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# Dilated Cardiomyopathy

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Gianfranco Sinagra • Marco Merlo  
Bruno Pinamonti  
Editors

# Dilated Cardiomyopathy

## From Genetics to Clinical Management

 Springer Open

*Editors*

Gianfranco Sinagra  
Cardiovascular Department  
Azienda Sanitaria Universitaria Integrata  
Trieste  
Italy

Marco Merlo  
Cardiovascular Department  
Azienda Sanitaria Universitaria Integrata  
Trieste  
Italy

Bruno Pinamonti  
Cardiovascular Department  
Azienda Sanitaria Universitaria Integrata  
Trieste  
Italy



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# Role of Cardiac Imaging: Cardiac Magnetic Resonance and Cardiac Computed Tomography

Giancarlo Vitrella, Giorgio Faganello, Gaetano Morea,  
Lorenzo Pagnan, Manuel Belgrano,  
and Maria Assunta Cova

## Abbreviations and Acronyms

2D	Two-dimensional
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CMR	Cardiac magnetic resonance
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTCA	Computed tomography coronary angiography
DCM	Dilated cardiomyopathy
ECV	Extracellular volume
FFR	Fractional flow reserve
GRE	Global relative enhancement
HF	Heart failure
ICD	Implantable cardioverter-defibrillator
LAV	Left atrial volume
LGE	Late gadolinium enhancement
LIE	Late iodine enhancement
LLC	Lake Louise criteria
LV	Left ventricular
LVEF	Left ventricular ejection fraction

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G. Vitrella (✉) · G. Faganello · G. Morea  
Cardiovascular Department, Azienda Sanitaria Universitaria Integrata di Trieste (ASUITS),  
Trieste, Italy  
e-mail: [giorgio.faganello@asuits.sanita.fvg.it](mailto:giorgio.faganello@asuits.sanita.fvg.it)

L. Pagnan · M. Belgrano · M. A. Cova  
Diagnostic and Interventional Radiology Department, Azienda Sanitaria Universitaria  
Integrata di Trieste (ASUITS), Trieste, Italy  
e-mail: [manuel.belgrano@asuits.sanita.fvg.it](mailto:manuel.belgrano@asuits.sanita.fvg.it); [cova@gnbs.univ.trieste.it](mailto:cova@gnbs.univ.trieste.it)

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LVR	Left ventricular reverse remodeling
MOLLI	Modified look-locker inversion recovery
RV	Right ventricular
RVEF	Right ventricular ejection fraction
SAPPHIRE	Saturation pulse prepared heart rate-independent inversion recovery
SASHA	Saturation recovery single-shot acquisition
SCD	Sudden cardiac death
Sh-MOLLI	Shortened modified look-locker inversion recovery
SSFP	Steady-state free precession
STIR	Short tau inversion recovery

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## 8.1 Cardiac Magnetic Resonance

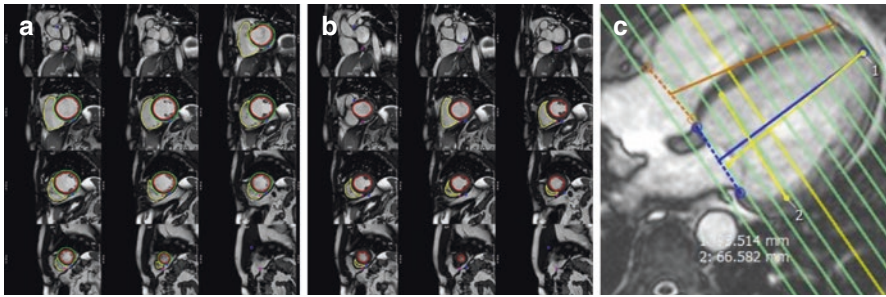
Cardiac magnetic resonance (CMR) has become an extensively validated noninvasive diagnostic imaging tool. Through its ability to assess cardiac morphology and function, and to characterize myocardial tissue in a reliable and reproducible fashion, it plays a pivotal role in the management of patients with dilated cardiomyopathy (DCM). In particular, it increases diagnostic accuracy and it aids in determining the etiology of left ventricular (LV) dysfunction and in prognostic stratification.

