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SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*

The Heart Hospital, 16–18 Westmoreland Street, London W1G 8PH, UK

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In 2008, The ESC Working Group on Myocardial and Pericardial Diseases proposed an updated classification of cardiomyopathies based on morphological and functional phenotypes and subcategories of familial/genetic and non-familial/non-genetic disease. In this position statement, we propose a framework for the clinical approach to diagnosis in cardiomyopathies based on the recognition of diagnostic 'red flags' that can be used to guide rational selection of specialized tests including genetic analysis. The basic premise is that the adoption of a cardiomyopathy-specific mindset which combines conventional cardiological assessment with non-cardiac and molecular parameters increases diagnostic accuracy and thus improves advice and treatment for patients and families.

Keywords Cardiomyopathy • Diagnosis • Phenotype • Genotype

Introduction

In 2008, The ESC Working Group on Myocardial and Pericardial Diseases proposed an updated classification of cardiomyopathies that was designed to integrate current and future knowledge of the molecular basis of heart muscle diseases into everyday clinical practice.[1] Being clinically oriented, this classification was based on morphological and functional phenotypes rather than putative pathophysiological mechanisms. Subcategories of familial/genetic and non-familial/non-genetic disease were proposed to highlight the importance of genetic mechanisms in cardiomyopathies.

In this position statement, we discuss the implications of this classification system for the diagnostic pathways that should be used in patients with a definite or suspected cardiomyopathy. The basic premise is that the adoption of a cardiomyopathy-specific mindset that combines conventional cardiological assessment with non-cardiac and molecular parameters increases diagnostic accuracy and improves advice and treatment for patients and families. A fundamental tenet of this approach is that the systematic search for diagnostic clues or 'red flags' can identify particular disorders and guide rational selection of diagnostic tests, including molecular genetic analysis. Importantly, each stage of the clinical pathway from history to molecular testing has value—in other words, the most technologically sophisticated (and expensive) examinations are not necessarily the most informative.

This statement is not meant to be an exhaustive compendium of all possible causes of heart muscle disease, but is designed instead to provide a conceptual template for diagnosing cardiomyopathies. The focus is predominantly on genetic forms of cardiomyopathy, but inflammatory diseases will be considered in a forthcoming position statement by the working group. The structure of the

* Corresponding author. Tel: +44 203 456 4801, Fax: +44 207 573 8827, Email: perry.elliott@ucl.ac.uk

document follows the traditional stepwise approach of history, physical examination, electrocardiography, and cardiac imaging. Tests that should be performed routinely in all patients with suspected heart muscle disease are proposed, along with more specialized tests and their indications. This document does not consider diseases confined exclusively to neonates and infants, but does refer to conditions that affect adolescents and which can be diagnosed in adulthood. Whenever possible, each of the main phenotypes (i.e. dilated, hypertrophic, restrictive, and right ventricular cardiomyopathies) is considered separately.

Rationale for a cardiomyopathy-focused clinical approach

Cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality.[1] They are grouped into specific morphological and functional phenotypes, with each phenotype subclassified into genetic and non-genetic forms (genetic in this context referring to single gene mutations). Patients with cardiomyopathy can present for the first time with symptoms of heart failure, arrhythmia (including cardiac arrest), syncope, and chest pain, but many are diagnosed incidentally or during family screening. Once a morphological diagnosis has been made, further investigations are often protocol rather than hypothesis driven, but this approach can fail to identify an underlying disease mechanism. In this document, we propose a complementary diagnostic strategy built on an understanding of the complex aetiology and clinical presentation of heart muscle disorders. This approach does not necessarily involve the use of novel or particularly sophisticated tests, but it does require deliberate analysis of every aspect of the individual and their family as well as an integrated probabilistic interpretation of cardiac investigations. The details of this scheme differ to a greater or lesser extent between cardiomyopathies, but there are some common principles:

- Elucidation of a specific cause for a cardiomyopathy can directly influence management of patients and their relatives.
- Some cardiomyopathies are caused by single gene mutations, whereas others show familial aggregation as a result of a complex genetic background and an interaction with environmental triggers.
- Diagnostic criteria in familial disorders can differ between probands and their relatives.
- In the context of a familial disease, the information provided by the relatives can offer diagnostic clues because of the variable expression of the disease.
- Reanalysis of clinical data is required throughout the diagnostic process as further information emerges.
- The approach to patients with definite or suspected cardiomyopathy should be multidisciplinary in nature.

We acknowledge from the outset that many recommendations and statements in this document are based on consensus opinion rather than a strong evidence base, but this is meant to be a flexible document that can be adapted to new knowledge as it emerges.

Clinical and family history

Although an unfocused dialogue with the patient may be necessary at the initial contact, this is not the optimal way of making a diagnosis. Deliberate exploration of diagnostic hypotheses is preferable; in other words, every question—however extemporary—needs to be hypothesis driven. The first step in achieving a diagnosis is to consider the personal and family history of the affected individual.

Age at diagnosis or first presentation is an important pointer to aetiology in all subtypes of cardiomyopathy. In neonates and infants, for example, inborn errors of metabolism and congenital dysmorphic syndromes are much more common than in older children or adults.[2–4] In contrast, wild-type transthyretin (TTR)-related amyloidosis is a disease of older individuals.

