technique focuses on obtaining these data by speckle-tracking strain analysis that directly measures myocardial strain derived from tracking natural acoustic markers within the myocardium. Recent addition of 3D speckle-tracking echocardiography to the pre-existing 2D speckle-tracking echocardiography enhances the ability to detect in-plane motion and follow the speckles in 3 dimensions.\textsuperscript{78–81} The entire LV data set can be acquired in full-volume mode from only 1 apical window with a reduction of processing time from ≈35 to <10 minutes, thus moving 3D speckle-tracking echocardiography from the realm of research into clinical practice.

Among modern imaging techniques, myocardial strain has stepped into reality and has particularly important applications in cardiomyopathies. Recent work has demonstrated that impaired myocardial deformation, as assessed by low global longitudinal strain, provides incremental prognostic information to LVEF.\textsuperscript{70,71} An understanding of anatomic distribution of myocardial fiber orientation of the heart and the difference in methodology between 2D speckle-tracking echocardiography and volumetric methods is central to recognizing strain and its application in modern imaging. LV myocardial fibers are oriented variously, with the midwall being occupied by circumferential fibers and longitudinal fibers forming a right-handed helix in the subendocardium and a left-handed helix in the subepicardium, thus representing 2 oppositely directed spirals.

Application of strain imaging in modern echocardiography thus enables differentiation of the HCM phenotype from hypertension-induced LV hypertrophy, RCM (specifically amyloidosis), early detection of Anderson–Fabry disease before the development of hypertrophy, and subclinical cardiomyopathy associated with Duchenne muscular dystrophy and normal LV function. In patients with HCM, variably located myocardial hypertrophy and fibrosis (both structural and tissue characteristics of these conditions) are responsible for abnormalities of LV function with both contributing to regional impairment of myocardial shortening. Patients with HCM demonstrate decrements in longitudinal strain and enhanced circumferential strain with attenuation of longitudinal strain correlating with the extent of hypertrophy. Impairment of deformation in the longitudinal direction has been linked to the fact that maximal myofiber disarray occurs in the inner region of the myocardium,\textsuperscript{82,83} and, therefore, muscle fibers within the subendocardial region, which are responsible for most of the longitudinal deformation, are likely to be the most impaired functionally.

An important clinical application of myocardial strain imaging is its capability to detect subclinical chemotherapy-induced cardiotoxicity because it allows early detection of subtle myocardial damage that may enable prevention of the progression to symptomatic HF. After anthracycline chemotherapy, altered LV diastolic strain in association with reduced
systolic function also has been reported and an approximate 15% reduction in longitudinal strain from baseline values has been reported to have high sensitivity and specificity for predicting long-term cardiac dysfunction after chemotherapy.84–87 Thus, 2D strain imaging and quantification of regional and global longitudinal strain recently have been recommended in the standard echocardiography protocols for patients during and after chemotherapy.87

LA strain in cardiomyopathies has been studied, and LA wall fibrosis, as part of structural remodeling, seems to be inversely related to LA strain and strain rate.88 Atrial strain has been used to quantitate atrial function and predict cardiovascular events and outcomes, with reduced atrial systolic strain seen to be associated with the development of atrial fibrillation, HF, and increased LV end-diastolic pressure, and to be an important predictor of diastolic HF.89–95 LA strain and strain rate also have been reported to be independent predictors of the maintenance of sinus rhythm after cardioversion.96,97 In the near future, atrial deformation parameters likely will constitute complementary echocardiographic data in the management of patients with cardiomyopathies and may help identify patients who have a higher thrombotic risk.

RV free wall myocardial velocity, strain, and strain rate by echocardiographic deformation imaging (by TDI or speckle-tracking) are promising tools for the quantification of global and regional ventricular function. Systolic strain and systolic strain rate by TDI have been shown to be reduced in patients with ARVD/C compared with healthy controls,98,99 and use of this technique has been suggested to detect subtle early abnormalities in asymptomatic mutation carriers.100