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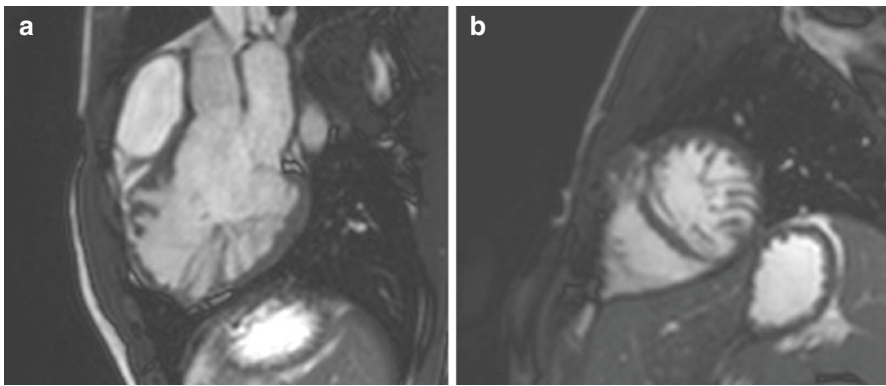
## 8.2 Diagnostic Accuracy

Steady-state free precession (SSFP) sequences are cornerstone sequences in CMR. Owing to their elevated spatial, temporal, and contrast resolution and lesser approximation in delineating endocardial borders than two-dimensional (2D) echocardiography, they minimize operator dependence and variability of intra- and interobserver reproducibility. SSFP cine imaging is currently regarded as the gold standard imaging technique for the evaluation of LV volume and systolic function [1, 2], as it is not affected by the geometric assumptions used in 2D echocardiography for the LV (such as the area-length method) [3] (Fig. 8.1). In addition, the precise identification of endocardial borders allows more accurate and reliable evaluation of the extent of non-compacted myocardium than does 2D echocardiography, thus allowing a more precise diagnosis of myocardial non-compaction [4] (Fig. 8.2). CMR also allows for accurate and reproducible, noninvasive measurement of the left atrial [5, 6] and right ventricular volume and function [7, 8].

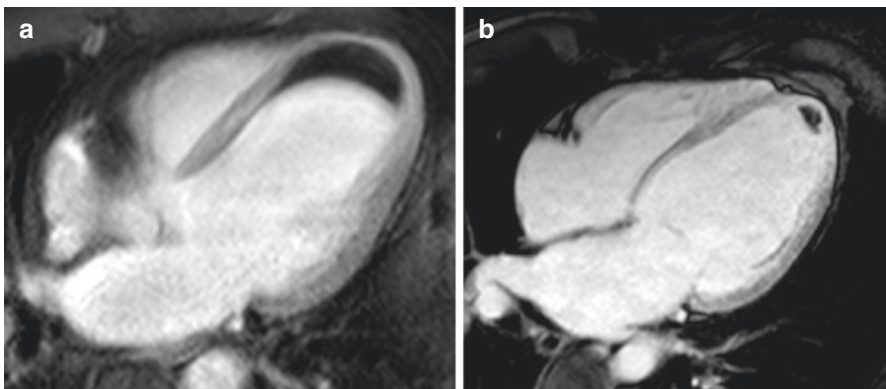
LV thrombus is a potential complication of severe LV dysfunction. Late gadolinium enhancement (LGE) CMR imaging is the most accurate imaging modality to detect left ventricular thrombus [9], in particular when acquiring LGE sequences with a long inversion time (compared to that needed to null normal myocardium) in order to selectively null the avascular thrombus [10] (Fig. 8.3).



**Fig. 8.1** Calculation of LV- and RVEF in MR with SSFP cine sequences. Diastolic (a) and systolic (b) endocardial contours are outlined in multislice short-axis cine runs covering the entirety of the ventricles (c); slices are 8–10mm apart. Diastolic and systolic volumes are thus obtained



**Fig. 8.2** SSFP imaging of left ventricular non-compaction in three-chamber (a) and short-axis (b) views



**Fig. 8.3** Inversion recovery images with long inversion time in four chamber of the left ventricular thrombus in patients with left ventricular dysfunction secondary to myocardial infarction (a), and myocarditis presenting as heart failure (b)