Personal and family history

After exclusion of common causes of ventricular dysfunction such as hypertension, myocardial ischaemia, valve dysfunction, and prior exposure to toxins and environmental pathogens, the cardiologist should systematically consider the probability of a genetic origin of the cardiomyopathy.[5,6] Cardiac and extra cardiac personal history should be recorded, especially when there is the possibility of a syndromic or metabolic cause of cardiomyopathy (*see section dedicated to symptoms and physical examination*). The next step is to take a detailed family history in order to identify other family members known or suspected to be affected by a myocardial disease or that have features suggestive of a genetic disorder; for example, a history of sudden cardiac death, heart failure, cardiac transplantation, pacemaker/defibrillator, stroke in a young individual, and skeletal muscle disease. This process is facilitated by the construction of a three- to four-generation family pedigree. This requires time and skill to create, but is essential as it helps to determine the probability of familial disease, the likely mode of inheritance, and identifies other clinical features that can provide aetiological clues. Importantly, a 'negative' family history does not exclude a genetic aetiology because the disease may be the result of a *de novo* genetic mutation or, more frequently, an unrecognized myocardial disease in the family. In addition, since a proportion of patients with suspected idiopathic dilated cardiomyopathy or suspected myocarditis may have an underlying immune-mediated inflammatory process, it is important to identify non-cardiac autoimmune diseases in the index case and in family members (e.g. type I diabetes mellitus, autoimmune thyroid disease, etc.), since familial aggregation is a feature of autoimmune disease.

A major objective of pedigree analysis is determination of the mode of genetic transmission. This not only allows identification of other clinically affected family members, but also helps refine the initial diagnosis of the proband. This aspect is especially relevant in families with mixed phenotypes. *Table 1* summarizes the type of inheritance of the most common cardiomyopathies.

Table 1 Pattern of inheritance of the main types of genetic cardiomyopathy

Cardiomyopathy	Pattern of inheritance			
	AD	AR	X-Linked	Matrilinear
Hypertrophic cardiomyopathies				
Sarcomeric	X			
Anderson–Fabry disease			X	
Danon disease			X	
Familial transthyretin-related amyloidosis	X			
Friedreich's ataxia		X		
Noonan/LEOPARD syndrome	X			
Mitochondrial cardiomyopathy				
Mitochondrial DNA mutations				X
Nuclear DNA mutations	X	X	X	
Dilated cardiomyopathies				
Lamin A/C mutation	X			
Emery–Dreifuss muscular dystrophy type 1			X	
Emery–Dreifuss muscular dystrophy type 2	X			
Dystrophinopathies (Duchenne, Becker, X-linked DCM)			X	
Desminopathies	X	X		
Arrhythmogenic right ventricular cardiomyopathy	X	X		

AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

The key features to note for different inheritance patterns are as follows:

(i) **Autosomal dominant** inheritance is characterized by the presence of affected individuals in every generation with male-to-male transmission and a 50% risk to offspring of affected parents. When the affected parent is the father, autosomal recessive and mitochondrial patterns can be excluded. When the affected parent is the mother, autosomal dominant inheritance is likely after ruling out mitochondrial diseases.

(ii) **Autosomal recessive inheritance** is the least common pattern in heart muscle diseases. It should be suspected when both parents of the proband are unaffected and consanguineous. Males and females are equally affected. Parents of an affected child are obligate carriers, with a 25% risk of having a carrier son/daughter in each pregnancy.

(iii) If males are the only or most severely affected individuals, **X-linked inheritance** should be suspected. In X-linked inheritance, all daughters of an affected father will be carriers and no male–male transmission is observed. A female carrier has a 50% risk of having affected sons and a 50% risk of daughters that carry the gene defect. X-linked inheritance is more likely if one or more patients in the family have symptoms of skeletal muscle involvement.

(iv) **Matrilinear inheritance** in which women but not men transmit the disease to offspring (male and female) is typical of mitochondrial disease caused by mutations in mitochondrial DNA. The presence of abnormalities in different organs (e.g. lactacidaemia, hypoacusia, palpebral ptosis, myopathy with ragged red fibres, ophthalmoplegia, encephalopathy, and retinitis pigmentosa) increases the level of suspicion for a mitochondrial disease.[7]

There are a number of common pitfalls to be aware of when interpreting family pedigrees:

- In some X-linked disorders such as Anderson–Fabry disease, female 'carriers' can develop milder and later disease because of unfavourable inactivation of the X-chromosome (Lyonisation).[8,9]
- Some autosomal dominant disorders with low clinical penetrance or small family pedigrees can give the appearance of sporadic disease.[6] Disease caused by *de novo* mutations can also be misattributed to environmental or acquired conditions.[6]

There are some additional hints that aid diagnosis:

- If father and son are affected, X-linked transmission can be ruled out.
- If mother and daughter are affected, X-linked transmission is highly unlikely.
- Different phenotypic types of cardiomyopathy can be found within the same pedigree, e.g. hypertrophic, dilated, and restrictive cardiomyopathies. This situation (albeit uncommon) is typical of sarcomeric mutations.[10,11]
- In other circumstances, phenotypic heterogeneity is found at organ level; for example, an affected family member may show hypertrophic or dilated cardiomyopathy, experience stroke-like episodes, or have hearing loss or liver dysfunction or diabetes, each in isolation in combination. This kind of heterogeneity suggests mitochondrial disease, particularly in the context of matrilinear transmission.

Symptoms and physical examination

Cardiomyopathies are a common feature of multi-system diseases. The mechanisms of multi-organ involvement are heterogeneous and include:

- Genetic mechanisms that result in the absence or dysfunction of important proteins shared by many organs (e.g. dystrophin, lamin A/C).
- Organ infiltration/storage (e.g. amyloidosis/Anderson–Fabry disease, haemochromatosis).
- Mitochondrial dysfunction (e.g. Kearns–Sayre syndrome and MELAS).
- Developmental abnormalities (e.g. cardiofaciocutaneous syndromes).

