IJC Heart & Vasculature 18 (2018) 52–57

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Reverse remodeling in Dilated Cardiomyopathy: Insights and future perspectives

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ARTICLE INFO

Article history:
Received 16 January 2018
Received in revised form 6 February 2018
Accepted 16 February 2018
Available online 8 March 2018

ABSTRACT

Dilated Cardiomyopathy (DCM) has been classically considered a progressive disease of the heart muscle that inexorably progresses towards refractory heart failure, ventricular arrhythmias and heart transplant. However, the prognosis of DCM has significantly improved in the past few years, mostly as the result of successful therapy-induced reverse remodeling. Reverse remodeling is a complex process that involves not only the left ventricle, but also many other cardiac structures and it is now recognized both as a measure of therapeutic effectiveness and as an important prognostic tool. Nevertheless, several aspects of reverse remodeling remain unclear, including the best timing for its quantification, its predictors and its interaction with individual genetic backgrounds. In this review, we summarize our current understanding of reverse remodeling in patients with DCM and provide practical recommendations for the clinical management of this challenging patient population.

1. Introduction

Dilated Cardiomyopathy (DCM) is a disease of the heart muscle characterized by left ventricular (LV) or biventricular dilation and systolic dysfunction in the absence of pressure overload or coronary artery disease sufficient to explain the observed myocardial dysfunction [1,2]. The estimated incidence and prevalence of DCM are 7 cases per 100.000 people/year and 1 in 2500 respectively in western populations, but there are marked race-related differences and geographical differences. The prevalence of DCM in Africa and Latin America has been shown to be double that of western populations, while the prevalence of the disease in Japan is about half of the one above reported [3]. DCM is regarded not as a single disease entity, but rather a nonspecific final common response to a number of genetic and environmental insults [4]. DCM etiologies can be classified as genetic or non-genetic [1]. Genetic causes account for 30–40% of DCMs and involve genes that encode cytoskeletal, sarcomere and nuclear envelope proteins among others. Transmission is variable but mostly with an autosomal dominant pattern [5]. Acquired causes include myocarditis, tachyarrhythmias, alcohol abuse, drugs, catecholamines, toxins, and metabolic or endocrine disturbances [3].

In the past, the prognosis of DCM was considered ominous [6]. During the last decades, the 10 year survival free from heart transplantation has improved impressively and currently it is close to 85% [7]. Nevertheless, the outcome of patients with DCM often remains unpredictable and major adverse events may occur in the first months following the diagnosis [2,8]. The societal and economic impact of these adverse events is amplified by the fact that DCM often affects patients in the first decades of life.

The most important determinants of the improvement in the prognosis of DCM observed over the past few years are: 1) the implementation of systematic familial screening programs for DCM that have enabled earlier diagnosis with long-term individualized follow-up; 2) the systematic implementation of evidence based medical and device therapies that promote Left Ventricular Reverse Remodeling (LVRR), defined as an improvement in Left Ventricular Ejection Fraction (LVEF), and a reduction in left ventricular dimension. Therapy-induced reverse remodeling has been recently recognized as an important prognostic tool [9,10] in the management of patients with DCM. Several recent reports have suggested that reverse remodeling might be a global myocardial process involving not only left ventricle contractile function, but also mitral regurgitation, left ventricular diastolic function and the right ventricle [11–13]. Here we review our current knowledge of reverse remodeling in DCM patients, highlighting persistent gaps of knowledge, and providing practical recommendations for the clinical management of DCM.