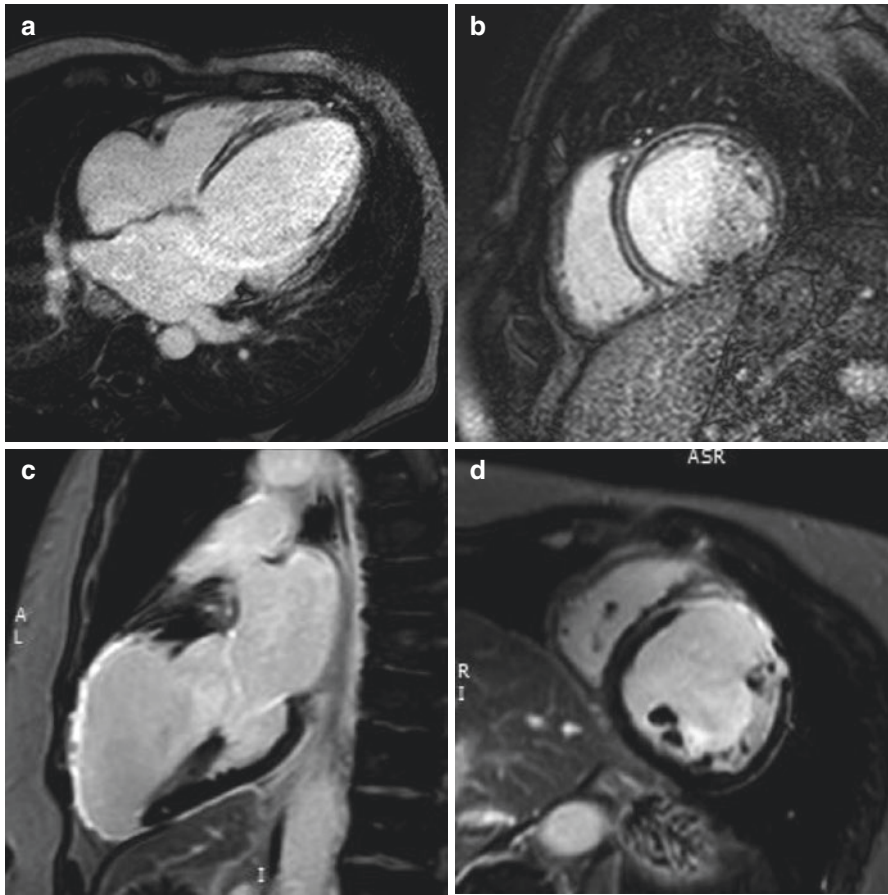
### 8.3 Differential Diagnosis

DCM is a condition characterized by LV dilatation and dysfunction and may represent the end stage of multiple cardiac disease processes of different etiology. The origin may be ischemic, inflammatory, infectious, hypertensive, or idiopathic. Accurate diagnostic characterization of DCM is of foremost importance in order to guide tailored treatment for patients affected by this condition. CMR is an important noninvasive imaging tool that helps to characterize the etiology of DCM. This is achieved by evaluating the presence and distribution of macroscopic myocardial fibrosis with LGE sequences (Fig. 8.3 differential diagnosis). In particular, LGE is usually found in patients with LV dysfunction secondary to coronary artery disease. The pattern of distribution follows coronary perfusion territories, and the scar may be subendocardial or transmural. In patients presenting with de novo acute heart failure (HF) and no clinical or electrocardiographic suggestion of ischemic etiology, LGE-CMR is sensitive and specific for the presence of underlying significant coronary artery disease (CAD) [11, 12]. Conversely, LGE is absent in most patients with left ventricular dysfunction of nonischemic origin. If present in DCM, LGE is typically found in a mid-wall distribution without an apparent correlation to coronary perfusion territories [13, 14] (Fig. 8.4). Mid-wall LGE was found in 10–28% of patients with DCM [13, 15]. Coexistent subendocardial LGE may indicate ischemic contribution to HF etiology despite the absence of angina and significant stenoses on coronary angiography, as infarction may follow coronary spasm or embolism, followed by spontaneous coronary recanalization [13, 16, 17].