Symptoms of multisystem disease may be volunteered by patients themselves or be easily determined on routine examination; for example, deafness, blindness, or dysmorphic appearance. Other features require specific enquiry—for example, acroparaesthesiae, mental retardation, carpal tunnel syndrome, or erectile impotence—or require laboratory or clinical testing. Some examples of signs and symptoms associated with specific diagnoses are shown in *Table 2*.

In multisystem disease, phenotypic expression in other organs frequently precedes cardiac manifestations and the cardiologist's role is to search for cardiac involvement in a patient who already has a diagnosis. In other cases, cardiomyopathy is the presenting feature—for example, in many cases of Becker's muscular dystrophy, Freidreich's ataxia, TTR amyloidosis, and Anderson–Fabry disease. In these circumstances, the chance of reaching the correct diagnosis is often dependent on the level of suspicion by the examining cardiologist.

Cardiomyopathies may be a feature of rare congenital dysmorphic syndromes[12–22] that are diagnosed during infancy and childhood. A detailed description of these disorders is outside the scope of this document, but cardiologists managing predominantly adult patients may encounter syndromes that present with cardiomyopathy. Among the most common are disorders of the RAS-MAPK pathway.[14–22] For example, Noonan syndrome, characterized by short stature, variable developmental delay, cutaneous abnormalities (cafe au lait spots), hypertelorism, ptosis, low set posteriorly rotated ears, and a webbed neck and LEOPARD syndrome, an acronym for lentigines (multiple), ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and sensory-neural deafness. Somatic features in these disorders can be subtle, particularly in early infancy, or become less evident in adulthood. The most common cardiac features are hypertrophic cardiomyopathy (more rarely restrictive cardiomyopathy) and congenital heart defects including pulmonary valve dysplasia, aortic coarctation, and patent ductus arteriosus.[17–22]

In older adults, cutaneous angiokeratomata, anhidrosis (less commonly hyperhidrosis), Raynaud's like symptoms, neuropathy (burning pain in the extremities), ocular manifestations (cornea verticillata and retinal vascular dilation), tinnitus, diarrhoea, and proteinuria are typical features of Anderson–Fabry disease.[23–25]

Skeletal muscle weakness suggests a primary neuromuscular disorder, for example, dystrophinopathy, motor ataxia (e.g. Friedreich's ataxia), mitochondrial disease (particularly if encephalopathy, ocular myopathy, or retinitis are present), a storage disorder (progressive exercise intolerance, cognitive impairment, and retinitis pigmentosa as in Danon disease), or disorders of intermediary metabolism (generally associated with hypoglycaemia, metabolic acidosis, hyperammonaemia, or specific biochemical abnormalities).[26–30] Skeletal muscle weakness usually precedes cardiac involvement and dominates the clinical picture, but occasionally, skeletal myopathy is subtle and the first symptoms or signs of the disease can be caused by cardiomyopathy (hypertrophic, dilated, or restrictive). This is relatively frequent in the following conditions: laminopathies, dystrophinopathies (excluding Duchenne), Danon disease, and adult onset mitochondrial diseases. In mitochondrial disease, a typical red flag is a discrepancy between normal cardiac haemodynamics and symptomatic limitation as well as objective measures of exercise capacity (low peak VO_2).

Standard electrocardiogram

The electrocardiogram is often the first test that suggests the possibility of myocardial disease. In this document, we propose a new approach to the interpretation of the electrocardiogram that integrates classical interpretation with a cardiomyopathy-specific approach that takes into account not only the ECG findings themselves but also the clinical context in which they occur. In other words, there is a need to reconsider traditional concepts such as 'hypertrophy', 'necrotic waves', and 'ischaemic abnormalities' derived from patients with hypertensive, valvular, and ischaemic heart disease.

The interpretation of the ECG in a patient with definite or suspected cardiomyopathy is guided by some general principles:

- An abnormal electrocardiogram may be the only phenotypic manifestation of a heart muscle disorder.
- The electrocardiogram should always be interpreted in the context of the findings on echocardiography and cardiac MRI.
- A number of electrocardiographic features can, in association with other specific clinical features, suggest the underlying diagnosis.

Some common ECG abnormalities that assist in diagnosis are shown in *Table 3*. Important examples include the following.

AV block

Progressive atrioventricular conduction delay due to disease of the AV node or His-Purkinjie system is common in many genetic diseases that affect the myocardium, including nuclear envelope disorders (laminopathies),[31–34] mitochondrial disease,[7,30,35] and storage or infiltrative diseases.[36–42] The coexistence of A-V block is, therefore, informative in the three main cardiomyopathy subtypes (*Table 3*). In a patient with a mildly dilated phenotype, AV block can also be the result of acute/subacute inflammation as in Lyme disease, giant cell myocarditis and sarcoidosis.[43–45]

Ventricular pre-excitation

Ventricular pre-excitation is a common feature of storage diseases (Pompe disease, *PRKAG2* mutations, Danon disease),[28,29,46,47] and

Table 2 Examples of signs and symptoms that should raise the suspicion of specific diagnoses grouped according to the main echocardiographic phenotype

