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REVIEW

Role of multimodality imaging in the diagnosis and management of cardiomyopathies

Rôle de l'imagerie multimodale dans le diagnostic et la gestion des cardiomyopathies

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Abbreviations: 2D, two-dimensional; 3D, three-dimensional; ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance imaging; CT, computed tomography; DCM, dilated cardiomyopathy; FDG, fluorodeoxyglucose; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVNC, left ventricular non-compaction; PET, positron emission tomography; RCM, restrictive cardiomyopathy; SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography.

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KEYWORDS
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Cardiomyopathy;
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Computed tomography scan;
Cardiac nuclear imaging

Summary Multimodality imaging plays an important role in the initial evaluation, diagnosis and management of patients suspected of having a cardiomyopathy. Beyond functional and anatomical information, multimodality imaging provides important variables that facilitate risk stratification and prognosis evaluation. Whatever the underlying suspected cardiomyopathy, echocardiography is the most common initial imaging test used to establish the presence of cardiomyopathy, by depicting structural and functional abnormalities. However, echocardiographic findings are non-specific, and therefore have a limited role in identifying the underlying aetiology. Cardiac magnetic resonance imaging allows characterization of myocardial tissue, which can be of great help in identifying the aetiology of the cardiomyopathy. When a specific aetiology is suspected, particularly inflammation, ^{18}F-fluorodeoxyglucose positron emission tomography is recommended. The clinician should be capable of selecting the appropriate imaging techniques for each clinical scenario. Each technique has strengths and weaknesses, which should be known. In order to improve diagnostic performance, and as proposed by the European Association for Cardiovascular Imaging, cardiovascular imaging groups must be composed of experts from all modalities. The future of multimodality imaging in the diagnosis and management of cardiomyopathies will also involve evolution of its use in care, teaching and research. Training goals for future cardiac imaging experts must be defined; academic and industry partnerships should enable the connection to be made between imaging data and clinical data on the one hand and outcomes on the other hand, using big-data analysis and artificial intelligence.

MOTS CLÉS
Imagerie multimodalité ;
Cardiomyopathie ;
Échocardiographie transthoracique ;
Imagerie par résonance magnétique cardiaque ;
Tomodensitométrie ;
Imagerie nucléaire cardiaque

Résumé L'imagerie multimodale joue un rôle important dans l'évaluation initiale, le diagnostic et la prise en charge des patients suspectés d'avoir une cardiomyopathie. Au-delà des informations fonctionnelles et anatomiques, l'imagerie multimodale fournit des variables importantes qui facilitent la stratification du risque et l'évaluation du pronostic. Quelle que soit la cardiomyopathie présumée sous-jacente, l'échocardiographie est le test d'imagerie initial le plus couramment utilisé pour établir la présence d'une cardiomyopathie, en décrivant des anomalies structurelles et fonctionnelles. Cependant, les résultats échocardiographiques ne sont pas spécifiques et ont donc un rôle limité dans l'identification de l'étiologie sous-jacente. L'imagerie par résonance magnétique cardiaque permet la caractérisation du tissu myocardique, ce qui peut s'avérer très utile pour identifier l'étiologie de la cardiomyopathie. Lorsqu'une étiologie spécifique est suspectée, en particulier une inflammation, la tomographie par émission de positron au ^{18}F-fluorodésoxyglucose est recommandée. Le clinicien doit être capable de sélectionner les techniques d'imagerie appropriées pour chaque scénario clinique. Chaque technique a ses forces et ses faiblesses qu'il convient de connaître. Afin d'améliorer les performances du diagnostic, et comme l'a proposé l'Association européenne pour l'imagerie cardiovasculaire, les groupes d'imagerie cardiovasculaire doivent être composés d'experts de toutes les modalités. L'avenir de l'imagerie multimodale dans le diagnostic et la gestion des cardiomyopathies impliquera également une évolution de son utilisation dans les soins, l'enseignement et la recherche. Les objectifs de formation des futurs experts en imagerie cardiaque doivent être définis; Les partenariats académiques et industriels devraient permettre d'établir un lien entre les données d'imagerie et les données cliniques, d'une part, et les résultats, d'autre part, en utilisant l'analyse de données massives et l'intelligence artificielle.

Background

Cardiomyopathies are a heterogeneous group of heart muscle diseases. According to the European classification, five patterns of cardiomyopathy can be defined:

- dilated cardiomyopathy (DCM);
- hypertrophic cardiomyopathy (HCM);
- restrictive cardiomyopathy (RCM);
- arrhythmogenic right ventricular cardiomyopathy (ARVC);
- non-classified cardiomyopathy (including left ventricular [LV] non-compaction and takotsubo cardiomyopathy) [1].

Multimodality imaging plays a central and major role in the initial evaluation, diagnosis and management of patients suspected of having a cardiomyopathy or admitted for heart failure. Beyond functional and anatomical description,

multimodality imaging provides important information that facilitates risk stratification (particularly sudden cardiac death), accurate evaluation of prognosis and monitoring of therapy in most confirmed cardiomyopathies [2].

The use of all imaging technique modalities should be encouraged in the initial assessment; these generally include transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (CMR), cardiac computed tomography (CT) and cardiac nuclear imaging (Table 1) [3]. These techniques should be perceived in most clinical scenarios as complementary imaging approaches: each provides incremental information and results, allowing a rapid and accurate diagnosis to be made (Fig. 1 and Table A.1). The clinician should be capable of selecting the most appropriate imaging techniques for each clinical scenario, based on local availability, resources and expertise, and acceptable cost, while trying to avoid duplication [3].

Multimodality imaging in DCM

Definition and epidemiology

DCM is a heart muscle disorder, with an estimated incidence of 7/100,000/year, and a prevalence of 40 per 100,000 people [1].

According to European recommendations, DCM is a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, arterial systemic hypertension, valvular disease or congenital heart disease sufficient to cause the observed myocardial abnormality [1]. Several familial and non-familial aetiologies have been described, which are summarized in Table A.2. History should help the clinician to identify the most likely aetiology of the cardiomyopathy. For example, heart failure diagnosed late in pregnancy or early postpartum suggests peripartum cardiomyopathy, recent history of cardiotoxic agent use evokes toxic cardiomyopathy and a family history of cardiomyopathy should raise suspicion for familial cardiomyopathies. Genetic and acquired disorders provide a spectrum of electrical and functional abnormalities that change with time (isolated ventricular dilatation without symptoms, arrhythmia, heart failure signs) [2].