### 8.4 Myocarditis Presenting as Left Ventricular Dysfunction

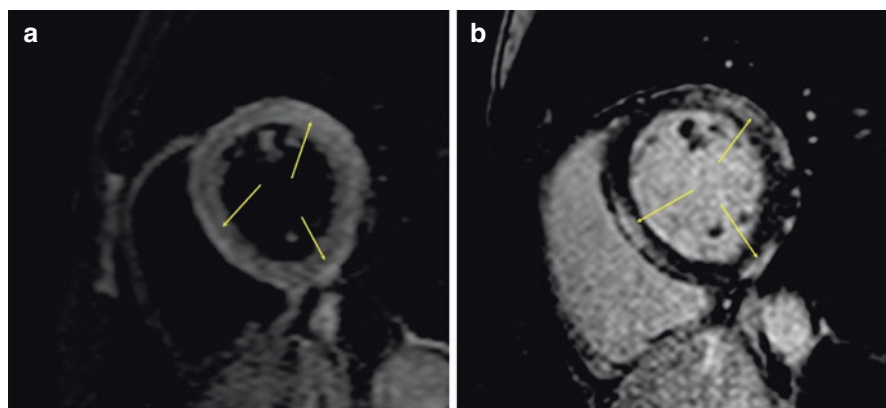
Patients presenting with HF and LV dysfunction with or without dilatation may be affected by active myocarditis. Inflammatory processes are characterized by increased water content due to edema. CMR may show edema at T2-weighted sequences such as short tau inversion recovery (STIR), diffuse hyperemia at global relative enhancement (GRE) sequences or T1-weighted sequences early after gadolinium administration, or LGE with a myocarditic pattern (patchy subepicardial and/or mid-wall) (Fig. 8.5). Finding at least two of the aforementioned three criteria, the Lake Louise criteria (LLC) was found to have good diagnostic accuracy in identifying myocarditis presenting with chest pain and troponin release [18]. However, the sensitivity of the LLC criteria is greatest for patients with infarct-like rather than HF or arrhythmic presentations [19, 20].

Recently, T2-mapping sequences were designed to obtain a T2 signal intensity decay curve of the myocardium, in order to estimate myocardial T2 value and generate a color T2 map off-line (Fig. 8.6). Normal native T2 time ranges between 39 and 59 ms. T2 relaxation time is increased in conditions characterized by myocardial edema [21]. In a recent study, patients with recent-onset HF and clinically suspected myocarditis revealed higher median global myocardial T2 values in those

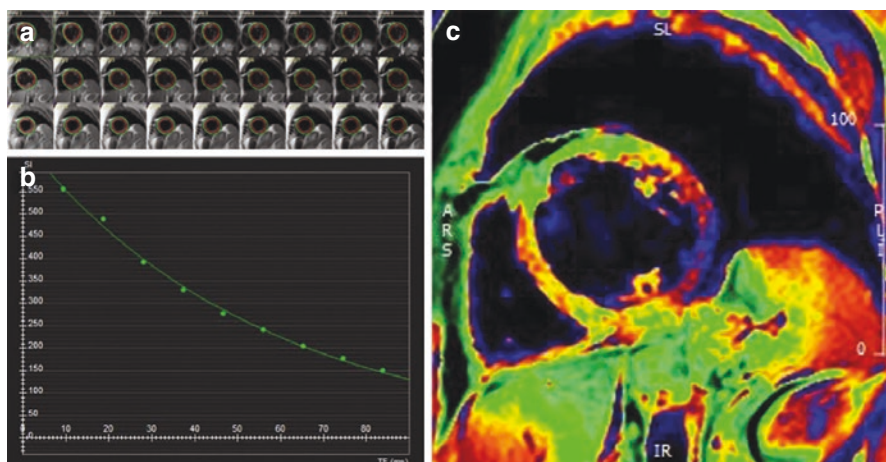


**Fig. 8.4** Late gadolinium enhancement imaging in a case of DCM in four-chamber (a) and short-axis (b) views showing patchy distribution of LGE (septal intramural and subepicardial free wall). LGE imaging in a case of LV dysfunction secondary to prior anterior myocardial infarction in two-chamber (c) and short-axis (d) views, showing transmural LGE in the left anterior descending territory

with biopsy-proven active myocarditis at T2 mapping, while there were no significant differences in native or post-contrast global myocardial T1 [22]. Caution must be applied when interpreting these results as T2 values may differ according to sequences and field strength [23, 24]. Furthermore, increased T2 values may be found in DCM patients without inflammation. Finally, differences between normal and pathological subjects can be very subtle and reported in the range of 10–20 ms, sometimes even overlapping normal T2 values, making it therefore difficult to define precise cutoff values [23, 25]. Nevertheless, despite these limitations T2 mapping can overcome the T2 or STIR sequence artifacts and is the only mapping sequence that allows for discrimination between inflammatory and noninflammatory cardiomyopathies [26].