2. Left Ventricular Reverse Remodeling

Cardiac remodeling in response to an inciting myocardial insult or an underlying genetic abnormality has been classically considered the hallmark of DCM. It can be defined as the result of molecular, cellular,

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https://doi.org/10.1016/j.ijcha.2018.02.005

and histological myocardial changes that determine macroscopic alterations in the size, shape, and function of the cardiac muscle [14,15]. In the last decade, several cohort studies have shown that a significant portion of patients with DCM (i.e. about 40%) can experience a reversal of this phenomenon, in a process generally referred to as reverse remodeling, specifically referring to LV (i.e. LVRR) (Table 1). These findings imply that DCM does not represent an irreversible progressive pathway of myocardial failure but it is rather a dynamic disease with non-linear progression [9,16]. Reverse remodeling can take place spontaneously upon removal of the inciting cardiac insult (for instance in tachycardia-induced cardiomyopathy or toxin-induced cardiomyopathy) but it is more often the result of evidence-based pharmacological and non-pharmacological therapies [17,18]. The classical medical management of DCM is based on treatment with ACE-inhibitors/angiotensin receptor blockers, beta-blockers and mineralocorticoid receptor antagonists [19]. In patients with Left Bundle Branch Block (LBBB) and possible consequent ventricular dyssynchrony, Cardiac Resynchronization Therapy (CRT) can successfully induce LVRR [17,18]. Notably, when comparing patients with ischemic and non-ischemic cardiomyopathy, non-ischemic etiology of heart failure (HF) seems to be a predictor of positive response to CRT. LVRR has also been observed in response to ventricular unloading with Left Ventricular Assist Devices (LVAD) [20].

In a sizeable portion of patients (up to 15%), LVRR was pronounced enough to result in a normalization of both LVEF and LV diameters, in a process that has been referred to as "apparent healing" or "myocardial remission" [20]. Interestingly, only about 10% of DCM patients showed persistent apparent healing at long term (>10 years) [21] and the vast majority of them experienced a recurrence of left ventricular dysfunction in the very long term, showing that the observed healing was only apparent and that true myocardial recovery is at most a rare event in DCM patients [21,22]. The mechanistic basis of apparent healing remains largely unknown. Recent work in animal models suggests that it might be secondary to an incomplete reversal of the gene expression changes characteristic of cardiac dysfunction [23], but data in humans are scarce, as is our understanding of the complex interplay that individual genetic backgrounds and environmental factors play in this process.

2.1. LVRR: a mechanistic view

From a pure mechanistic standpoint, LVRR is the result of either the removal of the noxious stimuli that triggered cardiac dysfunction or of the institution of therapies that interfere with the process of LV remodeling. Factors recognized to trigger or amplify LV remodeling include changes in myocardial wall tension and neurohormonal activation. According to Laplace's law, myocardial wall tension is mostly determined by LV diameter and LV wall thickness: LV dilation and wall thinning increase LV wall tension and worsen myocardial energetics. An increase in afterload, as observed in hypertension, can also increase wall tension, and patients with a long standing history of hypertension can develop LV dysfunction with a phenotype overlapping that of DCM [24]. Neurohormonal activation has been clearly shown to play a critical role in the pathophysiology of HF and DCM in several landmark studies. Initially a compensatory process, the release of hypovolemic hormones (such as renin, antidiuretic hormone and norepinephrine) eventually contributes to the progression of DCM and pharmacologic therapies that reduce neurohormonal activation have been shown to promote LVRR.

2.1.1. Beta blockers

The beneficial effects of beta blocker therapy in patients with HF with reduced Ejection Fraction (HFrEF) are likely the result of a reduction of the detrimental effects of chronic catecholamine stimulation on the kidneys (increased sodium retention) and the heart. The negative effects of continued catecholamine stimulation on the heart include elevated heart rate, increased myocardial energy demand, adverse remodeling due to cardiac myocyte hypertrophy and damage, interstitial fibrosis, impaired beta-adrenergic signaling and increased sodium retention [25]. Beta blockade has been shown to have beneficial effects on LV gene expression, geometry and mass [26] and to consistently improve LVEF in patients with HF [27]. Moreover, the improvement in LV geometry associated with beta blockade can diminish functional mitral regurgitation with subsequent improvement of LV shape and function [28]. These benefits require chronic therapy.