Torsion Imaging

As mentioned above, the myocardium is composed of complex helical patterns, with subendocardial fibers arranged in a right-handed helix and subepicardial fibers in a left-handed helix.69,101,102 During systole, the LV twists, storing elastic energy that is abruptly released with untwisting during diastole.103 When both layers contract simultaneously, a larger radius of rotation for the outer epicardial layer results in a mechanical advantage in dominating the overall direction of rotation, with basal rotation contributing significantly to torsional movement. Torsional velocity is calculated as the difference between the apical rotational velocity and the basal rotational velocity measured by speckle myocardial imaging. Alterations in torsion can be observed both in terms of magnitude of torsion, absolute direction of torsional motion, and rate of torsion. Patients with DCM experience complete reversal of the direction of LV apical rotation, resulting in negative net torsion.104 In HCM, torsion results vary depending on the site and extent of hypertrophy and the presence and absence of obstruction, whereas untwisting remains prolonged. Torsion is attenuated in early stages of nonobstructed HCM and reduced with significant obstruction.103,106 Similar results have been reported for amyloidosis.107,108 However, clinical utility is somewhat limited because of significant variations in normal torsion values, and torsion currently is considered a research tool rather than an established clinical modality.

Contrast Echocardiography

The qualitative and quantitative analyses of myocardial function and structure can be enhanced by the use of contrast agents during echocardiography. Contrast agents (safe with minimal adverse effects)109,110 are composed of microbubbles with a core containing a high molecular weight gas. These microbubbles are more effective at scattering the incident ultrasound waves than red blood cells and thus cause an increase in the intensity of the returning signal to enhance imaging of the blood pool.109,110 Commercial contrast agents, which traverse the pulmonary circulation, are used to delineate the LV chamber, LV structural abnormalities, and also myocardial perfusion.

Contrast echocardiography improves the delineation of the LV endocardial border for accurate assessment of LV systolic function and segmental wall motion analysis, particularly in patients with suboptimal 2D imaging. In the case of several cardiomyopathies, contrast echocardiography significantly improves visualization (50%–90%) of myocardial segments and interpretation of LVEF and can provide additional diagnostic information despite suboptimal image quality.111,112 Current guidelines recommend contrast opacification in patients with poor acoustic windows, that is, when the window is <80% of the circumference of the LV endocardium or when ≥2 consecutive segments cannot be clearly visualized.111

Although contrast echocardiography is particularly useful in stress echocardiography (treadmill, dobutamine, or vasodilator) for the assessment of regional wall motion abnormalities where it enhances the diagnostic accuracy of the test to detect ischemia, its routine use in the evaluation of cardiomyopathies helps alleviate near-field artifacts to significantly improve the assessment of LV apical anatomy, in particular ApHCM, noncompaction, apical aneurysm with and without a thrombus, and LV thrombi in general.

Opacification of the LV apex with the use of contrast agents is invaluable in the diagnosis of LVNC and ApHCM. In LVNC, contrast echocardiography allows demonstration of the intertrabecular recesses and provides a distinctive delineation of the compacted layer, which allows improved precision in measurements. This assumes importance because normal hearts have more trabeculated segments than other segments at the level of the papillary muscles and the apex, and it is mandatory to exclude normal LV trabeculations, which can be common variants of the normal heart.113 The use of contrast LV opacification can be extremely helpful in distinguishing LVNC from common mimickers of the disease,19 for example, false tendons, aberrant chords, cardiac fibromas, eosinophilic heart disease, endomyocardial fibrosis, and cardiac metastasis. In ApHCM, contrast echocardiography can, in addition to confirming the diagnosis, permit delineation of the size of the frequently associated apical aneurysm/pouch and exclude apical thrombus.

Downloaded from http://circres.ahajournals.org/ by guest on December 30, 2017

Contrast Echocardiography

The qualitative and quantitative analyses of myocardial function and structure can be enhanced by the use of contrast agents during echocardiography. Contrast agents (safe with minimal adverse effects) are composed of microbubbles with a core containing a high molecular weight gas. These microbubbles are more effective at scattering the incident ultrasound waves than red blood cells and thus cause an increase in the intensity of the returning signal to enhance imaging of the blood pool. Commercial contrast agents, which traverse the pulmonary circulation, are used to delineate the LV chamber, LV structural abnormalities, and also myocardial perfusion.