Diagnosis

Diagnostic criteria have relied upon the identification of an LV ejection fraction (LVEF) < 45%, in association with an LV end-diastolic dimension > 112% of the predicted value, corrected for age and body surface area (corresponding to an LV end-diastolic dimension > 2 standard deviations from normal according to normograms or > 31—32 mm/m^2) [4]. Pinto et al. proposed a revised definition combining several major and minor criteria, more adapted to clinical practice and the DCM clinical spectrum regarding clinical screening for DCM in relatives of patients with a definite disease (Table A.3) [2]. The likely presence of disease is indicated by presence of one major criterion and at least one minor criterion or one major criterion plus carrying the causative mutation identified in the proband. This new definition emphasizes the need to use multimodality imaging. Echocardiography is the key to the diagnostic evaluation of DCM. The apical biplane method of summation of discs (modified Simpson's rule) is the recommended method for measuring LV volume and LVEF. Contrast echocardiography using a specific agent for cavity opacification and real-time three-dimensional (3D) echocardiography significantly improves the accuracy and reproducibility of measurements of volumes and ejection fraction [5].

Aetiology

Echocardiography is the most common initial imaging test used to establish the presence of cardiomyopathy, by depicting structural and functional abnormalities (Fig. A.1). However, echocardiographic findings are non-specific, and therefore have a limited role in identifying the underlying aetiology. Typical features that favour DCM include diffuse wall thinning (< 6 mm in end-diastole) and spherical dilatation of the LV, global LV systolic dysfunction and right ventricular (RV) and LV enlargement, biatrial enlargement and malcoaptation of the mitral valve leaflets [4]. All echocardiographic variables, such as wall thickness, diastolic function, RV function and volume, intracardiac and pulmonary artery pressure estimations, stroke, cardiac output and wall motion abnormalities, should be collected at this stage. Rigorous aetiological evaluation may allow for specific treatment targeted to the underlying cause. At this stage, the absence of coronary artery disease, arterial systemic hypertension, valvular disease and congenital heart disease must be confirmed [1].

According to European recommendations, CMR is recommended in DCM for the assessment of myocardial structure and function (including the right heart) in subjects with a poor acoustic window [1]. CMR is also recommended for the characterization of myocardial tissue in case of suspected myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease, non-compaction cardiomyopathy and haemochromatosis [1]. Because the characterization of myocardial tissue can be of great help in identifying the aetiology of cardiomyopathy, CMR should be considered in all patients with DCM with an uncertain diagnosis, in absence of contraindications and according to local resources. Late gadolinium enhancement (LGE) in DCM is typically observed in the midwall of the interventricular septum in approximately 30% of patients [6]. Several LGE patterns have been described, and help with cardiomyopathy diagnosis (Fig. 1). Parametric mapping techniques have allowed the delineation of myocardial fibrosis, haemorrhage and oedema [7]. These methods are used increasingly to characterize cardiomyopathies. For example, advantages of T1 mapping over conventional CMR techniques include higher sensitivity and detection of early diffuse fibrosis [8]. T2-star CMR allows accurate non-invasive monitoring of cardiac iron for detection of DCM, specifically in transfusion-dependent patients. CMR is also particularly relevant for the detection of myocardial inflammation, and is considered as the non-invasive reference standard for the assessment of myocarditis. An accurate diagnosis is of importance, because 25% of patients with acute myocarditis will develop cardiomyopathy [9]. Using a combination of T2, early post-contrast T1 and late post-contrast T1-weighted imaging — the so-called Lake Louise Criteria — CMR has a sensitivity of 78% and a specificity of 88% for the diagnosis of acute myocarditis [10].

Table 1 Comparison of performance of imaging modalities.

	2D echo	TOE	3D echo	CMR	CT	SPECT	PET	ICA/HC/FFR
RV and LV volumes and function	●●	●●	●●●	●●●●	●●●	●●	●●	●●
Ischaemia	●●●	–	●●	●●●	●	●●●	●●●●	●●●●
Coronary arteries	–	–	–	●	●●●	–	–	●●●●
Tissue characterization	●●	●●	–	●●●●	●●	–	●●	●
Valves	●●●	●●●●	●●●	●●	●	–	–	●●●
Metabolism	–	–	–	●●	–	●●	●●●●	
Spatial resolution	●●	●●	●●	●●	●●●	●	●	●●●●
Temporal resolution	●●●	●●●	●●	●●	●	●	●	●●●
Limitations	Operator dependence; acoustic window	Operator dependence; acoustic window	Operator dependence; acoustic window	Availability; device artefact	Radiation	Radiation	Radiation; availability	Invasive; cost

2D: two-dimensional; 3D: three-dimensional; CMR: cardiac magnetic resonance imaging; CT: computed tomography; echo: echocardiography; ICA/HC/FFR: invasive coronary angiogram/heart catheterization/fractional flow reserve; LV: left ventricular; PET: positron emission tomography; RV: right ventricular; SPECT: single photon emission computed tomography; TOE: transoesophageal echocardiography. ● poor; ●● medium; ●●● good; ●●●● excellent/reference.

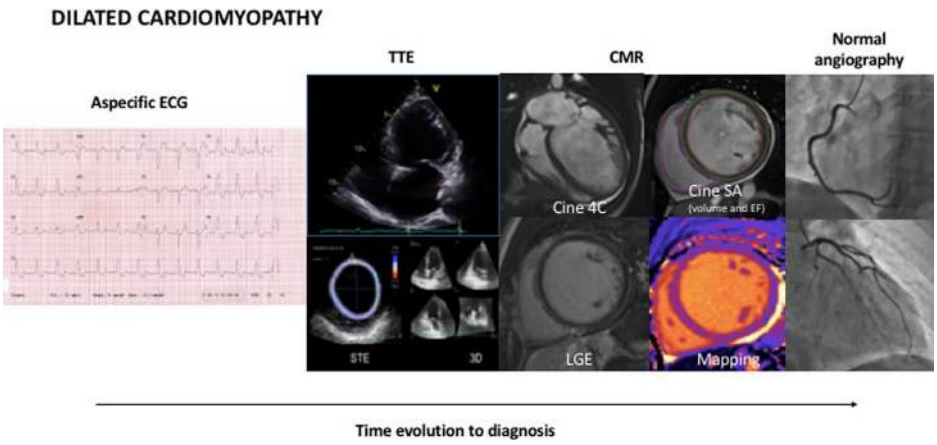

Figure 1. Several patterns of late gadolinium enhancement, according to the cardiomyopathy. 3D: three-dimensional; 4C: four-chamber; CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; EF: ejection fraction; LGE: late gadolinium enhancement; SA: short axis; STE: speckle-tracking echocardiography; TTE: transthoracic echocardiography.

Table 2 Multimodality imaging in the differential diagnosis between hypertrophic cardiomyopathy and cardiac amyloidosis (from Cardim et al. [26]).

Imaging data	HCM	Cardiac amyloidosis
Echo, CMR, cardiac CT		
LVH	Severe, asymmetric	Moderate, concentric, 'sparkling'
LVOT obstruction	Frequent	Rare (may exist in early stages)
Pericardial effusion	Rare	Frequent
IAS hypertrophy	Rare	Frequent
Apical sparing	Rare	Frequent
CMR		
LGE	RV insertion points, intramural	Diffuse, subendocardial (global or segmental)
T_1 mapping	Under research	Work in progress; typical patterns
Nuclear medicine		
^{99m}Tc-DPD uptake	No	Yes (transthyretin — senile and familial)

CMR: cardiac magnetic resonance imaging; CT: computed tomography; Echo: echocardiography; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LVH: left ventricular hypertrophy; LVOT: left ventricular outflow tract; RV: right ventricular; ^{99m}Tc-DPD: technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid; IAS: interatrial septum.