Finding	Main echocardiographic phenotype			
	HCM	DCM	ARVC	RCM
Learning difficulties, mental retardation	Mitochondrial diseases Noonan syndrome Danon disease	Dystrophinopathies Mitochondrial diseases Myotonic dystrophy *FKTN* mutations		Noonan syndrome
Sensorineural deafness	Mitochondrial diseases Anderson–Fabry disease LEOPARD syndrome	Epicardin mutation Mitochondrial diseases		
Visual impairment	Mitochondrial diseases (retinal disease, optic nerve) TTR-related amyloidosis (vitreous opacities, cotton wool type) Danon disease (retinitis pigmentosa) Anderson–Fabry disease (cataracts, corneal opacities)	*CRYAB* (polar cataract) *Type 2 myotonic dystrophy* (subcapsular cataract)		
Gait disturbance	Friedreich's ataxia	Dystrophinopathies Sarcoglycanopathies Myofibrillar myopathies		
Myotonia (involuntary muscle contraction with delayed relaxation)		Myotonic dystrophy (type 1 and type 2)		
Paraesthesiae/sensory abnormalities/neuropathic pain	Amyloidosis Anderson–Fabry disease			Amyloidosis
Carpal tunnel syndrome (bilateral)	TTR-related amyloidosis			Amyloidosis
Muscle weakness	Mitochondrial diseases Glycogenosis *FHL1* mutation	Dystrophinopathies Sarcoglycanopathies Laminopathies Myotonic dystrophy Desminopathy		Desminopathies (generally distal progressing to proximal)
Palpebral ptosis	Mitochondrial diseases Myotonic dystrophy			
Lentigines/café au lait spots	LEOPARD syndrome			
Angiokeratomata Hypohidrosis	Anderson–Fabry disease			
Pigmentation of skin and scars		Haemochromatosis		
Palmoplantar keratoderma and woolly hair		Carvajal syndrome	Naxos and Carvajal syndromes	

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin.

mitochondrial disorders (MELAS, MERFF).[7,30] Thus, age at diagnosis, inheritance pattern, the type of cardiomyopathy, and associated features such as a skeletal myopathy are key considerations when interpreting its significance as a diagnostic marker.

Repolarization abnormalities

Repolarization abnormalities are a very common but non-specific feature of heart muscle disease. When interpreting ST-T wave abnormalities in a patient with cardiomyopathy, it is important to keep in mind that they are rarely a consequence of myocardial ischaemia. More frequently, they are the expression of ventricular strain or the result of a specific distribution of the cardiomyopathic process; for example, negative T waves in the right precordial leads in patients with 'classic' ARVC.[48] In ARVC with biventricular (or left dominant) involvement, negative T waves can also be found in the inferior and/or lateral leads. Another common example of regionality is the presence of giant T wave inversion in the precordial and/or inferolateral leads in patients with HCM and apical localization of left ventricular hypertrophy.

Table 3 Electrocardiographic abnormalities that suggest specific diagnoses, grouped according to the main cardiac phenotype

Main phenotype	Finding	Specific diseases to be considered
HCM	Short P-R /preexcitation	Glycogenosis; Danon disease; PRKAG2; Anderson–Fabry disease
		Mitochondrial disease
	AV block	Amyloidosis
		Late-stage Anderson–Fabry disease
		Danon disease
		Acute myocarditis
	Extreme LVH (Sokolow >100)	Danon disease; Pompe
	Low QRS voltage (or normal voltages despite increased LV wall thickness)	Amyloidosis
	Extreme superior ('North-West') QRS axis deviation	Noonan syndrome
DCM	AV block	Laminopathy
		Emery Dreifuss 1
		Myocarditis, particularly Trypanosoma cruzi, Diphtheria and Lyme disease
		Sarcoidosis
		Desminopathy
		Myotonic dystrophy
	Low P wave amplitude	Emery Dreifuss 1 and 2
	Atrial standstill	Emery Dreifuss 1 and 2
	'Posterolateral infarction'	Dystrophin-related cardiomyopathy
		Limb-girdle muscular dystrophy
		Sarcoidosis
	Low QRS voltage + 'atypical RBBB'	ARVC with biventricular involvement
	Extremely low QRS amplitude	PLN mutation (very rare)
ARVC	Inverted T waves in inferolateral leads	ARVC with biventricular involvement
	Epsilon waves in inferolateral leads	ARVC with biventricular involvement
RCM	AV block	Desmin-related cardiomyopathy
		Amyloidosis

ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; PLN, phospholamban; RBBB, right bundle branch block; RCM, restrictive cardiomyopathy.

QRS voltage

Extremely high QRS voltage

Extremely large QRS voltage is a typical feature of storage diseases such as Pompe and Danon disease.[28,29] Occasionally massive voltage may also be the consequence of pre-excitation, which should be considered if there little or no hypertrophy of the ventricles.

Low QRS voltage

Low QRS voltage, in the absence of other possible causes, such as pericardial effusion, is frequent in amyloid heart disease but has low sensitivity. For example, although frequent in AL amyloidosis, less than one-third of patients with TTR-related amyloid have a low QRS voltage.[42] More important is the relation of the total or peripheral QRS scores (arithmetic sum of positive and negative QRS waves voltages in the limb or in the 12 leads) to left ventricular mass.[41,42] A low ratio in the presence of a hypertrophic phenotype is consistent with AL and TTR amyloidosis, whereas low QRS voltage is rare in patients with hypertrophic cardiomyopathy caused by sarcomeric protein gene mutations, but may be seen in patients with progressive myocardial fibrosis that is progressing to systolic dysfunction.[49,50]

Low voltage ECG may be typical of a phospholamban mutation[51] and should be considered when dilated cardiomyopathy is associated with a high rate of ventricular arrhythmias, although these mutations seem to be rare.