Contrast echocardiography improves the delineation of the LV endocardial border for accurate assessment of LV systolic function and segmental wall motion analysis, particularly in patients with suboptimal 2D imaging. In the case of several cardiomyopathies, contrast echocardiography significantly improves visualization (50%–90%) of myocardial segments and interpretation of LVEF and can provide additional diagnostic information despite suboptimal image quality. Current guidelines recommend contrast opacification in patients with poor acoustic windows, that is, when the window is <80% of the circumference of the LV endocardium or when ≥2 consecutive segments cannot be clearly visualized.

Although contrast echocardiography is particularly useful in stress echocardiography (treadmill, dobutamine, or vasodilator) for the assessment of regional wall motion abnormalities where it enhances the diagnostic accuracy of the test to detect ischemia, its routine use in the evaluation of cardiomyopathies helps alleviate near-field artifacts to significantly improve the assessment of LV apical anatomy, in particular ApHCM, noncompaction, apical aneurysm with and without a thrombus, and LV thrombi in general.

Opacification of the LV apex with the use of contrast agents is invaluable in the diagnosis of LVNC and ApHCM. In LVNC, contrast echocardiography allows demonstration of the intertrabecular recesses and provides a distinctive delineation of the compacted layer, which allows improved precision in measurements. This assumes importance because normal hearts have more trabeculated segments than other segments at the level of the papillary muscles and the apex, and it is mandatory to exclude normal LV trabeculations, which can be common variants of the normal heart. The use of contrast LV opacification can be extremely helpful in distinguishing LVNC from common mimickers of the disease, for example, false tendons, aberrant chords, cardiac fibromas, eosinophilic heart disease, endomyocardial fibrosis, and cardiac metastasis. In ApHCM, contrast echocardiography can, in addition to confirming the diagnosis, permit delineation of the size of the frequently associated apical aneurysm/pouch and exclude apical thrombus.
**3D Echocardiography**

Three-dimensional echocardiographic imaging represents a major innovation in cardiovascular ultrasound with advances in computer and transducer technologies permitting real-time 3D acquisition and presentation of cardiac structures from any spatial point of view. In its present form, 3D imaging is performed with a matrix array probe, enabling collection of a real-time single beat with pyramidal information. However, despite significant advances in technology, the limitation of low frame rates persists (low temporal resolution) and color Doppler information remains rudimentary. Three-dimensional echocardiography has shown better correlation with CMR imaging than 2D assessments, because 3DE has lower temporal variability and substantially improved test-retest variability compared with 2DE since there are no geometric assumptions made in the calculation of heart volumes.

In the evaluation of cardiomyopathies, quantification of LV volume and mass by 3DE is accurate and reproducible; by avoiding the foreshortening of the true long-axis, compared with LVEF derived from 2D echocardiography, LVEF measured using 3D analysis has been shown to be more closely associated with all-cause mortality and cardiac hospitalization in high-risk patients. However, although the accuracy of LV imaging is improved by 3DE, small volume underestimation compared with CMR imaging remains.

In addition to the assessment of the LV, evaluation of the LA by 3DE has demonstrated improved accuracy and reliability compared with 2D techniques, with excellent correlation with CMR imaging. In fact, recently, LA volumes by 3DE have shown an incremental prognostic value for detection of major adverse cardiovascular events and arrhythmias.

Three-dimensional echocardiography is also an emerging tool that shows promise for accurate estimation of RV volumes and RVEF, and RV volume calculated using this technique has been shown to have less variability than similar calculations by 2DE.

In the evaluation of cardiomyopathies, 3DE currently complements routine 2DE in daily clinical practice by providing additional volumetric information although its full complementary potential has not been exploited. The recently acquired ability to obtain a single-heartbeat full-volume data set with higher temporal and spatial resolution and live 3DE color Doppler imaging with a larger angle will be feasible, which will enhance 3DE utility and efficiency in daily clinical practice.

**Cardiac Magnetic Resonance Imaging**

The use of CMR imaging has advanced rapidly in the past decade, and CMR is steadily becoming an indispensable tool to aid in clinical decision making in patients with cardiomyopathy. Although echocardiography continues to be the main anchor of cardiac imaging in cardiomyopathy, CMR provides information that is both complementary and incremental, allowing insights into the disease processes that were not possible until recently.