Combining LGE with T2 imaging helps to distinguish acute inflammation from chronic injury [10]. The Lake Louise Criteria have recently been updated, taking into account T2 and pre- and post-contrast T1 mapping techniques, with the aim of improving the diagnostic accuracy of CMR for the detection of myocardial inflammation [11]. However, CMR is less sensitive in the detection of chronic myocardial inflammatory diseases. In case of suspected cardiac sarcoidosis, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is recommended after first-line CMR to accurately detect myocardial inflammation, guide immunosuppressive therapy, assess prognosis and monitor response to therapy [12]. The incremental value of endomyocardial biopsy in the diagnostic work-up of DCM must be considered on an individual case basis.

Cardiac CT may be used to assess anatomy, and to provide tissue characterization in the presence of suboptimal echocardiographic images and contraindications to CMR [1].

DCM is a final common pathway of several cardiac diseases. In cases in which the diagnosis is not obvious after the first step, CMR may be helpful to identify the dilated phase of HCM or ARVC, and to confirm the absence of coronary artery disease, arterial systemic hypertension, valvular heart disease and congenital heart disease (Fig. 2 and Fig. 3).

Non-invasive stress imaging may be considered to exclude coronary artery disease, but may fail to identify extensive coronary artery disease in a significant proportion of patients [1]. Invasive coronary angiography is therefore recommended, particularly in patients with angina. However, the use of invasive coronary angiography alone may lead to a 13% incorrect assignment to DCM caused by coronary recanalization after infarction [13]. The coupling of CMR with invasive coronary angiography appears to be a powerful tool for differentiating true DCM from LV dysfunction related to coronary artery disease [14]. Coronary CT angiography may be an alternative to invasive coronary angiography, especially in patients with a low or intermediate likelihood of coronary artery disease.

Table 3 Value of different imaging modalities in various forms of restrictive cardiomyopathy.

	TTE	TDI and strain imaging	CMR	Nuclear imaging	Cardiac CT	PET
Apparently idiopathic RCM	+++	++	++	0	+	0
Cardiac amyloidosis	+++	+++	+++	+++	+	+
Other causes of familial/genetic RCM						
Haemochromatosis	+++	+	+++	+	0	0
Fabry cardiomyopathy	++	++	+++	0	0	0
Glycogen storage disease	++	++	++	+	0	0
Pseudoxanthoma elasticum	++	+	++	+	0	0
Inflammatory CM with a restrictive component						
Cardiac sarcoidosis	+	0	++	++	+	+++
Systemic sclerosis	++	++	++	+	0	0
Radiation therapy and cancer drug therapy-induced RCM						
Cardiac toxicity of radiation therapy	++	+	++	+	0	0
Cancer drug-induced RCM	+++	++	++	0	0	0
Endomyocardial RCM						
Endomyocardial fibrosis	+++	+	+++	0	0	0
Hypereosinophilic syndrome	+++	+	+++	0	0	0
Carcinoid heart disease	+++	0	++	0	0	0
Drug-induced endomyocardial fibrosis	+++	0	++	0	0	0
Differential diagnosis with constrictive pericarditis	+++	++	++	0	+++	0

+ indicates poor value; ++ medium value; +++ good value. CM: cardiomyopathy; CMR: cardiac magnetic resonance imaging; CT: computed tomography; PET: positron emission tomography; RCM: restrictive cardiomyopathy; TDI: tissue Doppler imaging; TTE: transthoracic echocardiography.

Another challenge is to differentiate athlete's heart from DCM in the setting of intensive endurance training. The European Association for Cardiovascular Imaging proposed a simple algorithm for this purpose. On TTE, a LV end-diastolic diameter < 60 mm and a normal LVEF are evocative of athlete's heart. A LV end-diastolic diameter > 60 mm when combined with reduced LVEF and abnormal diastolic function should raise suspicion of DCM, and the clinical assessment should then be completed by CMR, in which situation the presence of LGE is indicative of DCM [15]. Exercise echocardiography may be useful in cases of mildly-reduced LVEF. Absence of significant improvement in systolic function at peak exercise favours a pathological dilatation [16]. In case of doubt, deconditioning and evolution of imaging variables can be proposed.

Prognosis and guiding therapy

Precise measurement of LVEF is of importance for making decisions about defibrillator implantation and biventricular pacing treatment. Beyond LVEF, TTE provides several important haemodynamic variables for assessing prognosis, such as end-systolic volume index, left atrial volume index, mitral E-wave deceleration time, tricuspid annular peak systolic excursion, pulmonary artery systolic pressure and cardiac output. Global longitudinal strain improves risk stratification compared with LVEF [17]. Stress echocardiography is also of value, as contractile reserve predicts good response to therapy. On CMR, the presence and extent of LGE is also known to affect prognosis after resynchronization therapy in patients with DCM [18]. The presence and extent of LGE may help when making a decision about defibrillator implantation [19]. RV ejection fraction as assessed by CMR also appears to be a strong prognostic variable [6]. Precise assessment of left atrial volume predicts adverse outcomes in DCM, and left atrial strain appears to be a promising technique in this setting [20,21].

A myriad of mechanical dyssynchrony indexes have emerged, based on two-dimensional (2D) or 3D echocardiography, CMR, CT, single-photon emission computed tomography (SPECT) and PET/CT [22]. However, no index can currently be recommended to predict treatment response for cardiac resynchronization therapy, and QRS duration remains the best index.

Follow-up

Reassessment of myocardial structure and function is recommended during follow-up, and TTE is the first imaging modality in this setting. The use of 3D echocardiography and global longitudinal strain is preferable because of superior reproducibility. These methodologies are also especially