**Fig. 8.5** CMR imaging in a patient with acute myocarditis: short-axis T2-weighted images (a) show edema, and short-axis LGE images (b) show patchy subepicardial LGE in the septum, inferior and anterolateral walls



**Fig. 8.6** T2 mapping with multi-echo spin-echo sequence: endocardial and epicardial contours are traced in all slices for each echo time (a). A T2 decay curve fit is obtained, and the T2 value is calculated for the region of interest (b). Results can also be depicted in color-coded maps (c)

As native T1 values increase with increasing myocardial water content, native T1 mapping may serve as a complementary technique to T2-weighted imaging for assessing myocardial edema in myocarditis presenting as infarct-like syndrome [22, 27] or where gadolinium is contraindicated. However, since native T1 values increase both with water content and with diffuse fibrosis, it is not able to discriminate between inflammatory and noninflammatory cardiomyopathies in patients presenting with heart failure [28].

## 8.5 Other Secondary Forms of DCM

CMR may help in diagnosing Chagas cardiomyopathy, caused by *Trypanosoma cruzi* infection, which results in LV dysfunction, HF, and ventricular arrhythmias. Its typical pattern is characterized by DCM with aneurysm formation with preferential sites at the apex and infero-lateral walls, which can be easily detected with SSFP cine imaging. The pattern of LGE is variable and may involve any or all layers of the myocardial wall [29, 30]. CMR was also found to identify the early stages of the disease [29].

Cardiac involvement of sarcoidosis may manifest itself as LV dilatation and dysfunction. Patients with sarcoidosis develop large areas of LGE with variable distribution, which can precede the occurrence of LV dilatation, frequently involving the mid-wall of the basal septum, basal and lateral segments of the LV, and papillary muscles, unrelated to vascular territories [31].

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## 8.6 Prognostic Stratification

Risk stratification is of foremost importance in DCM, particularly regarding the risk of sudden arrhythmic cardiac death (SCD). LV ejection fraction (LVEF) is the strongest predictor of progression to HF [32], while LV volume and mass are independently correlated with mortality and morbidity. Therefore, accurate quantification of all these parameters is essential to adequately evaluate patients and to monitor progression of disease and response to different therapeutic agents [33]. LVEF is the main criterion to select patients for primary prevention of SCD with implantable cardioverter-defibrillator (ICD) [34–36]. However, LVEF has low sensitivity and low specificity for the prediction of SCD [34, 37]. The use of low LVEF alone as an indicator for ICD placement is associated with both a low event rate of SCD in the control and treatment groups and a significant number of inappropriate ICD shocks [38]. Risk stratification for SCD among patients with nonischemic cardiomyopathy remains inadequate, causing ongoing clinical challenges in the appropriate identification of candidates for primary prevention ICDs [39].

In DCM, the remodeling process is characterized by changes in the extracellular matrix and interstitial fibrosis. The fibrous tissue constitutes a substrate for ventricular arrhythmias by inducing slow and heterogeneous conduction, favoring reentrant circuits, and producing vulnerability to life-threatening ventricular tachyarrhythmias [40]. Areas of LGE detected by CMR correlate well with histologically detected regional myocardial fibrosis in animal models and human explanted hearts [41, 42].

Several studies demonstrated that LGE is associated with an increased risk of adverse remodeling, hospitalization for HF, ventricular arrhythmia induction, and SCD in patients with DCM [43–52]. A recent meta-analysis showed that LGE was present in a considerable proportion of patients with DCM (44%), and

it had a strong and significant association with the risk for ventricular arrhythmias and SCD. This association was consistently observed in patients at different stages of their cardiomyopathy and was independent of LVEF [53]. In DCM patients undergoing ICD placement for primary prevention of SCD, the presence of myocardial fibrosis is also predictive of appropriate device therapy [46, 54] regardless of LVEF. Mid-wall LGE may also identify a subgroup at high risk of SCD despite mild or moderate LV systolic impairment, not meeting conventional criteria for ICD implantation [55, 56]. Moreover, LGE extent is also associated with adverse outcomes [44]. However, LGE extent is variably described in studies, and there is no current consensus on the best method of LGE quantification [50]. A relationship between patterns of myocardial scar and arrhythmogenesis was also suggested: a scar with a transmural of 26–75% is predictive of inducible ventricular tachycardia [43]. The detailed characterization of the heterogeneous boundary zone surrounding the LGE-CMR base scar has been linked to all-cause mortality and the most frequent ventricular arrhythmias although its role in DCM patients is still controversial [57]. Despite the abovementioned strong evidences, however, current guidelines from European Society of Cardiology [35] and more recently from American College of Cardiology/American Heart Association/Heart Rhythm Society [36] do not mention arrhythmic risk stratification with LGE-CMR.