CMR is uniquely capable in the evaluation of cardiomyopathies and provides information on biventricular volumes and function, underlying cause, and potential modifiable components of the disease processes. A comprehensive CMR examination takes advantage of the varied imaging techniques for tissue characterization with T1- and T2-weighted sequences, cine functional analysis, infarct/fibrosis imaging with late gadolinium enhancement (LGE), and contrast-enhanced myocardial perfusion imaging. The meaningful role of CMR in cardiomyopathies is supported by extensive literature, and it has contributed to our understanding of DCM, myocarditis, HCM, ARVC, iron-overload cardiomyopathy, amyloidosis, sarcoidosis, and LVNC.

Modern CMR techniques utilized in the assessments of cardiomyopathies focus on (1) evaluation of LV structure and function; (2) tissue characterization, including the presence and extent of fibrosis; and (3) LV thrombus.

**Structure and Function**

In general, quantitative assessment of ventricular size and function is an integral part of every CMR examination, and a CMR evaluation for cardiomyopathy begins with a complete functional assessment of the LV and RV using cine imaging in the 2-, 3-, and 4-chamber long-axis as well as a series of short-axis images that cover the entire LV. Slice thickness is 6 to 8 mm, with a 0- to 4-mm interslice gap in an adult. Using the functional data set, it is possible to quantify EF, ventricular mass (1.05 × [epicardial volume−endocardial volume]) and volumes. In the setting of possible myocarditis, T2-weighted imaging is performed before contrast administration. Acquiring functional data in other imaging planes is important in certain conditions, such as a stack of sequential axial cine images for better visualization of the RV in cases of suspected ARVD/C.

CMR is now an effective and helpful complementary imaging tool for the diagnosis of HCM (Figures 9 and 10) and follow-up of patients after either surgical myectomy or open heart procedure.
alcohol septal ablation therapy. CMR is now commonly used in the comprehensive assessment of patients with HCM. In addition, CMR imaging can help discriminate HCM from closely related morphological cardiomyopathies and cardiac disorders, for example, amyloidosis, Fabry disease, and athlete’s heart. CMR is ideally suited to the diverse HCM phenotype, including ApHCM, providing images with high spatial resolution, sharp contrast between myocardial borders and blood pool, and tomographic reconstruction of the heart with nonoblique visualization of all LV segments.

In HCM, CMR can accurately determine the site (eg, segmental hypertrophy) and extent of hypertrophy (Figure 9). CMR seems to have expanded the definition of the complex hypertrophic cardiomyopathic process in several respects, for example, quantitative assessment of LV mass, extension of hypertrophy into the RV wall, noncontiguous segmental hypertrophy, elongated mitral valve leaflets responsible for outflow obstruction, aberrant LV muscle bundles relevant to strategic planning for surgical myectomy, and de novo onset of LV hypertrophy in adults.

**Tissue Characterization**

**Late Gadolinium Enhancement**

This is a CMR technique (eg, breath-held inversion recovery segment gradient-echo sequence 10–15 minutes after the injection of 0.1–0.2 mmol/kg of gadolinium) used to evaluate areas of myocardial scar. The technique for imaging LGE uses electrocardiogram gating with data acquired every other heartbeat for adequate relaxation between inversion pulses. Gadolinium chelates are extracellular contrast agents that concentrate in areas of extracellular matrix expansion. The latter can result from conditions that cause replacement fibrosis or in the presence of infiltrative heart disease. Areas of fibrosis therefore have a shorter T1 because of the presence of gadolinium. Against the dark background of normal myocardium, LGE appears as white or light gray. The excellent spatial resolution of CMR makes it particularly useful in the detection and assessment of scar tissue in the myocardium.

Acquiring images for LGE is crucial in differentiating types of cardiomyopathies. Whereas LGE in ischemic cardiomyopathy occurs in the subendocardial region or has some degree of transmural involvement beginning in the subendocardium and progressing toward the epicardium, its pattern in nonischemic cardiomyopathies (NICM) is in a noncoronary distribution and may be varied, including midwall patchy hyperenhancement, epicardial involvement, or global subendocardial enhancement. Approximately one fourth of patients with DCM have evidence of midwall fibrosis, with a minority of these patients (13%) having LGE in an infarct pattern.