2.1.2. ACE inhibitors and angiotensin receptor blockers (ARBs)

In the context of HF, Angiotensin II has many renal and hemodynamic effects similar to those of catecholamines, such as an increase in sodium reabsorption and induction of systemic and renal vasoconstriction. Angiotensin II can also act directly on cardiomyocytes, promoting pathologic remodeling and inducing myocyte hypertrophy, re-expression of fetal protein isoforms, myocyte apoptosis, and alterations in the interstitial matrix. In light of this, the beneficial effects of treatment with ACE inhibitors and ARBs should not be entirely ascribed to their effects of the kidneys and the vasculature but also keep into account their direct effects on cardiomyocytes [29].

2.1.3. Mineralocorticoid receptor antagonists

In the pathophysiology of HFrEF, mineralocorticoid excess promotes sodium retention, electrolyte imbalance and endothelial dysfunction

Table 1
Main studies evaluating LVRR in DCM patients.

Study	N° of pts	Assessment of Left Ventricular Reverse Remodeling	Time of LVRR	Prevalence LVRR
Merlo M et al. J Am Coll Cardiol 2011	242	LVEF increase ≥10% points or ≥50% and LVEDD reduction ≥10% or to ≤33 mm/m^2	24 months (follow-up 10 years)	37%
Amorim S et al. Rev Port Cardiol 2016	113	LVEF increase >10% points and decrease LVEDD (not specified) in absence of CRT	24 months (follow-up 7 years)	35%
Matsumura Y et al. Am J Cardiol 2013	19	LVEDD decreased to ≤55 mm and fractional shortening improved to ≥25%	12 months (follow-up 10 years)	37%
Kubanek M et al. J Am Coll Cardiol 2013	44	LVEF increase ≥10% points (>35%) and decrease in LVEDD ≥10%	12 months	45%
McNamara DM et al. J Am Coll Cardiol 2011	373 (DCM + myocarditis)	1. LVEF increase ≥10% points 2. LVEF increase ≥20% points	6 months (follow-up 48 months)	70% 39%
Hoshikawa E et al. Am J Cardiol 2011	33	LVEDD decreased to ≤55 mm and fractional shortening improved to ≥25%	5 years	42%
Ikeda Y et al. Heart vessels 2015	207	LVEF increased to >10% points and decrease in iLVEDD ≥10%	<24 months ≥24 months	40% Further 12%
Masci PG et al. Circ Card Imag 2013	58	LVEF increased ≥10% points and decrease in LVEDV ≥10% as assessed by cardiac magnetic resonance	24 months	38%

LVRR: Left Ventricular Reverse Remodeling; LVEF: Left Ventricular Ejection Fraction; LVEDD: Left Ventricular End Diastolic Dimension; LVEDV: Left Ventricular End Diastolic Volume; CRT: Cardiac Resynchronization Therapy; DCM: Dilated Cardiomyopathy; iLVEDD: indexed Left Ventricular End Diastolic Dimension.

contributing to myocardial fibrosis. Selective and non-selective mineralocorticoid receptor antagonists have been shown to reduce mortality, hospitalizations and sudden deaths if used on top of ACE inhibitors and beta blockers [30].

Secondary hyperaldosteronism in HF has been thought to reflect Angiotensin II-mediated stimulation of the adrenal glands. However, there is also evidence of local production of aldosterone in the failing heart in proportion to the severity of HF [31]. This has been linked to the induction of aldosterone synthase (CYP11B2) by Angiotensin II in the failing ventricle [32]. Blockade of the adverse effects of aldosterone-induced stimulation of cardiac mineralocorticoid receptors is thought to contribute to the survival benefit associated with the administration of this class of drugs in HF with reduced ejection fraction [30].