The presence and extent of LGE in patients with DCM also predicts a lack of improvement in LV function despite optimal medical treatment compared to a significant improvement in patients without LGE [48, 58–61]. Furthermore, LGE detected at CMR correlates with LV diastolic function evaluated by Doppler echocardiography. Patients with DCM and positive LGE have indices of higher diastolic filling pressure [62–64]. The presence and extent of LGE also correlates with echocardiographic measures of LV systolic dyssynchrony, an indicator of poor clinical outcome [65].

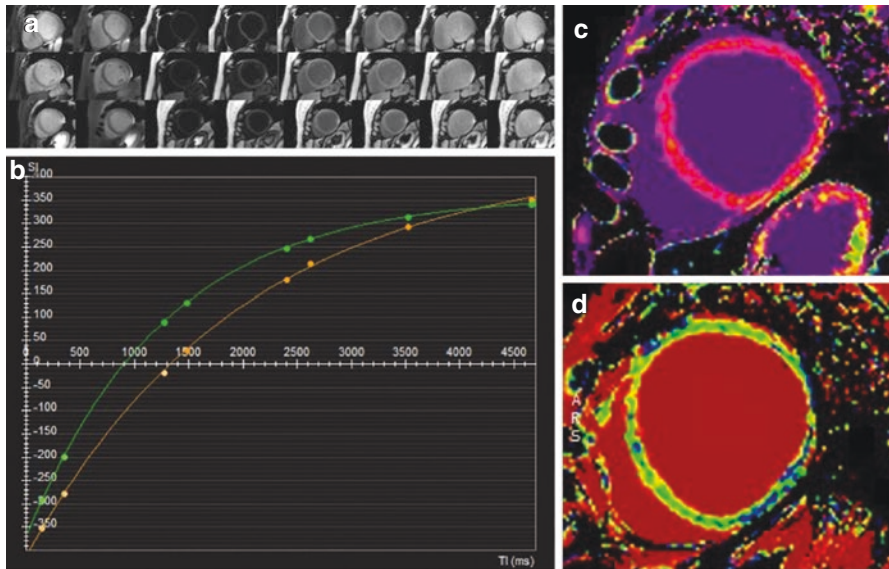
Scar burden was also found to be predictive of poor response to cardiac resynchronization therapy (CRT) [66]. Specifically, pacing over scar was associated with a higher risk of cardiac mortality or HF hospitalizations compared with pacing viable myocardium [67, 68]. Moreover, pacing a transmural scar was associated with a worse outcome than pacing a subendocardial scar [69]. Scar in the vicinity of right ventricular (RV) lead during CRT may also be associated with suboptimal left ventricular reverse remodeling (LVRR) [70]. However, the strategy avoiding myocardial scar in lead implantation has not been evaluated by multicenter, randomized, controlled trials.

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## 8.7 Macroscopic vs. Diffuse Fibrosis

Myocardial scar is the main substrate for ventricular arrhythmias, but not all patients with DCM have identifiable scars, especially in cases of diffuse fibrosis. In most patients with DCM, myocardial fibrosis does not progress focally but instead