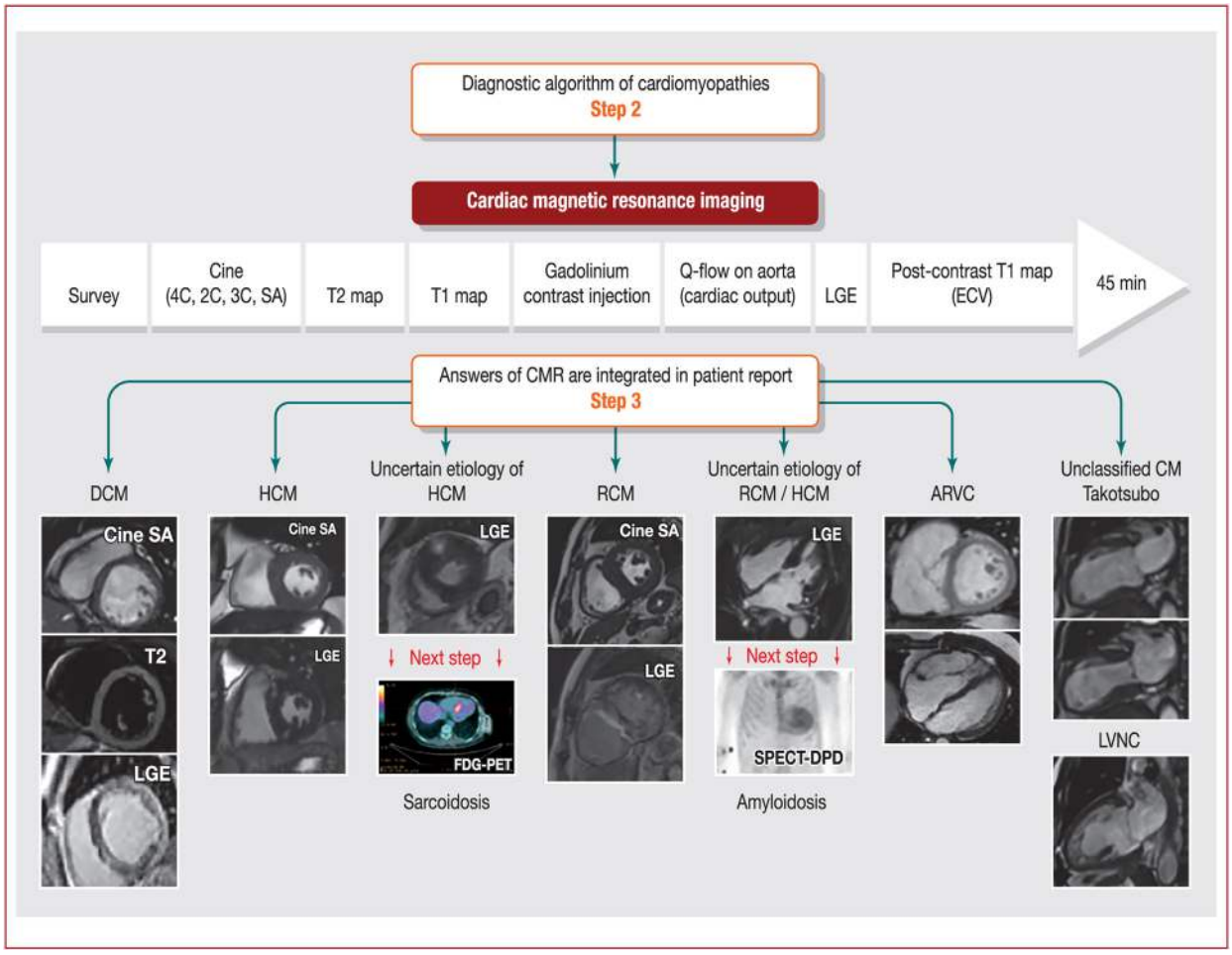

Figure 2. Steps 2 and 3 of the diagnostic algorithm for cardiomyopathies. 2C: two-chamber; 3C: three-chamber; 4C: four-chamber; ARVC: arrhythmogenic right ventricular cardiomyopathy; CM: cardiomyopathy; CMR: cardiac magnetic resonance imaging; DCM: dilated cardiomyopathy; DPD: diphosphono-1,2-propanodicarboxylic acid; ECV: extracellular volume; FDG: fluorodeoxyglucose; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LVNC: left ventricular non-compaction; PET: positron emission tomography; RCM: restrictive cardiomyopathy; SA: short axis; SPECT: single-photon emission computed tomography.

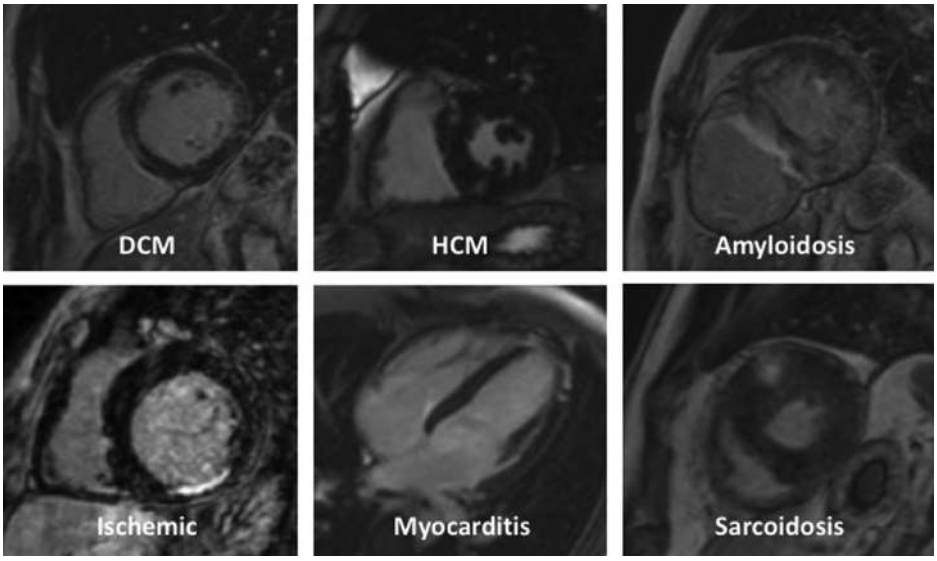

Figure 3. Example of use of multimodality imaging, which must be integrated with all file elements of the patient, for the diagnosis of dilated cardiomyopathy. DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy.

efficient for the serial monitoring of patients receiving cancer therapy, in order to early detect cardiotoxicity. All prognostic haemodynamic variables should be collected.

Multimodality imaging in HCM

Definition and epidemiology

HCM of sarcomeric origin is the most common cardiovascular disease of genetic origin, and is the leading cause of sudden death in athletes aged < 35 years [23]. In nearly 50—60% of cases it is caused by a genetic variation transmitted in an autosomal dominant mode. At least 17 genes are currently involved with variations encoding for heavy chain proteins of myosin (MYH7) and cardiac C protein (MYBPC3), accounting for about 80% of the identified pathogenic variations [24], but it can also be secondary to rare diseases (Table 2) [25].

HCM is defined by an unexplained maximal end-diastole wall thickness ≥ 15 mm in non-familial HCM, and ≥ 13 mm in familial HCM. This measurement should be performed preferentially in parasternal short-axis views [25].

TTE and CMR allow the assessement of anatomy (hypertrophy, mitral valve and apparatus analysis, intraventricular obstruction) and cardiac function. TTE is considered as the first-line imaging technique for the description of anatomy in patients with HCM. TTE allows depiction of the distribution of LV and RV hypertrophy. For the analysis of maximal LV wall thickness, measurements should be performed at end-diastole, at the level of maximal wall thickness, reviewing every echocardiographic reference view [26—28]. RV wall thickness should be measured in subcostal or parasternal long-axis view at end-diastole, at the level of the tricuspid chordae.