2.1.4. Cardiac Resynchronization Therapy (CRT)

LBBB is common in DCM and it is mechanically disadvantageous because it results in intraventricular dyssynchrony of the septum (when compared to the lateral or posterior walls) and paradoxical septal motion. Abnormal contraction patterns promote pathologic LV remodeling by increasing LV volumes, reducing diastolic filling, and prolonging the duration of MR. In DCM, LBBB may be either causative or secondary to the underlining disease. LBBB may in fact be the cause of non-ischemic cardiomyopathy and in selected patients its resolution through CRT has been associated with normalization of LV function [33]. On the other hand, DCM is associated with ventricular rearrangements and conduction delays, ultimately leading to LBBB [34]. Thus, CRT has become an established treatment for selected patients with refractory symptomatic systolic HF [35].

Notably, the response to evidence-based therapies is variable, and reverse remodeling is not evident in all cases. The reasons for this variability in therapeutic success are not completely known. However, they are partially related to the variable etiology of DCM that encompasses both non-genetic and genetic variants.

2.2. Non-genetic DCMs

A comprehensive integrated approach to patients with a newly diagnosed DCM is essential in order to achieve an accurate early prognostic stratification. After excluding common etiologies of reduced ejection fraction such as ischemic heart disease, primitive valve disease, congenital disorders and long-lasting hypertension, healthcare providers should systematically undertake a more detailed etiological classification. Every possible reversible cause of cardiomyopathy should be excluded in clinical practice to identify any needed therapeutic intervention specific to a particular etiology. The most common forms of non-genetic DCM that all providers should be aware of are listed below.

- **Sustained supraventricular arrhythmias or very frequent ventricular ectopic beats (tachycardiomyopathy)**: both sustained supraventricular arrhythmias and very frequent ventricular ectopic beats can precipitate DCM. The mechanisms leading to left ventricular dysfunction are different depending on the type of underlining arrhythmia. Sustained supraventricular arrhythmias promote cardiac dysfunction through high ventricular rate and increased oxygen consumption. Conversely, frequent ectopic ventricular beats are thought to determine dyssynchrony-induced ventricular dysfunction. In both type of arrhythmias, treatment of the arrhythmia (i.e. maintenance of sinus rhythm or control of ventricular rate) invariably results in improvement in cardiac function, often until complete normalization [5]. The role of genetic background in tachyarrhythmia-induced cardiomyopathy remains unclear and the early distinction between real tachycardia-induced cardiomyopathy and DCM presenting with high rate supraventricular arrhythmia or frequent ventricular ectopic beats remains a clinical challenge.
- **Substance abuse** (e.g. alcohol, cocaine) can induce a form of cardiomyopathy that is often reversible, at least to a certain extent, after interruption of the causing agent.
- **Cardiotoxic agents** mostly related to anthracycline and trastuzumab used in oncologic treatments can cause cardiac dysfunction that could improve upon removal of the offending drug. Repeated exposure to the offending drug often causes worsening cardiac function.
- **Systemic autoimmune disease** (e.g. Churg-Strauss syndrome and sarcoidosis) can cause cardiac dysfunction that requires aggressive immunosuppressive therapy.
- **Peripartum cardiomyopathy**, defined as LV dysfunction that occurs during the last trimester of pregnancy or the early puerperium, frequently shows normalization of LV function after the delivery. However, this can be a state of myocardial remission that can deteriorate rapidly with subsequent pregnancies and requires specific counseling about future pregnancies
- **Active myocarditis**, mainly caused by poorly understood interactions between viral infection and individual genetic background. It is treated with standard HF therapy and, in selected cases, with immunosuppressive therapy. It can resolve rapidly with favorable outcome or evolve to post-myocarditis DCM [36]. Patients with heart failure and severe systolic dysfunction carry the poorest diagnosis. In these patients, when refractory to standard therapy, endomyocardial biopsy might be important to confirm the clinical diagnosis and guide specific therapies.