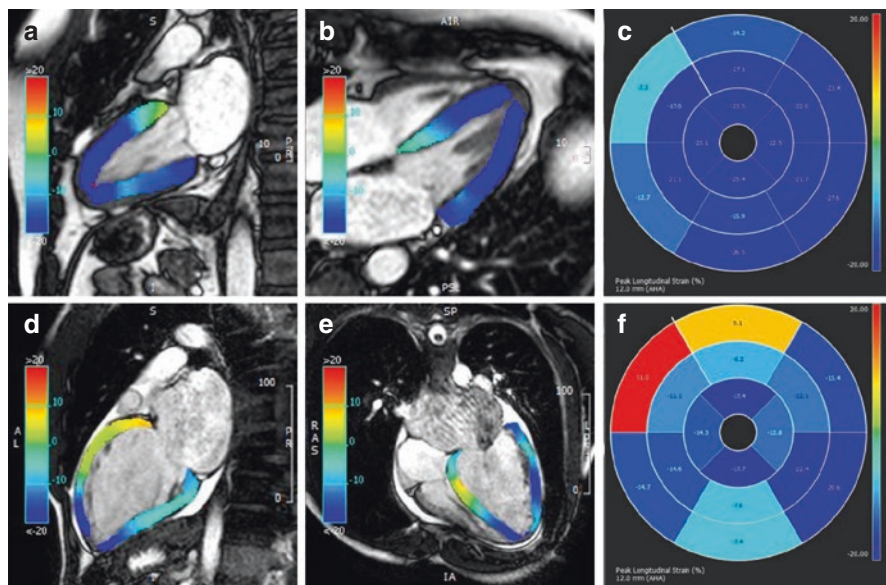
gradually and randomly, leading to irreversible replacement fibrosis [42, 71]. LGE sequences are designed to improve signal contrast differences between zones of normal myocardium and zones with focal fibrosis or necrosis [72, 73]. The technique is however very limited in the quantification of widespread tissue fibrosis [72, 74, 75]. This impairment has been nowadays overcome with the introduction of another family of sequences (MOLLI, Sh-MOLLI, SASHA, and SAPHIRE) that are able to quantitatively identify real myocardial T1 recovery time, native and post-contrast, and to quantify extracellular volume (ECV). It is also possible to assess all the collected data in color maps (Fig. 8.7) [76–78]. T1-mapping techniques correlate with myocardial histology [79–82] and may allow the early differentiation of diseased myocardium from healthy myocardium, in the absence of LGE [80, 83]. Native T1 and ECV are increased, and post-contrast T1 is decreased in nonischemic DCM patients [81, 83, 84]. All T1-mapping measures have been linked to prognosis in nonischemic DCM patients [85–88]. However, native T1 was found to be the sole independent predictor of all-cause and HF composite endpoints in a recent large prospective multicenter observational study [86]. Native T1 has also shown a strong relationship with markers of structural and functional LV remodeling, diastolic impairment, and the severity of functional mitral regurgitation [89–91].



**Fig. 8.7** T1 mapping with modified look-locker sequence: inversion recovery images with different inversion times are obtained (a) in short-axis views, before (native) and after (contrast-enhanced) gadolinium administration. The signal intensity is measured in each image, and a T1 relaxation curve (b) is obtained for the myocardium (green) and blood (orange). Results can be depicted as color-coded maps of native myocardial T1 (c) and ECV (d)

## 8.8 Strain Analysis

In DCM, the occurrence of nonhomogeneous fibrous substitution of cardiomyocytes may alter mechanical activity in these areas [92], thus leading to a heterogeneous compromise of regional contractile function [93]. Myocardial deformation analysis can supply useful information for the evaluation of global and regional myocardial function [94, 95]. CMR tagging is considered a reference standard for the assessment of myocardial regional function [96]. By adding grids or lines to the imaging plane through selective saturation pulses, and following them throughout the cardiac cycle, myocardial deformation can be quantitatively analyzed. However, the need for additional acquisition sequences and time-consuming protocols have limited its clinical application. Recently, new CMR feature tracking technology, which agrees well with CMR tagging, has allowed for the assessment of global and regional myocardial strain by tracking patterns of features or irregularities comprised between the endocardial and epicardial borders during cardiac cycle using SSFP long-axis and short-axis cine images (Fig. 8.8). This technology, similar to speckle tracking, can be applied to routine cine-CMR acquisitions, thus avoiding the need for dedicated pulse sequences [97]. Global longitudinal, circumferential, and radial strain are significantly impaired in patients with DCM [98]. More importantly, there is growing evidence that CMR-derived strain analysis is a predictor of adverse events in patients with nonischemic DCM [99–101]. In particular, global longitudinal strain analysis has independent and incremental prognostic value to



**Fig. 8.8** Strain analysis in a normal subject (a–c) and in a patient with DCM (d–f) at 1.5T. Color-coded maps of peak longitudinal strain in two-chamber (a, d) and four-chamber (b, e) views. Bull’s-eye graphic depicting peak longitudinal strain values in all AHA segments (c, f)

other risk factors including LVEF, LGE, and ECV [99–103]. Peak circumferential strain in association with the absence of LGE and LV mass were found to be predictive of LVRR [104].

Cardiac dyssynchrony assessed by CMR strain analysis, associated with LGE imaging, was also suggested to better predict improvement in functional class after CRT implantation [105], compared to currently recommended parameters for patient selection [106].

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## 8.9 Other Prognostic Indicators

Biventricular involvement in DCM identifies a subset of patients with poor outcome [107, 108]. CMR is considered the gold standard for noninvasive assessment of RV function [7, 8]. RV ejection fraction (RVEF)  $\leq 45\%$  was shown to be independently associated with adverse outcome in nonischemic DCM patients [109]. Furthermore, RV longitudinal strain is also an independent predictor of outcome and offers additional prognostic information over RVEF [110].