CMR can also be used to assess LV and RV hypertrophy. CMR seems to detect LV hypertrophy more frequently compared with TTE, and can assess hypertrophy extension, particularly in difficult cases with poor echogenicity, localized hypertrophy or apical localization [26].

Finally, cardiac CT for the evaluation of anatomy is limited by radiation exposure, and is restricted to patients with poor echogenicity on TTE and contraindication to CMR; cardiac nuclear imaging has a limited role because of its low spatial resolution and radiation exposure [26].

TTE is the first-line imaging technique for describing and assessing systolic and diastolic function in patients with HCM [25]. Quantification of LVEF is also possible with CMR, allowing a reproducible measure, particularly in patients with poor echogenicity or local hypertrophy.

Echocardiography enables description of the mitral valve and apparatus, which are found to be abnormal in 25—50% of patients with HCM [26]. The presence and severity of systolic anterior motion can be suspected in 2D, but is better described and characterized using M-mode. CMR can also provide similar information to that provided by TTE regarding the mitral valve and apparatus, and could be used when TTE is not conclusive [26].

LV outflow tract (LVOT) obstruction, mechanism and anatomical level of obstruction should be described using 2D TTE. LVOT obstruction is defined by a typical Doppler envelope, described as dagger-shaped, a late peaking curve and a peak gradient > 30 mmHg (at rest or after the Valsalva manoeuvre, standing or during exercise echocardiography) [25].

CMR provides tissue characterization, by giving the location and extension of myocardial fibrosis. The extent of fibrosis has been related to progressive LV dilatation and systolic dysfunction, and is potentially associated with prognosis [27].

Prognosis and guiding therapy

According to the most recent recommendations from the European Society of Cardiology concerning HCM, echocardiography is now considered to be a key examination for the assesment of prognosis. Among the seven criteria used to assess risk of sudden death at 5 years in HCM, three echocardiographic variables are used: maximal wall thickness; LV outflow tract gradient at rest or during the Valsalva manoeuver; and left atrial diameter [25].

According to current guidelines, septal reduction therapy can be proposed in HCM patients with LVOT obstruction ≥ 50 mmHg who are in New York Heart Association functional class III—IV, despite maximum tolerated medical therapy [25]. Echocardiography allows this gradient to be monitored, which helps with decisions of about septal reduction therapy. In case of septal alcohol ablation, myocardial contrast echocardiography is essential before alcohol injection [25].

Follow-up

Clinical evaluation, a 12-lead electrocardiogram and TTE are recommended every 12—24 months in clinically-stable patients presenting with HCM, and earlier in case of changed symptoms. CMR may be performed every 5 years in clinically-stable patients or every 2—3 years in patients with progressive disease. Finally, exercise testing may be performed every 2—3 years in stable patients (or less frequently in case of new symptoms) [25].

Multimodality imaging in RCM

RCM is defined as the combination of restrictive physiology, normal or reduced diastolic function, normal or near-normal LV systolic function and normal or near-normal wall thickness. RCM emcompasses an heterogeneous group of cardiomyopathies, and can correspond to several aetiologies, including familial, genetic and acquired disease [29]. RCM can be subclassified into familial/genetic cause and non-familial/non-genetic cause. The most frequent aetiologies are represented by amyloidosis, infiltrative disease, inflammatory cardiomyopathy with a restrictive physiology (sarcoidosis), storage disease, radiation therapy, drugs and endomyocardial disease (Table 3). The diagnosis pathway generally requires a combination of imaging techniques, such as TTE, CMR and — in some cases — cardiac nuclear imaging (sarcoidosis, amyloidosis), in order to caracterize the RCM. Imaging techniques allow identification of some specific patterns that can orientate aetiology and reduce the need to perform an endomyocardial biopsy in several clinical scenarios. However, endomyocardial biopsy is still needed to identify specific forms of RCM for which targeted

therapies are available, when non-invasive imaging methods are inconclusive (i.e. sarcoidosis, amyloidosis and Fabry disease) [30].

It should be noted that a certain degree of overlap may exist between specific aetiologies for HCM and RCM, and that RCM can progress in the late stage of the disease to DCM (e.g. haemochromatosis/iron overload, amyloidosis). These aetiologies need to be considered in the differential diagnosis between RCM and DCM.

Characterization of RCM with TTE

TTE is the first-line imaging modality in patients with a suspected diagnosis of RCM. The distinction between infiltrative and/or restrictive cardiomyopathies generally requires CMR to be performed, based on its unique ability to facilitate tissue characterization [27].

The diagnosis can be suspected based on a combination of TTE indices, such as normal RV and LV volumes and LVEF, normal RV function, biatrial enlargement and restrictive diastolic filling variables. Increased LV wall thickness may be seen in infiltrative processes after exclusion of aortic stenosis, HCM or hypertensive cardiomyopathy.

Characterization of RCM with CMR

CMR is generally performed after TTE, and allows function analysis and tissue characterization. Similarly to TTE, the RCM is characterized on CMR by normal or near-normal ventricular volumes associated with biatrial enlargement [30].

LGE, parametric imaging (T1 and T2 values) and static, cine and contrast-enhanced imaging are necessary to allow the accurate characterization of myocardial tissue (fibrosis, scar, inflammation, oedema or infiltration) that can contribute to a positive diagnosis, differential diagnosis and risk stratification. Elevated native T1 and increased extracellular volume are highly suggestive of cardiac amyloidosis [7], but subtype characterization requires complementary radionuclide imaging with bone avid radiotracers, and screening for an abnormal monoclonal protein or light chain in the blood sample [31]. By comparison, a low native T1 is suggestive of Fabry disease or iron overload [7], while decreased T2-weighted signal intensities are only found in iron overload myocardial disorders. Fast spin-echo T2-weighted sequences and increased native T2 are markers of myocardial oedema and inflammation.

Cardiac CT

Cardiac CT does not allow identification of restrictive physiology or aetiology, but is able to identify some of the features associated with restrictive physiology, such as dilated atrium, parodoxical septum motion, inferior vena cava dilation and pleural effusion. In some cases, it also allows the differential diagnosis to be made with pericardial constriction, by identifying pericardial thickening and calcification. Finally, cardiac CT may play a particular role when TTE and/or CMR cannot perform the diagnosis or are contraindicated. However, radiation exposure and iodine injection limit its use [30].

Cardiac nuclear imaging

Cardiac nuclear imaging, in combination with TTE and CMR, plays an important role in the diagnosis of cardiac amyloidosis. In clinical practice, radiolabelled SPECT bone avid tracers (technetium-99m-3,3-diphosphono-1,2-propanodicarboxylic acid [^{99m}Tc-DPD], technetium-99m-hydroxymethylene diphosphonate [^{99m}Tc-HMDP] and technetium-99m-pyrophosphate [^{99m}Tc-PYP]) are used to differentiate cardiac amyloidosis subtypes. Bone scintigraphy is depicted in four grades on the basis of the Perugini classification. A positive scan is not specific for transthyretin amyloidosis, and can be seen in other subtypes, particularly AL amyloidosis [30]. However, positive bone scintigraphy above Perugini grade 2, combined with the absence of a monoclonal protein or light chain in blood samples, was reported to be 100% specific for transthyretin amyloidosis [31]. ^{18}F-FDG PET is helpful after first-line CMR in case of suspicion of cardiac sarcoidosis, as it allows discrimination between the inflammatory and fibrotic phases of the disease, and thus can guide therapy, assess prognosis and monitor immunosuppressive therapy [32,33].

