

Myocardial remodelling and recovery in dilated cardiomyopathy

Journal of the Royal Society of
Medicine Cardiovascular Disease
Volume 6: 1–7
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DOI: 10.1177/2048004017734476
journals.sagepub.com/home/cvd



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Abstract

Myocardial reverse remodeling has been reported to occur in 25–70% of patients with dilated cardiomyopathy. It is not yet fully understood whether remodeling represents disease remission or cure and which hearts retain this capacity to recover. In this review article we discuss the capacity for recovery in DCM, the prognostic implications of this recovery and potential clinical and imaging predictors for myocardial remodeling.

Keywords

Dilated cardiomyopathy, myocardial cardiomyopathy disease, cardiology

Received 10 August 2017; revised 4 September 2017; accepted 6 September 2017

Introduction

Dilated cardiomyopathy (DCM) is a heart muscle condition affecting up to 1 in 250 individuals,¹ in which predominantly the left ventricle becomes dilated, with impaired systolic function. The majority of cases are idiopathic, though examples of identifiable causes are listed in Table 1. Although the disease is associated with adverse outcomes, including a 20% 5-year mortality,² there has been longstanding recognition of the potential for improvement in DCM. Spontaneous improvement in symptoms and potentially complete recovery of left ventricular (LV) function is reported in approximately 25–70% of DCM patients.^{3–10} In this review article, we discuss the capacity for recovery in DCM, the prognostic implications of this recovery, and potential predictors for myocardial remodeling.

Methods

Articles included in this review were identified through electronic searching of main databases including PubMed, Web of Science, and Google Scholar, using index terms, named author searches, and free text. Terms “dilated cardiomyopathy”, “myocardial recovery”, “myocardial remodeling”, and “reverse remodeling” were used. Citation scanning of articles was used to identify additional articles.

Variable definitions for reverse remodeling limit our understanding of the capacity for LV remodeling in DCM

Higher estimates of the percentage of DCM patients who demonstrate myocardial recovery are reported in more contemporary cohorts. However, there is no universal definition of improvement in LV function, with studies reporting either absolute change in left ventricular ejection fraction (LVEF)^{3,5,8,9,11,12} (from 5% to 20%) or improvement above a threshold level, often set at LVEF 50%,^{6,8,13} with some studies reporting the additional metric of reduction in LV dilation.^{5,6,8} However, an LVEF-based definition of recovery may also be inadequate as subtle dysfunction in cardiac strain or energetics can remain, even in the presence of apparently normalized LVEF.^{13,14}

Remission or cure?

The terms myocardial recovery and reverse remodeling are often used interchangeably but they may represent

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Table 1. Examples of identifiable causes of dilated cardiomyopathy.

Cause	Examples
Genetic and syndromic	Over 60 genes reported to be associated with DCM including TTN (up to 25%), LMNA, MYH7, and TTNT2 (<5%). Duchenne muscular dystrophy, Barth syndrome
Infectious	Viral: Coxsackie, HIV, influenza, adenovirus, cytomegalovirus, varicella, hepatitis, Epstein-Barr, echovirus, parvovirus Bacterial: Streptococci, mycobacteria Spirochetal: Lyme disease, syphilis Fungal: Histoplasmosis, cryptococcosis Parasitic: Toxoplasmosis, trypanosomiasis, schistosomiasis
Drugs	Chemotherapeutic agents including anthracyclines and cyclophosphamide Antiretroviral drugs including zidovudine, other, e.g. phenothiazines, chloroquine, clozapine
Toxins	Alcohol, cocaine, amphetamines, cobalt, lead, mercury
Nutritional deficiencies and electrolyte disturbances	Thiamine, selenium, carnitine, niacin Hypocalcemia, hypophosphatemia, uremia
Endocrine	Hypo- or hyper-thyroidism, diabetes mellitus, Cushing's syndrome, pheochromocytoma, growth hormone excess or deficiency
Inflammatory and autoimmune	Systemic lupus erythematosus, scleroderma, rheumatoid arthritis, autoimmune myocarditis, dermatomyositis
Other	Tachycardia-induced cardiomyopathy, pregnancy

Table 2. Description of terms relevant to LV remodeling and recovery.