2.3. The emerging role of genetics in predicting LVRR

The advent of high-quality next-generation sequencing (NGS) extended panels has shown that DCM is genetically determined in a much larger number of cases (i.e. up to 40–50%) than previously appreciated. In the genetic landscape of DCM, mutations in the gene for Titin are the most frequently encountered. Other genes involved encode components of cardiac sarcomere, desmosome, cytoskeleton, nuclear envelope, mitochondria and ion channels [37]. Genotype-phenotype correlations in DCM are currently still scarce. However, the interplay between genetic background and response to therapy, as measured by LVRR, is an upcoming frontier for investigators studying DCM. Recently, a cohort study of 152 patients with DCM found a significant relationship between gene cluster mutation type and probability of LVRR [38]. In particular, a lower rate of LVRR was found in patients carrying structural cytoskeleton Z-diskgene mutations (Desmin [*DES*], Filamin C [*FLNC*] and Distrophin [*DMD*], *OBSL1*, *NEXN*, *MYPN*, *NEBL*, *LDB3*) [38]. These findings reinforce the importance of collecting a detailed family history and planning familial screening as part of the initial assessment of DCM patients. Moreover, they endorse the need for a detailed clinical and instrumental evaluation aimed at detecting clues of genetic determinants of disease (i.e. the so called red-flags: mental retardation, deafness, muscle disorders, increased creatine-kinase or lactates, infero-posterior pseudonecrosis or 1st degree atrio-ventricular block at ECG, aneurisms at echocardiography or cardiac magnetic resonance) [39,40]. In fact, the presence of familial forms or “red-flags” on exam should trigger immediate genetic testing [41]. In the future GWAS studies investigating specific individual genetic predispositions associated with a favorable response to therapy will be needed to improve the granularity of prognostic evaluation of patients.

3. Beyond LV and LVRR: comprehensive reverse remodeling

LVRR is a dynamic process and may take up to two years to complete [9]. A number of different factors beyond LV ejection fraction and size have recently emerged as determinants of the course of DCM. Together they constitute the pathophysiological basis for the concept of *comprehensive cardiac reverse remodeling* and should be systematically assessed both as possible early measures of therapeutic benefits and prognostic factors:

- **Right ventricular function** has a dichotomous role. At diagnosis it is an important prognostic marker in DCM [11,42]. Interestingly, it frequently shows a rapid recovery under therapy (up to 6 months).

Right ventricular function normalization is part of a global hemodynamic improvement induced by therapy and precedes LVRR. It is emerging as an early therapeutic target and an independent prognostic predictor [11]. Improvement in right ventricular function is also described in CRT implanted patients, probably due to a hemodynamic improvement very early after resynchronization, and it is associated with an improvement in survival rates [12]. Conversely, the development of right ventricular dysfunction during follow-up is an expression of structural progression of the disease and portends a negative outcome [11].

- **Functional mitral regurgitation**: significant mitral regurgitation may be considered not only as a functional bystander but also as an independent predictor of progressive adverse remodeling [43]. A tight relation between mitral regurgitation and CRT has been described [44]. Moderate to severe mitral regurgitation that persists despite optimal medical treatment or CRT is associated with poorer outcomes [12,44]. Patients with DCM and persistent severe MR despite pharmacological therapy should be evaluated for possible invasive therapeutic strategies such as percutaneous repair of the mitral valve (i.e. MitraClip®). However, outcome data supporting this therapeutic intervention in DCM patients is still lacking. Mechanical circulatory support or even heart transplantation should be also considered early in these patients.
- **Left Bundle Branch Block** is a frequent ECG marker at diagnosis and is associated with low likelihood of LVRR [9]. Importantly, the development of new LBBB during follow-up has emerged as a strong independent predictor of major cardiac events [45].
- The onset of **atrial fibrillation** during follow-up probably represents a sign of structural progression of the disease and negatively impacts prognosis [46].

It follows from the above that a multiparametric approach is crucial in the early management and follow up of DCM under optimal medical therapy. The clinician should not focus only on left ventricular systolic function and size but should comprehensively evaluate the behavior of all heart structures during follow-up (Fig. 1).