The presence and extent of LGE also is known to affect prognosis in patients with NICM. It is thought that LGE in a nonischemic distribution likely represents myocardial fibrosis from a variety of pathologies and is predictive of increased cardiac events even after adjusting for LV EF and class of HF. Thus, in DCM patients with an LVEF <35%, the presence of LGE has been shown to be associated with an 8-fold increase in HF, appropriate implanted cardiac device firing, and cardiac death.

In a meta-analysis of 9 studies involving 1488 patients who had NICM and were monitored for an average of 30 months, the presence of LGE was noted in 38% of the patients and was associated with odds ratios of 3.3 for mortality and 5.3 for sudden cardiac death or aborted sudden cardiac death. The presence of LGE in this meta-analysis identified subjects with NICM who were at a higher risk of hospitalization for HF, thus suggesting that CMR may allow detection of patients with NICM who require closer follow-up and evaluation after diagnosis and may help reduce the significant costs incurred because of repeat admissions in this patient population. It has been suggested that NICM patients with LGE ≥5% of LV mass are at greater risk of cardiovascular events than those with LGE <5% of LV mass, suggesting that there might be a critical threshold of enhancement above which patients may be at higher risk of adverse events.

Current studies examining LGE by CMR in patients with NICM use varying definitions to define the presence and extent of LGE, and currently there is a lack of consensus on an acceptable threshold for the diagnosis of LGE and on the best method of LGE quantification. Although such limitations exist, the presence of LGE alone by visual assessment has been found to be a predictor of adverse cardiovascular events and can help with risk stratification in these patients.

In HCM, extensive LGE also is known to be evidence of myocardial fibrosis/replacement scarring, which is a source of ventricular tachyarrhythmias and an independent prognostic marker for sudden death or appropriate implantable cardioverter-defibrillator discharges. LGE ≥15% of LV mass is
associated with a doubling of risk and raises consideration for the primary prevention of sudden death with an implantable cardioverter defibrillator in young patients with or without other conventional risk markers, whereas the absence of LGE is associated with lower risk.\textsuperscript{141}

CMR also can help differentiate sarcomeric HCM from HCM phenocopies, for example, amyloidosis in which similar septal and LV free wall thicknesses combined with global sub-endocardial LGE is highly specific. Similarly, symmetrical LV hypertrophy patterns associated with postero-lateral LGE are reported in Fabry disease, and massive LV hypertrophy and extensive LGE may suggest LAMP-2 (lysosome-associated membrane protein-2) cardiomyopathy. Distinguishing LVNC also is aided by identifying the deep trabeculations characteristic of noncompaction.

**Vasodilator Stress Perfusion Imaging**

As CMR has progressed to being a powerful imaging tool, vasodilator stress perfusion imaging is now increasingly recognized as a valuable adjunct to delayed enhancement imaging, providing incremental benefit in evaluating regional hibernation and even serving as an accurate surrogate for fractional flow reserve on angiography.\textsuperscript{112} CMR stress perfusion imaging is performed using dynamic saturation recovery imaging with accelerated (parallel) imaging, allowing acquisition of multiple slices per R–R interval. In some centers, stress wall motion CMR is sometimes performed as an adjunct, although with high-dose dobutamine, logistic difficulties remain. A meta-analysis comparing contrast-enhanced dobutamine stress echocardiography, single-photon emission computed tomography (SPECT), and stress CMR in the detection of obstructive coronary artery disease concluded that magnetic resonance imaging was superior to SPECT and dobutamine stress echocardiography and that SPECT and dobutamine stress echocardiography had similar overall performance. It further concluded that stress CMR led to a significant reduction in subsequent invasive testing while maintaining a similar if not superior diagnostic accuracy.\textsuperscript{143} In this context, it still needs to be emphasized that stress CMR is a not only comprehensive study assessing perfusion but also powerful tool for quantitative functional analysis and high-resolution scar imaging for viability assessment in segments with fixed perfusion defects.