Term	Definition
Left ventricular reverse remodeling	Improvement in left ventricular ejection fraction with or without improvement in left ventricular volume indices. Variable definitions in literature, no absolute threshold.
Myocardial recovery	Normalization of molecular, cellular, myocardial and LV geometric changes, permitting the heart to maintain preserved LV structure or function, with freedom from future heart failure events.
Myocardial remission	Normalization of molecular, cellular, myocardial, and LV geometric changes, permitting the heart to maintain preserved LV structure or function, without freedom from future heart failure events.
Myocardial cure	Evidence of myocardial recovery that persists without ongoing medical (including device) therapy.

distinct entities (Table 2).¹⁵ In addition, this improvement in myocardial function often occurs in the presence of medical or device therapy, therefore it is unknown whether LV recovery represents disease remission¹⁶ or disease cure. In one study of 85 patients with reported LV recovery, the rate of recurrence of LV dysfunction, even in the presence of ongoing medical therapy was as high as 38%.¹⁷ Baseline age, LV end diastolic diameter, and a history of diabetes were the only independent predictors of recurrent dysfunction.¹⁷ There are two ongoing randomized studies of withdrawal of medical therapy in recovered DCM patients that may address the remission versus cure conundrum (Withdrawal of Medication in Recovered DCM

(WrecEF), ClinicalTrials.gov identifier NCT02770443; Therapy withdrawal in REcovered Dilated cardiomyopathy trial (TRED), EU Clinical Trials register identifier 2015-005351-27).

When is myocardial recovery possible?

Intuitively, it is plausible that recovery of LV function can occur after withdrawal of an environmental trigger (e.g. alcohol, virus). It has also recently been shown that recovery is possible in genetic DCM, specifically titin cardiomyopathy, both in response to medical therapy¹⁸ and advanced device therapy such as left

ventricular assist device implantation in apparently “end-stage” patients.¹⁹

There are other specific situations in which LV recovery may occur. Tachycardia-induced cardiomyopathy, developing in response to atrial (atrial fibrillation or tachycardia most frequently) or ventricular arrhythmia (slow ventricular tachycardia or ventricular ectopy), can improve upon restoration of sinus rhythm. A small case series of 24 patients, however, showed that recurrence of tachycardia could lead to a rapid decline in ventricular function, long after apparent normalization,²⁰ suggesting that LVEF recovery does not equate with complete normalization of myocardial substrate. In other words, LV reverse remodeling does not imply molecular myocardial recovery.¹⁵ Recovery has also been reported in cases of acute myocarditis,⁷ peri-partum cardiomyopathy,²¹ and some forms of chemotherapy-induced cardiomyopathy (trastuzumab, as opposed to anthracycline).²² Takotsubo cardiomyopathy is a distinct clinical entity characterized by transient left ventricular dysfunction.²³

Prognostic implications of LV remodeling

Improved LVEF has been associated with a survival benefit, though this has mainly been demonstrated in heart failure cohorts, including ischemic aetiologies. In the BEST trial (Beta-blocker Evaluation of Survival Trial), amongst 2484 patients (not all DCM) with at least two serial evaluations of LVEF by radionuclide ventriculography, a change of LVEF by at least 5% was associated with a reduced hazard ratio for all cause mortality (0.62, [0.52–0.73]).²⁴ Similarly, in the Veterans Affairs Cooperative Vasodilator-Heart Failure Trials (V-HeFT), serial evaluation of 1446 patients with heart failure showed that a change in LVEF >5% from baseline to 6 months was the strongest predictor of mortality.²⁵