Multimodality imaging in ARVC

ARVC is a rare inherited disease, with an estimated prevalence of 1:2000 to 1:5000; it affects men more frequently than women (3:1). A genetic mutation is found in up to 50—60% of probands, mostly affecting desmosomal genes. ARVC is characterized by progressive replacement of the ventricular myocardium by inflammatory cell infiltrate and a fibrofatty process of the RV wall and, in 50—60% of cases, of the LV wall [34]. ARVC exposes the patient to an increased risk of ventricular arrhythmias, sudden cardiac death, ventricular dysfunction and heart failure. The diagnosis is generally suspected in patients with palpitations or syncope, and in patients presenting with ventricular arrhythmias, typically with left bundle branch block morphology and superior axis.

Cardiac imaging is used to assess ARVC diagnosis, disease staging and progression and risk of ventricular arrhythmias and heart failure, and to differentiate ARVC from other diseases (myocarditis, sarcoidosis, systemic sclerosis, athlete's heart, Brugada syndrome and congenital heart diseases with RV overload) [34,35].

Diagnostic criteria were initially published in 1994, and were updated in 2010, with the main goal being to improve diagnostic criteria sensitivity while maintaining specificity.

The 2010 Task Force Criteria propose combining data from different examination categories, including family history, genetic testing, tissue properties, electrical variables (electrocardiogram and Holter monitoring), and imaging modalities (TTE, CMR) to diagnose ARVC. Cardiac CT and radionuclide angiography/SPECT/PET are not yet recommended for evaluating patients in whom ARVC is suspected, but these techniques could be used in patients with a contraindication to CMR or with a poor acoustic window. The use of contrast agents has not been investigated to improve the diagnostic accuracy of TTE for the diagnosis of ARVC [34].

2D echocardiography

As a result of its availability, versatility, lack of radiation and validation in ARVC, echocardiography is the first-line imaging modality when ARVC is suspected. According to the 2010 Task Force Criteria, imaging criteria assessed with 2D echocardiography to diagnose ARVC include regional wall motion abnormalities and global RV dysfunction and/or RV dilatation (Table 4). In addition to these variables, the recently-published expert consensus proposes the addition of tricuspid annular plane systolic excursion (TAPSE), RV basal diameter, RV global longitudinal strain and RV free wall strain, despite the fact that none of these variables has been validated as yet in multicentre studies [34,35].

3D echocardiography

3D echocardiography allows measurement of RV volumes, overcoming the limitations of conventional 2D echocardiography, but requires expertise for RV acquisition and analysis, and good image quality. However, the value of 3D echocardiography and cut-off values for ARVC diagnosis and risk stratification need to be established [34].

CMR

RV regional dysfunction, reduced RV ejection fraction and enlarged indexed RV end-diastolic volume, as well as localized RV wall thinning and aneurysmal formations, are the main CMR features that allow the diagnosis of ARVC. Despite the ability of CMR to detect myocardial fibrofatty replacement, LGE was not considered by the 2010 Task Force Criteria as a robust diagnostic criterion, notably because of the difficulty in assessing the presence or not of LGE in a thin RV wall. However, LV involvement in arrhythmogenic cardiomyopathy and LV dominant forms are described increasingly, and LV LGE on CMR can be the only structural sign of the disease [36].

Multimodality imaging in takotsubo syndrome

Definition and epidemiology

Takotsubo syndrome is an unclassified cardiomyopathy, characterized by temporary regional wall motion abnormalities of the LV in a clinical context, evoking acute coronary syndrome (chest pain, electrocardiogram abnormalities, elevated cardiac biomarkers), with emotional or physical triggers. Takotsubo syndrome is estimated to represent approximately 1—3% of all patients presenting with suspected acute coronary syndrome, with a majority of elderly women (mean age 67—70 years) [35]. The precise pathophysiological mechanisms of takotsubo syndrome are incompletely understood, but there is considerable evidence that sympathetic stimulation is central to its pathogenesis.

Table 4 Imaging criteria for arrhythmogenic right ventricular cardiomyopathy from the modified Task Force Criteria.

Global or regional dysfunction and structural alterations
Major
2D echo criteria
Regional RV akinaesia, dyskinaesia or aneurysm, and one of the following measured at end-diastole
PLAX RVOT $\geq$ 32 mm
PSAX RVOT $\geq$ 36 mm
Fractional area change $\leq$ 33%
CMR criteria
Regional RV akinaesia or dyskinaesia or dyssynchronous RV contraction, and one of the following
Ratio of RV end-diastolic volume to BSA $\geq$ 110 mL/m^2 (male) or $\geq$ 100 mL/m^2 (female)
RV ejection fraction $\leq$ 40%
RV angiography criteria
Regional RV akinaesia, dyskinaesia or aneurysm
Minor
2D echo criteria
Regional RV akinaesia or dyskinaesia, and one of the following measured at end-diastole
PLAX RVOT $\geq$ 29 to < 32 mm
PSAX RVOT $\geq$ 32 to < 36 mm
Fractional area change > 33% to $\leq$ 40%
CMR criteria
Regional RV akinaesia or dyskinaesia or dyssynchronous RV contraction, and one of the following
Ratio of RV end-diastolic volume to BSA $\geq$ 100 to < 110 mL/m^2 (male) or $\geq$ 90 to < 100 mL/m^2 (female)
RV ejection fraction > 40% to $\leq$ 45%

2D: two-dimensional; BSA: body surface area; CMR: cardiac magnetic resonance; echo: echocardiography; PLAX: parasternal long axis; PSAX: parasternal short axis; RV: right ventricular; RVOT: right ventricular outflow tract.

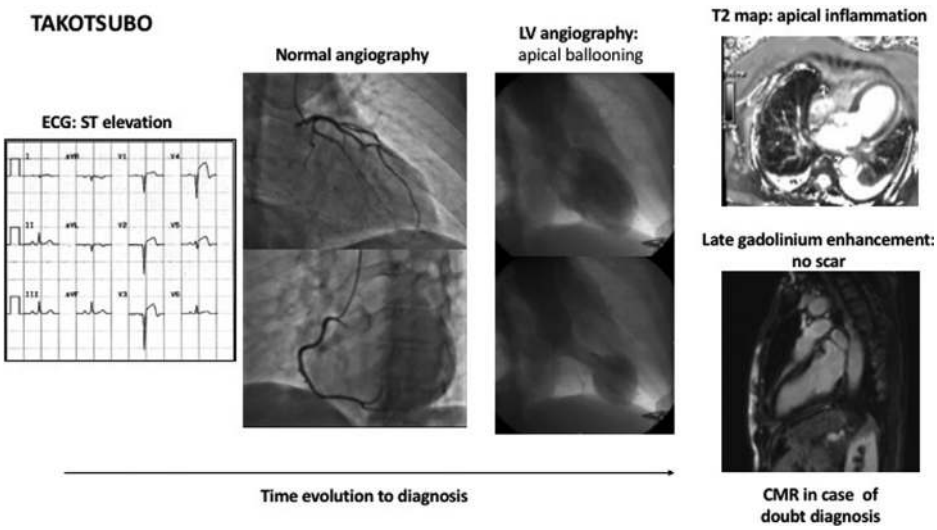

Figure 4. Example of use of multimodality imaging, which must be integrated with all file elements of the patient, for the diagnosis of left ventricular (LV) non-compaction. CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram.