Pseudo-infarction pattern

Pseudo-infarction pattern, in spite of normal coronary arteries, is a feature of many cardiomyopathies, but is particularly frequent in hypertrophic cardiomyopathy and amyloid heart disease.[41,52] In hypertrophic cardiomyopathy, this phenomenon is explained by asymmetric hypertrophy or myocardial scar.[53] Patients with hypertrophic cardiomyopathy may also have Q waves with upright T waves in the same leads (discordant QT vector),[50] a feature that is seen in few if any other conditions.

A posterior or postero-lateral infarct pattern in dilated cardiomyopathy should prompt consideration of dystrophin-related diseases, including Duchenne's or Becker's muscular dystrophy[26,54,55] and isolated X-linked dilated cardiomyopathies. In dilated cardiomyopathy, pseudo-infarction pattern in the precordial chest leads may also be present, but is probably explained by anticlockwise rotation of the heart. This pattern is sometimes

Table 4 First-level (to be performed in each patient) and second-level examinations (to be performed in selected patients that show features suggesting specific diagnoses)

	HCM	DCM	RCM
First level	CK Renal function Proteinuria Liver function tests	CK Renal function Proteinuria Liver function tests Haemoglobin and white blood cell count Serum iron, ferritin Calcium, phosphate, thyroid stimulating hormone	CK; Renal function; Proteinuria Liver function tests Haemoglobin and white blood cell count Serum iron, Ferritin Urine and plasma protein immunofixation,[a] free light chains[a]
Second level	alpha-Galactosidase A levels (or DNA for AFD suspected in women) Lactic acid[b]; myoglobinuria[b] Urine and plasma protein immunofixation,[a] free light chains[a]	Organ and non-organ specific serum autoantibodies; Titres for suspected infection: coxsackievirus, echovirus, influenza virus; HIV; Borrelia bugdorferi (suspected Lyme disease), Chagas disease (geographic exposure). Thiamine (alcohol abuse, nutritional deficiency). Urinary/plasma catecholamines (suspected phaeochromocytoma) Serum angiotensin converting enzyme (sarcoidosis)	Serum angiotensin converting enzyme (sarcoidosis) Organ and non-organ specific serum autoantibodies

AFD, Anderson–Fabry disease; CK, creatine kinase; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin.
[a]AL amyloidosis.
[b]Mitochondrial diseases.

associated with reduced voltage in the limb leads and deep S waves in right precordial leads (so-called Goldberger triad).[56]

Routine laboratory findings

Laboratory tests can be helpful in the detection of extra-cardiac conditions that cause or exacerbate ventricular dysfunction (for example thyroid disease and diabetes mellitus), but the value of routine laboratory testing lies mostly in the assessment of secondary organ dysfunction, as in severe heart failure, or in the detection of non-specific markers of disease severity such as natriuretic peptides. *Table 4* describes tests that should be performed in all patients with a cardiomyopathy and those tests that should only be considered in specific circumstances. *Table 5* summarizes abnormalities that raise the suspicion of specific cardiomyopathies, according to the main echocardiographic phenotype.

Special considerations

Autoimmune studies

Connective tissue diseases commonly affect the cardiovascular system but often remain subclinical. Patients can present with features of pericarditis, myocarditis, endocarditis, and vasculitis, but there is usually no correlation between the severity of systemic disease and cardiac involvement. In the context of dilated cardiomyopathy or myocarditis, particularly with positive family or personal history of autoimmune disease, serological testing for organ-specific and non-organ specific autoantibodies, and cardiac-specific autoantibodies in the index patient and in first-degree relatives may be considered.[57] In the presence of a positive cardiac-specific autoantibody test in a first-degree symptom-free relative, non-invasive cardiological assessment (clinical, ECG, and standard echocardiography) and immunological assessment should be repeated at 1 year intervals, since positive antibody status may precede development of a dilated cardiomyopathy phenotype.[58]

Creatine phosphokinase

Serum creatine phosphokinase (CK) should be measured in all patients, since an increase of plasma values represents a particularly useful hint in all the main cardiomyopathy phenotypes (*Table 5*). When interpreting CK values, one must consider some general rules and some possible pitfalls[59–64]:

- transient increases in CK can be due to many causes including muscle injuries and intramuscular injections. Consequently, only constantly elevated (on at least two occasions) serum CK levels are useful in diagnosing myopathies or lower motor neuron diseases.
- CK increase associated with neuromuscular disease varies from mild (2-fold increase) to marked (more than 10-fold). In general, the highest elevation of serum muscle enzymes is seen in dystrophinopathies, whereas more modest elevations occur in other dystrophies and in primary neurological disorders, particularly lower motor neuron disease.