4. Gaps of knowledge and future perspectives

Despite an ever-increasing understanding of the pathophysiology of DCM, prognostic stratification of patients with DCM remains a challenge for cardiologists, especially in the early phases of the disease. DCM remains a dynamic disease with a poorly predictable clinical course and several issues remain unresolved regarding the prospective assessment of the likelihood of reverse remodeling:

- The best timing of evaluation remains debated (Table 2). After removing any possible cause of LV dysfunction, if detectable at diagnosis, it is reasonable to evaluate patients 3 to 9 months after implementation of optimal medical treatment in order to identify candidates for ICD implant. However, in patients with persistent severe LV dysfunction, normalization of right ventricular function, improvement of mitral regurgitation and improvements in diastolic function could portend LVRR. It has been described indeed that LVRR takes up two years to be completed in response to medical therapy. Therefore, in these patients, implantation of ICD might be reasonably delayed. This is especially true in light of the results of the DANISH trial [47], that did not find a survival benefit in patients with non-ischemic cardiomyopathy who had received an ICD. Further studies are needed to clarify this issue and to improve the risk stratification of DCM patients in terms of risk of sudden death.
- Early prediction of LVRR remains a major knowledge gap in the clinical management of DCM patients. New technologies could improve our capacity to identify early reverse remodeling. The presence of late gadolinium enhancement at CMR has been demonstrated as associated with low probability of LVRR in DCM [48]. However there is not a definite agreement in the literature in regards to CMR late gadolinium enhancement as a predictor of LVRR [49]. Future large studies are needed to confirm the role of CMR in the early prognostication of DCMs, particularly to assess its ability to prospectively differentiate responders to therapy from non-responders. The ability to efficiently differentiate early responders from non-responders would pave the way to studies aimed at understanding weather these two group of patients warrant different management strategies (i.e. early device therapy or early insertion in transplant list) in order to improve outcomes.
- There is very little data regarding the management and risk stratification of patients with normalized ejection fraction. Recently Adamo et al. found that in patients with a recovered LVEF, a persistent abnormal echocardiographic global longitudinal strain predicted the likelihood of having a decreased LVEF during follow-up [21]. However, these authors studied a single retrospective cohort and further validation of their findings is pending.