Diagnosis

Several diagnostic criteria exist, but no actual consensus has been reached. Recently, the European Society of Cardiology published an international expert consensus document containing the diagnostic criteria summarized in Table A.4 (see also Fig. 4). All guidelines emphasize the importance of not ignoring a pheochromocytoma. For imaging diagnosis, coronary angiography with left ventriculography is considered as the diagnostic gold standard to exclude or confirm takotsubo syndrome. Invasive coronary angiography excludes significant coronary artery disease, and ventriculography shows regional wall motion abnormalities. Four patterns of takotsubo syndrome have been described: the typical pattern (akinesia of apical LV and mid-ventricular segments); the apical sparing variant (akinesia of mid-ventricular segments); the inverted takotsubo (akinesia of basal LV segments); and the controversial focal pattern. Haemodynamic assessment can be of importance, and shows LVOT obstruction and increased LV end-diastolic pressure. If diagnosis is uncertain following invasive coronary angiography, the case is considered as myocardial infarction with non-obstructed coronary arteries (MINOCA), and CMR is then especially relevant [37,38]. Recently, specific CMR criteria for takotsubo syndrome diagnosis were established. Steady-state free precession sequences show typical regional wall motion abnormalities, with LV apical ballooning, and basal segments are hyperkinetic. T2-weighted images (short-axis view) demonstrate normal signal intensity of the basal myocardium, but global oedema of the mid and apical myocardium, and usually no scars are identifiable by LGE [39]. In several cases, subtle fibrosis has been described, which indicates worse outcomes [40]. Whatever the clinical presentation and pattern, a complete recovery of LV contractility within 4-8 weeks is usually observed by TTE, and this should be systematically assessed before definitively concluding that the patient has takotsubo syndrome. In the presence of life-threatening co-morbidities, a non-invasive imaging strategy can be discussed, and European Society of Cardiology guidelines propose the use of TTE and CT angiography in patients presenting with non-ST-segment elevation myocardial infarction [34]. Advanced echocardiographic techniques, such as speckle-tracking imaging, can help to evidence decreased longitudinal systolic strain of mid-apical segments and LV twist mechanics, which are more severely impaired in takotsubo syndrome compared with myocardial infarction [35].

Cardiac nuclear imaging can be used to measure perfusion in dysfunctional segments, using SPECT (^{201}thallium chloride or ^{99m}technetium sestamibi), metabolism (^{18}F-FDG-PET) and innervation (^{123}I-metaiodobenzylguanidine [^{123}I-MIBG; imaged with SPECT]), in order to better understand the underlying physiopathology, but these elements do not change the management strategy.

Prognosis

Assessment of prognosis is mostly performed in the acute phase with several serious events (cardiogenic shock, cardiac arrhythmias, ventricular thrombus, pulmonary oedema, RV dysfunction, mitral regurgitation or LVOT obstruction). Indeed, the rates of cardiogenic shock and death in the acute phase [40], as well as long-term event rates, are similar to those in patients with acute coronary syndrome [41]. LVEF < 45%, E/e' ratio, reversible moderate to severe mitral regurgitation, systolic pulmonary artery pressure and RV involvement are the main echocardiographic variables that can contribute to risk stratification [40].

Follow-up

Close echocardiographic follow-up is necessary to confirm complete recovery of LV systolic function after the acute phase. No imaging modality can predict the risk of recurrence, which is estimated to be approximately 5% at 4-year follow-up [41,42].

Multimodality imaging and LV non-compaction

Definition and epidemiology

According to the European recommendations, LV non-compaction (LVNC) is an unclassified cardiomyopathy that may have some similarities to familial DCM. The genesis of LVNC has been speculated to represent arrest of the final stage of myocardial morphogenesis (myocardial compaction) [43].

Diagnosis

TTE and CMR have been used for diagnostic purposes, complemented by genetic testing for the identification of causative genes and screening of family members. Clinical manifestations are variable (arrhythmia, heart failure signs), with no specific electrocardiogram abnormalities. Several diagnostic criteria have been defined for TTE [44–47], CMR [48,49], CT [50] and fractal analysis.

The main measured variable for the diagnosis of LVNC is the ratio of the thickness of the non-compacted layer to the thickness of the compacted layer (Table 5). Measurements are performed in end-systole for TTE and in end-diastole for CMR. Advanced TTE technology, such as speckle tracking, 3D and contrast, can help to diagnose LVNC (Fig. 5).

However, the absence of definitive diagnostic criteria can lead to under- or overdiagnosis of LVNC. In some patients, the differentiation of pathological trabeculations consistent with LVNC from normal LV trabeculations or hypertrabeculations may be difficult. Indeed, increased or excessive

Table 5 Diagnostic criteria for left ventricular non-compaction.

	Trabeculation	Acquisition	View
TTE criteria			
Jenni et al.	NC/C ratio > 2.0 Evidence of intratrabecular recesses filled by blood flow from the LV cavity (Doppler) Absence of coexisting cardiac structural abnormalities Predominant localization in the lateral, apical or inferior walls of the LV	End-systolic	Short-axis view
Chin et al.	Distance between the epicardial surface and trough of a trabecular recess/distance between the epicardial surface and peak of the trabeculation < 0.5	End-diastolic	Short-axis and apical views
Stöllberger et al.	Three trabeculations protruding from the LV wall, apically to the papillary muscles Intertrabecular spaces perfused (Doppler) Trabeculations with the same echogenicity, and moving synchronously with myocardium contractions	Unspecified	Unspecified (trabeculations visible in one image plane)
Belanger et al.	Maximal NC/C and area of trabeculation by planimetry Severe form NC/C ratio ≥ 2 or area ≥ 5 cm	Unspecified	Apical view and any view for analysis of apex
CMR criteria			
Petersen et al.	NC/C ratio > 2.3	End-diastolic	Three long-axis views (i.e. horizontal and vertical long-axis views and LVOT)
Jacquier et al.	Trabecular LV mass > 20% of global LV mass	End-diastolic	Short-axis view
Captur et al.	Global LV fractal dimension ≥ 1 Maximal apical fractal dimension ≥ 1	End-diastolic	Short-axis view
CT criteria			
Melendez-Ramirez et al.	NC/C ratio ≥ 2.2 in at least two myocardial segments	End-diastolic	Short-axis views (i.e. basal, mid-ventricular and apical); long-axis views (i.e. two-, three- and four-chamber); segment 17 was excluded

CMR: cardiac magnetic resonance; CT: computed tomography; LV: left ventricular; LVOT: left ventricular outflow tract; NC/C: non-compacted/compacted; TTE: transthoracic echocardiography.