Raised CK in patients with a dilated cardiomyopathy phenotype can suggest a dystrophin related disorder (e.g. Becker's or X-linked dilated cardiomyopathy), a laminopathy, or, more rarely, a disease of sarcoglycans, desminopathy, or a myofibrillar myopathy. X-Linked dilated cardiomyopathy is a typical example of dystrophin-related cardiomyopathy with an exclusively cardiac phenotype. In this rare, but underdiagnosed condition, raised serum CK may be the single diagnostic clue.[64] In patients with

Table 5 Abnormalities in routine laboratory tests that should raise suspicion of specific cardiomyopathies, grouped according to the main cardiac phenotype

Finding	Main cardiac phenotype		
	HCM	DCM	RCM
↑ Creatine kinase	Mitochondrial diseases Glycogenosis Danon disease	Dystrophinopathies Sarcoglycanopathies Zaspopathies (*LDB3* gene) Laminopathies Myotonic dystrophy *FKTN* mutations Desminopathies Myofibrillar myopathies	Desminopathies
Proteinuria with/without ↓ glomerular filtration rate	Anderson–Fabry disease Amyloidosis		Amyloidosis
↑ Transaminase	Mitochondrial diseases Glycogenosis Danon disease		
High transferrin saturation/ hyperferritinaemia		Haemochromatosis	Haemochromatosis
Lactic acidosis	Mitochondrial diseases	Mitochondrial diseases	
Myoglobinuria	Mitochondrial diseases	Mitochondrial diseases	
Leucocytopenia	Mitochondrial diseases (*TAZ* gene/Barth Syndrome)	Mitochondrial diseases (*TAZ* gene/ Barth Syndrome)	

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

HCM phenotype, metabolic disorders such as Danon or mitochondrial disease should be considered. Desmin-related cardiomyopathies are the typical example of RCM associated with elevated CK levels. When CK is raised, a detailed examination by a neurologist should be considered.

Metabolic storage disease

Storage diseases rarely present in adults, the major exception being Anderson–Fabry disease, which accounts for between 1 and 3% of adult patients with otherwise unexplained left ventricular hypertrophy.[23–25] Anderson Fabry disease is an X-linked lysosomal storage disease caused by deficiency in alpha galactosidase A. Hypertrophy is usually seen in men over the age of 30 and women over the age of 40 years of age. Routine measurement of alpha galactosidase A is probably justified in male patients with HCM over the age of 30 years.[24] In females with HCM, the diagnosis of Anderson–Fabry disease is problematic as plasma and leukocyte enzyme levels are often within the normal range. In this setting, it may be more efficient to perform genetic testing to exclude the diagnosis.[23,24]

Plasma cell dyscrasia

Cardiac amyloidosis is caused by a group of disorders that share the common characteristic of an extracellular deposition of insoluble fibrils derived from aggregation of misfolded but normally soluble proteins.[41,65] The commonest form, AL amyloid, is derived from monoclonal immunoglobulin light chains associated with plasma cell dyscrasias. A number of biochemical tests can be used to detect the abnormal clonal immunoglobulin production, including serum immunoglobulin free light chains assay, serum and urine immunofixation, and urine electrophoresis. However, when interpreting blood and urine tests, one must remember that up to 5% of the general population of elderly people has MGUS (monoclonal gammopathy of uncertain significance) and that is not necessarily an abnormal condition. For this reason, the diagnosis of amyloidosis remains histological.

Genetic testing

The basic principles of gene testing in cardiomyopathies have been discussed in a prior statement by the WG.[5] Whenever possible, genetic testing should be targeted to the likely diagnosis. However, we acknowledge that the pace of change in genetic sequencing technologies is already challenging the conventional approach to molecular diagnosis. The majority of Mendelian diseases are caused by rare mutations that affect the function of individual proteins; approximately 85% of these mutations occur in the coding region or in canonical splice sites. As coding regions constitute only approximately 1% of the human genome, sequencing of complete coding regions of genomes (the 'exome') can be an efficient strategy for the identification of novel rare functional mutations.[66,67] More recently, enrichment of targeted genomic segments by hybridization has been extended to the whole exome in rare Mendelian disorders.[67] Inevitably, there will be growing pressure to perform less targeted screening in patients with cardiomyopathy, but this approach is bound to result in the identification of numerous sequence variants, often novel, with low penetrance and unknown interactions with genetic and environmental modifiers. In our view, this development places even more emphasis on clinical phenotyping and the definition of sub-phenotypes.

Table 6 Echocardiographic clues to diagnosis grouped according to main morphological phenotype

Main cardiac phenotype	Finding	Specific diseases to be considered
HCM	Increased interatrial septum thickness	Amyloidosis
	Increased atrioventricular valve thickness	Amyloidosis; Anderson–Fabry disease
	Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson–Fabry disease
	Mild–moderate pericardial effusion	Amyloidosis, myocarditis
	Ground-glass appearance of ventricular myocardium	Amyloidosis
	Concentric LVH	Glycogenosis, Anderson–Fabry disease
	Extreme concentric LVH	Danon disease, Pompe disease
	Global hypokinesia (with/without LV dilatation)	Anderson– Fabry; mitochondrial disease; TTR-related amyloidosis; PRKAG2 mutations; Danon disease; myocarditis; end-stage sarcomeric HCM
DCM	LV non-compaction	Genetic DCM (more frequently sarcomeric mutations)
	Postero-lateral akinesia/dyskinesia	Dystrophin-related cardiomyopathy
	Mild (absent) dilatation + akinetic/dyskinetic segments with non-coronary distribution	Myocarditis Sarcoidosis
ARVC	Coexistent LV segmental dysfunction	Biventricular ARVC
RCM	Partial LV or RV apical obliteration	Endomyocardial fibrosis/hypereosinophilia

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; RCM, restrictive cardiomyopathy; RV, right ventricular; TTR, transthyretin.

Echocardiography

Two-dimensional and Doppler echocardiography remains the first line imaging tool for most forms of heart muscle disease. A detailed description of the diagnostic criteria for individual cardiomyopathy subtypes is beyond the scope of this statement, but some features are important diagnostic red flags (*Table 6*). As with the electrocardiogram, these are only useful when interpreted in the context of other phenotypic findings. Important examples include the following.