Left atrial enlargement is associated with adverse outcome in patients with DCM [111, 112]. Left atrial volume (LAV) provides the most accurate estimate of left atrial size compared to linear dimension in M-mode and area in 2D echocardiography [113]. Echocardiographic measures systematically underestimate LAV compared to CMR [6], even though both methods are reproducible and have limited intra- or interobserver variability. A LAV index  $>72$  mL/m<sup>2</sup>, measured with the biplane area-length method, was found to be an independent predictor of adverse events in DCM [114]. Conversely, LAV index  $<38$  mL/m<sup>2</sup> is predictive of LVRR [115].

Finally, RV dysfunction [109], but not greater degrees of trabeculation [116], is an independent predictor of survival and HF outcomes in patients with DCM.

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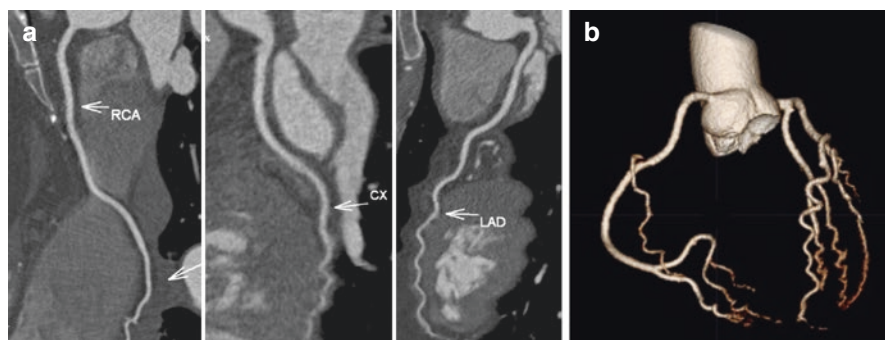
## 8.10 Computed Tomography

Cardiac computed tomography (CCT) is a noninvasive cardiac imaging technique that is increasingly gaining importance in DCM patients. It is mainly used to test for the presence of CAD but may also play a role in the evaluation of cardiac volumes and function, characterization of the type of cardiomyopathy, and treatment planning.

Calcium score may be useful in excluding CAD as the etiology for HF. In patients with HF, an Agatston score of 0 has been shown to have 100% specificity in excluding left main or  $\geq 2$ -vessel coronary artery disease [117, 118]. Computed tomography coronary angiography (CTCA) (Fig. 8.9) is a highly accurate diagnostic modality for excluding CAD in patients with DCM of undetermined cause [119–122], especially in the low- to intermediate-risk population due to its high specificity (95–98%) and negative predictive value (95–100%) [123–125].

Prospective ECG triggering is the preferred CTCA mode to minimize radiation dose, although this is possible only if the heart rate is slow and regular. Retrospective





**Fig. 8.9** Curved multiplanar reconstructions (cMPR) of the right coronary (RCA), left circumflex (CX), and left anterior descending (LAD) arteries obtained from a coronary CTA in a patient with normal coronary arteries (a). Three-dimensional volume reconstruction (3DVR) is shown in panel (b)

ECG gating must be used if the heart rate is high or irregular. This mode is also used for the evaluation of cardiac function and volumes, wall motion, and valvular abnormalities, with good correlation with CMR and contrast-enhanced echocardiography [2, 126–129]. Latest technologies such as CT perfusion and CT-FFR may give additional important information on the hemodynamic significance of coronary artery disease [130–135].

There is increasing evidence supporting the usefulness of CCT for the detection of myocardial fibrosis in patients with hypertrophic cardiomyopathy [136] and after myocardial infarction [137, 138] through late iodine enhancement (LIE), although CMR remains more sensitive. However, data in DCM patients are still limited. Initial data suggest that LIE-CCT correlates well with LGE-CMR and electro-anatomic mapping [139, 140]. LIE may also be used for ECV assessment [141]. It has good correlation with T1-mapping methods and is associated with increased LV volume and reduced EF and circumferential strain [142]. Dual-energy CT reduces imaging artifacts and increases contrast to noise ratio and thus may improve LIE images compared to conventional CT [143, 144].

A number of challenges still remain, relating to the required contrast dose, image quality, and radiation exposure. CTCA has been given a high appropriateness rating for the evaluation of ischemic etiology in patients presenting with HF [145, 146]. However, for all other indications, CCT should still be reserved for patients with contraindications or suboptimal results of other imaging tests.

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