**T1 and T2 Mapping**

T1 and T2 mappings are parametric quantitative sequences that provide tissue-specific T1 and T2 values, allowing the comparison of quantified myocardial parameters with normal reference values acquired under the same scanning conditions, such as scanner type, contrast agent, and scan time.\textsuperscript{144}

T1 relaxation time (also referred to as spin–lattice or longitudinal relaxation time) is a biological CMR parameter that indicates how quickly nuclei recover toward thermodynamic equilibrium. The native T1 value is a tissue-specific time constant, and its value in the myocardium is dependent on age and sex—men and older subjects exhibit slightly higher values than do women and younger subjects. Because tissues contain water and a variety of molecules, pathological processes that alter the water composition or local molecular environment of the myocardium generally alter the T1 values. Normal myocardial native T1 values have been reported to be 930±21 ms at 1.5 T and 1052±23 ms at 3 T. Representative myocardial pathologies leading to T1 changes include diffuse myocardial fibrosis, edema, inflammation, and infiltrative diseases such as amyloidosis, Fabry disease, and hemosiderosis.

T2 relaxation time (also referred to as spin–spin or transverse relaxation time), on the contrary, is another biological parameter of CMR imaging. Similar to T1 relaxation time, T2 relaxation time is a tissue-specific time parameter used to distinguish between normal and abnormal myocardial tissues. Normal myocardial T2 values acquired using steady-state free precession magnetic resonance imaging have been reported to be 52.18±3.4 ms at 1.5T and 45.1 ms at 3T. The increase in the water content of myocardial tissues is the main cause for longer T2 relaxation times. Therefore, myocardial edema is the main pathology responsible for variation in T2 values. T2 mapping sequences are useful for the detection of myocardial edema in patients with acute myocardial infarction, myocarditis, stress cardiomyopathy, sarcoidosis, and cardiac allograft rejection.

T1 mapping provides a pixel-wise quantification of the T1 values in the myocardium. T1 mapping in CMR can be performed before (called native T1 or pre-contrast T1) or after administration of contrast. Native T1 reflects composite water signal from extracellular space and myocytes, whereas post-contrast T1 allows determination of extracellular volume fraction.\textsuperscript{145,146} The hallmarks of an increased T1 signal include edema because of an increase in tissue water (recent infarction or inflammation) and an increase in interstitial space because of fibrosis, either focal (infarction scar, replacement fibrosis as in HCM) or diffuse (HCM and DCM) or to an infiltrative disorder like amyloidosis. On the contrary, myocardial diseases that result in deposition of lipid (lipomatous metaplasia, Anderson–Fabry) or iron (hemochromatosis) reduce T1 signal.

In selected patient populations with hypertrophic phenotypes, a proof-of-concept study\textsuperscript{147} showed that myocardial T1 mapping can be instrumental in discriminating between HCM and systemic hypertension. In this study, patients with HCM had T1-mapping indices that were significantly different from the hypertensives’, and second, native T1 was identified as the strongest independent discriminator, even when controlling for LGE and similar magnitudes of LV wall thickness. The study also showed that genotype-positive and phenotype-negative HCM patients had significantly elevated T1 values compared with controls, as well as with patients with mild hypertension. This finding supports the detection of subexpressed disease and separation of these subjects from cases with mild hypertension.

Native T1 times have been shown to be significantly prolonged in patients with amyloid light chain and ATTR cardiac amyloidosis compared with patients with HCM (\(P<0.0001\)) and normal subjects (\(P<0.0001\)).\textsuperscript{148,149}

Extracellular volume estimation using native and post-contrast T1 mapping typically assessing native T1, 15 minutes post-gadolinium-contrast administration, and LGE imaging at 20 minutes, helps in the detection of abnormalities of expansion of the extracellular space in the myocardium, as occurs
in amyloidosis and other infiltrative cardiomyopathies. The expansion of extracellular volume is demonstrated even in myocardial segments without apparent LGE, suggesting incremental diagnostic value.150

Although T1 mapping is evolving rapidly and is touted as a noninvasive biopsy of the heart, it still requires methodological standardization. The strength of this method includes its high reproducibility and immediate clinical applicability without the use of contrast media. Objective quantification of abnormal myocardium with threshold-based T1 analysis will pave the way to better define the prognosis and contribute to monitoring therapy in various myocardial diseases.