Infiltrative phenotype

Echocardiographic features that should prompt consideration of infiltrative myocardial diseases (in particular cardiac amyloidosis) include biventricular hypertrophy with involvement of the right ventricular free wall, increased thickness of the atrio-ventricular valves, thickening of the inter-atrial septum, and the presence of a small pericardial effusion.[41,42] Functional abnormalities consistent with an infiltrative disease include severe impairment of myocardial deformation indices.[68]

Left ventricular non-compaction

The diagnosis of non-compaction is challenging and its nosology is debated since this morphological trait can be shared by different cardiomyopathies and non-cardiomyopathic conditions.[69–71] However, when a definite diagnosis of non-compaction is made, the diagnostic process should orient towards a genetic disease with a relatively high probability of sarcomeric mutations.[70,71]

Massive hypertrophy in the young

Severe (maximal thickness more than 3 cm or equivalent in children) and concentric ventricular hypertrophy in a child, adolescent, or young adult is consistent with metabolic or storage disorders, in particular Pompe disease in the infantile period and Danon disease in adolescent males.[27–29,72]

Concentric hypertrophy with left ventricular systolic impairment

Concentric hypertrophy is common in metabolic, storage, infiltrative, and mitochondrial disorders. These diagnoses are more likely when there is co-existent systolic impairment. In this situation, the age of presentation is a fundamental clue to the differential diagnosis. For example the observation of a hypokinetic left ventricle with marked, concentric left ventricular hypertrophy in a child or a young adult should lead to the suspicion of a mitochondrial or storage myocardial disease. The same phenotype in a middle aged or elderly man is a hint towards the diagnosis of a TTR-related (mutant or wild-type) amyloidosis.

Myocarditis

Myocarditis is an inflammatory disease of the heart muscle characterized by histological evidence of myocardial inflammatory infiltrates associated with myocyte degeneration and non-ischaemic necrosis. It is caused by infectious agents, autoimmunity, systemic diseases, drugs, and toxins, but the aetiology is frequently not identified. Standard echocardiography can be entirely normal in myocarditis, but in the setting of an acute or subacute presentation of arrhythmia, heart failure or chest pain with angiographically normal coronary arteries, an inflammatory disorder should be considered in the presence of the following[73,74]:

(1) Segmental akinesis or dyskinesis that is unrelated to a coronary artery territory (particularly the basal or posterior basal

Table 7 Cardiac magnetic resonance imaging: main hints to orient an aetiological diagnosis for each morphological phenotype

Main phenotype	Hint	Condition to be suspected
HCM	Posterolateral LGE + Concentric LVH	Anderson–Fabry disease
	Diffuse subendocardial LGE	Amyloidosis
	Intense myocardial 'avidity' for Gadolinium	Amyloidosis
DCM	Short T2 *	Haemochromatosis
	Patchy, midwall LGE	Post-myocarditis
		Dystrophinopathy
	Akinesia/dyskinesia + LGE at the anterobasal septum or papillary muscles	Sarcoidosis
	Fatty replacement (T1w FS) within LV wall	ARVC 'Left Dominant'
ARVC	Fatty replacement (T1w FS) within LV wall	Biventricular involvement
RCM	Partial LV or RV apical obliteration + LGE at endocardial level	EMF/hypereosinophilia

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; EMF, endomyocardial fibrosis; HCM, hypertrophic cardiomyopathy; LGE, late Gadolinium hyperenhancement; LV, left ventricular; LVH, left ventricular hypertrophy; RCM, restrictive cardiomyopathy; RV, right ventricular; T1w FS, T1-weighted imaging.

segment of the left ventricle) associated with normal wall thickness, with or without a mild pericardial effusion.

(2) Severe left ventricular dysfunction and increased wall thickness with mild dilatation of the left ventricle (in fulminant cases).

Cardiac magnetic resonance imaging

The incremental contribution of cardiac magnetic resonance (CMR) imaging to the diagnosis of cardiomyopathies derives from accurate assessment of the morphology and function of the heart without the need for an 'anatomical window' and tissue characterization.[75–87] The combination of these two features enables CMR to resolve important questions of differential diagnosis and recognize some specific forms of myocardial disease.

Cardiac magnetic resonance imaging is able to characterize myocardial substrate on the basis of intrinsic magnetic properties of different tissues and the distribution patterns of Gadolinium-based contrast agents. Abnormal CMR findings may relate to myocardial oedema, fatty replacement, iron storage, amyloid infiltration, and myocardial fibrosis. However, just as with ECG and echo, the interpretation of CMR images must be made in the light of the overall clinical picture (*Table 7*). Some general concepts are useful in order to understand both the incremental value and the limits of CMR in the field of cardiomyopathies.

Storage diseases

In the majority of storage diseases, there are no specific diagnostic CMR signals. One exception is iron overload (genetic or acquired) in which T2* imaging can be used to detect and quantitate the severity of iron deposition within the myocardium, generally in the context of a dilated phenotype.[75] The technique can also be used to monitor the response to chelation therapy. In Anderson–Fabry disease, the intracellular accumulation of glycosphingolipid is not known to cause any signal abnormality by itself, but the diagnosis should be suspected in the presence of posterolateral late gadolinium hyperenhancement, concentric left ventricular hypertrophy with prominent left ventricular papillary muscles and trabeculae, and right ventricular involvement.[76]

Myocarditis

In a recent International Consensus Group on CMR Diagnosis of Myocarditis, the use of T2-weighted oedema imaging, T1-weighted early enhancement imaging, and T1-weighted late gadolinium enhancement was recommended in cases of suspected myocarditis.[83] It is suggested that myocarditis is likely if two of these three CMR techniques are abnormal, but this has not been prospectively evaluated against endomyocardial biopsy as a gold standard.