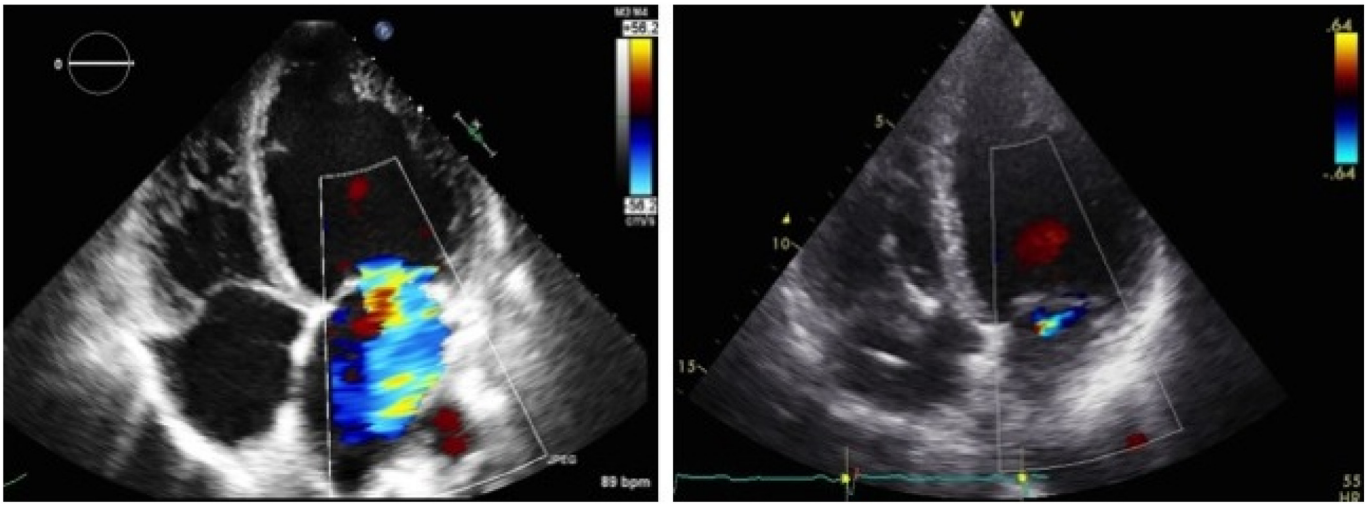

Fig. 1. Example of comprehensive reverse remodeling in DCM: note the improvement of LV shape/dimension and the improvement in MR severity between baseline (left panel) and follow-up after 12 months of optimal medical therapy. LVEF and right ventricular function also significantly improved at follow-up. Basal (left side): LVEF 16%; LVEDD 81 mm; LVEDVi 150 ml/m2; Severe MR; RV-FAC 13%; E/E' 18; LA area 34 cm2; LA volume 125 ml. Follow-up (right side): LVEF 56%; LVEDD 55 mm; LVEDVi 58 ml/m2; Mild MR; RV-FAC 48%; E/E' 6,1 LA area 23 cm2; LA volume 72 ml. Legend. LVEF: Left Ventricular Ejection Fraction; LVEDD: Left Ventricular End Diastolic Dimension; LVEDVi: Left Ventricular End Diastolic Volume indexed for body surface area; MR: Mitral Regurgitation; RV-FAC: Right Ventricle Fractional Fractional Area Change; LA: Left Atrium.

Table 2
The main steps of reverse remodeling evaluation throughout the natural history of DCM.

Time to evaluation	Diagnostic work-up[a]
Baseline	– Exclude secondary forms of DCM • Tachycardiomyopathy • Substance abuse • Cardiotoxic agents • Systemic autoimmune disease • Peripartum cardiomyopathy • Endocrine diseases • Active myocarditis • DCMs secondary to hypertension – Obtain genetic data (in presence of familial forms or presence of red-flags) – ECG features (LBBB)
3–6 months	– Right ventricular recovery – MR quantification – Left atrial size – Onset of atrial fibrillation – Diastolic impairment evaluation
12–24 months	– Assess LV function to detect LV Reverse Remodeling

DCM: Dilated Cardiomyopathy; LBBB: Left Bundle Branch Block; MR: Mitral Regurgitation; LV: Left Ventricular; RV: Right Ventricular.
[a] Need of large future studies to confirm the role of LGE in identifying the possible reverse remodeling in response to the therapy.

Further studies based on multimodal approaches (including echo 3-D, speckle tracking, morphological and functional cardiac magnetic resonance including quantification of late gadolinium enhancement, measurement of natriuretic peptides, and genetic characterization) are needed in order to build reliable multiparametric scores that could encompass the information discussed here and simplify the bedside risk stratification of patients with DCM.

In the near future, extensive genetic characterization of patients with DCM will probably improve our understanding of DCM. Furthermore, pharmacogenomics is poised to empower the implementation of pharmacologic treatments optimized for each and every patient. Finally, the rapidly increasing knowledge of the dynamic interaction between genetic determinants and environmental factors will likely bring about better tools to predict the clinical course of DCM.

5. Conclusions

Reverse remodeling is the main measure of therapeutic effectiveness and one of the most important prognostic tools in the management of patients with DCM. An integrated approach to the evaluation of DCM patients, including a deeper etiological classification and a comprehensive evaluation of cardiac remodeling beyond the left ventricle, is essential to properly risk stratify and treat this patient population. New technologies such as echocardiographic speckle tracking, cardiac magnetic resonance and genetic testing are progressively improving the clinician's ability to predict the probability of reverse remodeling and of its persistence.

Disclosures

None.

Acknowledgment

We are thankful for the support of the Amici del Cuore association and of the CRTrieste Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.02.005.

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