Ancillary Imaging in Cardiomyopathy
Modern imaging techniques in cardiomyopathy may include nuclear cardiac imaging using SPECT or positron emission tomography (PET) cameras and cardiac CT (CCT). Although these techniques are used predominantly in patients with ischemic or valvular heart disease, they may play a role in the identification of specific organ involvement and risk stratification in amyloidosis. The bone imaging agents (Tc-99 m pyrophosphate and Tc-99 m 3,3-diphenyl-1,2- ropanodicarboxylic acid)—are taken up via a calcium-mediated mechanism and are helpful in the identification of mutant (familial) transthyretin (ATTR) amyloidosis. Phosphate-based radiotracersbind the high calcium content in transthyretin amyloid fibrils, compared with the amyloid light chain subtype, and may be able to distinguish between the ATTR and amyloid light chain subtypes noninvasively.

Direct imaging of amyloid fibrils using PET tracers of C-11 Pittsburgh B compound offers the potential quantitation of amyloid burden and identification of early cardiac involvement before overt cardiac structural changes. It is currently under investigation.151

Similar to amyloid, several imaging modalities exist for elaboration in the diagnosis of cardiac sarcoidosis. Among these, perfusion imaging obtained from a resting SPECT study using Tc-99 m or Th-201 or PET perfusion imaging using N-ammonia-13 or rubidium-82 (Rb) tracers provides an effective means of assessing myocardial perfusion and inflammation, whereas the most useful method to evaluate for myocardial inflammation is with 18F-FDG (18F-fluorodeoxyglucose) PET. 18F-FDG is a glucose analog that is useful for imaging organ involvement in patients with sarcoidosis because of its increased uptake in macrophage-dense regions, where the activated macrophages show a high metabolic rate making them more reliant on external glucose as a source of fuel. For accurate diagnosis, imaging with both a resting perfusion scan by SPECT or PET and 18F-FDG PET imaging is needed to assess for the presence of both active inflammation and scar.

Although CCT is not an especially influential tool in the overall evaluation of cardiomyopathies, it can guide management decisions when, given appropriate hemodynamics, pericardial calcification is detected and constrictive pericarditis versus RCM is in question. Most recently, CCT using 100 KV has been suggested as an alternative method to CMR in the assessment of delayed enhancement (patchy, transmural, subendocardial, epicardial, and mesocardial) in patients with cardiomyopathy,152 particularly those with contraindications to CMR although large studies will be needed in the future to cement this claim. In this context, late-enhanced multislice CT has shown that CCT enables demonstration of late enhancement in patients with HCM.153 CCT also can be utilized in the diagnosis of LVNC, applying the same morphological findings reported for CMR. In fact, CCT diagnostic criteria for LVNC report a noncompaction-to-compaction ratio >2.2 in at least 2 segments to be diagnostic of LVNC.154 Similarly, the feasibility of equilibrium contrast material-enhanced dual-energy CCT to determine extracellular volume fraction in nonischemic cardiomyopathy compared with CMR has also been explored. In such cases, it has been demonstrated that among patients with HCM, patients with DCM, cardiac amyloidosis, and sarcoidosis there is higher myocardial extracellular volume fraction at dual-energy equilibrium contrast-enhanced CCT in per-segment analysis, which is in good agreement with CMR and suggests the potential of myocardial tissue characterization with CCT.155

Acknowledgments
We are grateful to Matt Umland, RCDS, and Lindsey Kalvin, RCDS, of Aurora Cardiovascular Services for their echocardiographic expertise, Rahul Sawlani, MD, Department of Radiology at Aurora St. Luke’s Medical Center for his CMR expertise, and Brian Schurrer and Brian Miller of Aurora Research Institute for assistance with the figures, as well as Jennifer Pfaff and Susan Nord of Aurora Cardiovascular Services for editorial preparation of the article.

Disclosures
None.

References
Jan and Tajik  Modern Imaging Techniques in Cardiomyopathies 887


dimensional echocardiography to CMR.

JACC Cardiovasc Imaging


Modern Imaging Techniques in Cardiomyopathies
M. Fuad Jan and A. Jamil Tajik

Circ Res. 2017;121:874-891
doi: 10.1161/CIRCRESAHA.117.309600
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/121/7/874

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/