Myocardial infiltration

Gadolinium enhanced CMR can be used to detect expansion of the myocardial interstitium caused by inflammation, fibrosis, or extra cellular deposition of amyloid proteins. Cardiac magnetic resonance imaging cannot distinguish these entities by their magnetic properties alone, but the distribution and severity of interstitial expansion can, in the appropriate clinical context, be very suggestive of a specific diagnosis. In the case of AL amyloidosis, there is often global, sub-endocardial, or segmental late gadolinium enhancement and abnormal myocardial and blood-pool gadolinium kinetics with a dark appearance of the blood pool which reflects similar myocardial and blood T1 caused by high myocardial uptake and fast blood pool washout.[85]

Myocardial fat

Fibrofatty replacement of the right ventricular myocardium is the histological hallmark of ARVC, but its detection on CMR can be challenging because of frequent ventricular ectopy and overlying epicardial fat. In addition, fat alone is insufficient for a diagnosis of ARVC as it can be present in normal individuals. The probability that fatty replacement in the right ventricle represents ARVC should be considered only when it is associated with functional and morphological right ventricular abnormalities (aneurysms,

dilatation), ECG abnormalities indicative of right ventricular disease, arrhythmia of right ventricular origin, or a suspicious family history (e.g. young sudden cardiac deaths). The coexistence of late gadolinium enhancement in the left ventricle (particularly the posterior-lateral wall) is also suggestive.

Nuclear imaging

In most cardiomyopathies, the contribution of nuclear imaging to diagnosis is limited. Possible exceptions are sarcoidosis and TTR-related amyloidosis. In the past, thallium-201 and gallium-67 radionuclide scintigraphy were frequently used to detect cardiac sarcoidosis and to monitor response to treatment.[88] Gallium-67 accumulation, in particular, is thought to indicate active inflammation. Measurement of 18F-fluorodeoxyglucose (18F-FDG) uptake using positron emission tomography (PET) may have a higher sensitivity and spatial resolution for cardiac sarcoidosis, but heterogeneous uptake of 18F-FDG is also seen in other conditions such as idiopathic dilated cardiomyopathy and in healthy tissue leading to false positives.[89] Concomitant abnormal 18F-FDG PET uptake in extra cardiac tissues can be useful in suspected cardiac sarcoidosis.

In amyloidosis, I^{123}-labeled serum amyloid P (SAP) binds with all types of fibril (via a calcium-mediated mechanism) and is used to detect systemic amyloid deposits.[90] However, SAP scanning cannot be used to detect cardiac amyloid. Recently, studies have suggested that ^{99m}Tc-3,3-diphosphono-1,2-propanodi-carboxylic acid (^{99m}Tc-DPD) scintigraphy can image TTR amyloid (wild type or mutant) deposition in the myocardium.[91,92] This avidity for ^{99m}Tc-DPD is highly specific for the myocardium infiltrated by TTR-related amyloidosis as sarcomeric HCM does not take up this tracer at all.[92]

Role of endomyocardial biopsy

Use of endomyocardial biopsy varies enormously between centres and individual cardiologists. In asymptomatic patients with chronic disease, the role of routine biopsy and its incremental value over other diagnostic methods are unclear. For this reason, the working group recommends adherence with the current joint guidelines,[93] but recognizes that there will be individual circumstances in which endomyocardial biopsy may be useful. In the context of cardiomyopathy, endomyocardial biopsy remains a gold standard for the diagnosis of specific disorders including amyloidosis, sarcoidosis, and myocarditis. Endomyocardial biopsy is the only diagnostic tool for establishing aetiological diagnosis (viral or immune-mediated) in inflammatory cardiomyopathy (N.B. *The diagnosis and treatment of myocarditis/inflammatory cardiomyopathy will be the discussed in a forthcoming position statement of the working group*). There may also be a role for endomyocardial biopsy in patients with haemochromatosis, although genetic diagnosis and non-invasive imaging with CMR may be sufficient to establish the diagnosis.

Extra-cardiac biopsy (salivary glands, fat tissue, rectal tissue) can be considered for the diagnosis of amyloidosis when endomyocardial biopsy is not performed at first line.

Skeletal muscle biopsy can be also considered as an alternative to endomyocardial biopsy in case of CK elevation or clinical muscular symptoms.

Summary

In this position statement, we endeavour to create a framework for the clinical approach to diagnosis in cardiomyopathies. A key message is that the clinical assessment should not be restricted to cardiological examinations as the cardiomyopathies represent a challenging interface between cardiology and many other medical specialities. Another important aspect is the recognition of 'red flags' that guide rational selection of further diagnostic tests including genetic analysis and thereby identify specific subtypes of cardiomyopathy. Inevitably, gaps in knowledge remain and in many cases application of this scheme will fail to identify a likely cause for disease. Nevertheless, it is our assertion that disorders with very specific management strategies can be identified by applying the cardiomyopathy mindset outlined in this statement. Our long-term goal is to validate the approach through prospective multicentre collaborations such as the forthcoming ESC registry for cardiomyopathies.

Conflict of interest: none declared.

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