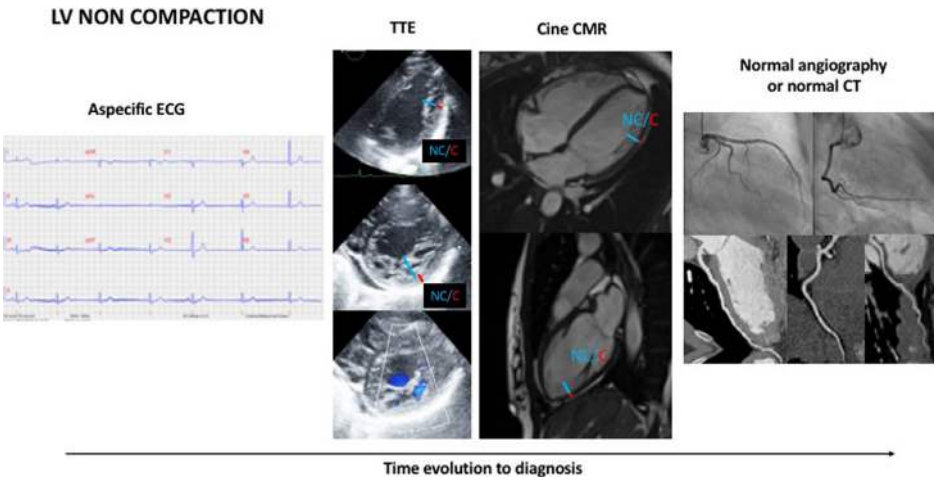

Figure 5. Example of use of multimodality imaging, which must be integrated with all file elements of the patient, for the diagnosis of takotsubo syndrome. CMR: cardiac magnetic resonance imaging; CT: computed tomography; ECG: electrocardiogram; LV: left ventricular; NC/C: non-compacted/compacted ratio; TTE: transthoracic echocardiography.

LV trabeculations, as assessed from end-diastolic images in individuals representing an asymptomatic population, appeared benign, and were not associated with deterioration in LV volumes or function over an almost 10-year period. Several non-genetic LVNC cases were also reported in athletes, pregnancy, haematological diseases (e.g. sickle cell anaemia) and chronic renal failure with polycystic kidney. In these difficult cases, the analysis of all data from the patient file by the cardiovascular imaging group allowed a diagnostic conclusion to be reached.

Prognosis

The degree of LV trabeculation seems to have no prognostic impact over and above LV dilation, LV systolic dysfunction and the presence of LGE. LGE has been shown to affect both non-compacted and normal walls, and is associated with more severe clinical forms.

Treatment of heart failure, use of implantable-cardioverter defibrillators and cardiac resynchronization represent therapeutic options if the patient meets the criteria recommended in published guidelines. A particularity is that the thromboembolic risks associated with LVNC are well known. Here, imaging can help to analyse the severity and distribution of hypokinetic segments and trabeculations (apical > basal segments), to evaluate the risk of LV thrombi. CMR is particularly useful for identifying LV thrombi.

Definition of a cardiovascular imaging group

In the context of cardiomyopathy, because of the variety of scientific fields involved, the large number of imaging modalities, the rapid development of these methods and the need for medical evaluation in clinical practice, collaborative work is required, with the creation of cardiovascular imaging groups combining cardiologists, radiologists and nuclear medicine physicians (Fig. A.2). A multimodality imaging approach should be encouraged, which is the efficient integration of various cardiovascular imaging methods, to improve the ability to diagnose, guide therapy or predict outcomes. Each technique has strengths and weaknesses that should be known, trying to avoid redundant information and to take into account availability, benefits, risks and cost. As proposed by the European Association for Cardiovascular Imaging, cardiovascular imaging groups must be composed of experts from all modalities, including at least one person with European Level 3 for each modality. All members of the cardiovascular imaging group should be strongly encouraged to obtain the ability to perform and interpret images in additional modalities (Level 2) [3]. Imaging should be performed in centres with recognized expertise in heart muscle diseases. Experts in different imaging techniques should collaborate, and the different methods should be complementary, but not competitors. Cardiac imaging groups implement consensus clinical indications for imaging in cardiomyopathies to guide patient management through the rigorous application of international recommendations. Cardiovascular imaging groups must define standardized technical protocols for the acquisition, interpretation and reporting of these imaging techniques in the evaluation of cardiomyopathies. Regular consultation meetings must be organized for the care of patients. Because images from all imaging modalities are usually performed and interpreted by multiple physicians, standardized communication is essential; this will make it possible to manage patient care in a collegiate way, and to have a pedagogical virtue. No imaging tests must be performed or interpreted as a referee test, but rather all tests must be integrated with all the available information from the patient's file [3]. Cardiac imaging is important in identifying cardiomyopathy, but the final diagnosis has to be based on multiple factors, including medical history, familial history, symptoms, ability to exert effort, age, sex, electrocardiogram, 24—48-hour Holter monitoring, blood tests and genetic analysis. Identification of a specific underlying aetiology may allow targeted disease-specific treatment and guide the potential need for family screening,

Perspectives

Echocardiography remains crucial for the non-invasive diagnostic evaluation of cardiomyopathies, because of its high spatiotemporal resolution, cost-effectiveness, availability and (mostly) portability, in constant evolution. CMR will probably allow the increasingly accurate analysis of the myocardium, as a result of the development of new sequences becoming available in large-scale clinical practice, such as mapping of its functioning by four-dimensional flow. The excellent spatial resolution of cardiac CT, together with ongoing technological advances, will probably lead to an increasingly important place for this methodology in the evaluation of coronary artery disease. The development of new tracers for nuclear molecular imaging will provide insights into physiopathological phenomena. Hybrid PET-CMR is emerging as a promising combination of the strengths of each imaging modality. Multimodality imaging approaches will probably be necessary in the near future, to better stratify the patient's individual risk. Ultimately, the last frontier in cardiomyopathy imaging may be the individualization of therapy using multimodality imaging, to identify the mechanisms responsible for disease in each patient. Fusion imaging will most certainly have an increasing role in interventional treatments. The future of imaging in the diagnosis and management of cardiomyopathies will also involve an evolution of its use in care, teaching and research. Training goals for future cardiac imaging experts must be defined; academic and industry partnerships should enable the connection to be made between imaging data and clinical data on the one hand and outcomes on the other hand, using big-data analysis and artificial intelligence.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://doi.dx.org/10.1016/j.acvd.2019.07.004.

Disclosure of interest

The authors declare that they have no competing interest.

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