In the largest study to date, a meta-analysis incorporating data from almost 70,000 heart failure patients across 30 mortality trials and almost 20,000 heart failure patients across 88 remodeling trials, the odds of mortality decreased with increasing LVEF and decreasing LV end diastolic and end systolic volumes.²⁶ In line with the studies before it, a 5% increase in mean LVEF corresponded to an improvement in survival (OR for all cause mortality with 5% improvement in LVEF 0.86, 95% CI 0.77–0.96, $p = 0.013$).²⁶

In a study of over 700 patients with ICD therapy in the MADIT-CRT trial, LVRR occurred in 25% of patients (defined as >15% reduction in LV end systolic volume at 1-year follow up) and that this was associated with a reduced risk of heart failure or death.²⁷ Finally, in the subset of patients with repeat echocardiography imaging in the Valsartan Heart Failure Trial

(Val-HeFT), 321 of 3519 (9.1%) patients with initial LVEF <35% (including ischemic aetiologies) improved LVEF to >40% at 1-year follow up, and recovery was associated with improved survival at 2-year short-term follow up (log-rank p -value comparing survival in group with improved LVEF compared to group without improved LVEF = 0.005).²⁸

In a small, retrospective DCM specific study of 59 patients, ~37% of 19 patients surviving beyond 12 years showed LV reverse remodeling and amongst the 33 patients who died or had a heart transplant, no LV reverse remodeling was noted prior to the event.⁴ A cautious conclusion of the study would therefore be that any reverse remodeling, even limited, is associated with an improved prognosis. This of course requires replication and confirmation in a larger prospective study of DCM patients. In a retrospective observational study of 408 DCM patients, 63 patients with improved LV function (LVEF >50% and normal LV end diastolic volume) had a greater freedom from death or heart transplant compared to patients without evidence of recovery ($p < 0.001$).⁶

In summary, recovery has been shown to be possible in the setting of DCM secondary to a diverse range of etiologies, albeit to a varying extent. This suggests that the potential for LV recovery is intrinsically conserved in the setting of cardiac dysfunction (largely irrespective of etiology), and even in the presence of apparently severe myocardial dysfunction. The complicating issue is that recovery is not universal, so identifying which hearts retain this potential for recovery is a major unmet need.

Predictors of LV remodeling

Identification of DCM patients with a high probability of recovery has the potential to improve outcomes, by permitting tailored therapy, stratifying early intensive and advanced therapy to patients deemed less likely to recover.

There have been limited studies in the contemporary era of medical therapy evaluating predictors of recovery for all-cause DCM beyond the removal of any initial environmental trigger (Table 3).

Left ventricular parameters and clinical predictors of LV remodeling

A key study in the field was from the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) investigators.⁷ In total, 373 subjects from 16 centers with recent onset (<6 months) idiopathic DCM or myocarditis with an initial LVEF <40% were followed up for a mean of 2.2 years, with reassessment of LV function after 6 months. Crucially, 82% of patients

Table 3. Table summarizing the studies evaluating predictors of LV remodeling in DCM patients.

Study year/imaging modality	Cohort size	Interval to repeat assessment of LVEF	Predictors of LV remodeling
2011 ⁷ Echo	373 (DCM and myocarditis)	6 months	LV end diastolic volume, systolic blood pressure, race, NYHA class
2012 ²⁹ CMR	68 DCM	5 months	CMR-late gadolinium enhancement
2013 ⁵ CMR	44 DCM	1 year	CMR-late gadolinium enhancement, CMR myocardial edema ratio, 3 month BNP (not baseline)
2015 ¹⁰ CMR	97 DCM	1 year	LV end diastolic volume, symptom duration
2016 ⁹ CMR	113 DCM	7-year follow up	ACE inhibitor use
2016 ¹² CMR	44 DCM	3.5-year follow up	LA volume

received beta blocker therapy and 91% of patients were on angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers. Many previous studies in the field predated the widespread use of these prognostic medications.³ All imaging was performed by echocardiography. Mean baseline LVEF was 24%, increasing to 40% at 6 months. In multivariable analysis, baseline left ventricular end diastolic diameter was the strongest predictor of follow-up LVEF (standardized coefficient -0.41 , $p < 0.0001$).⁷ Other independent predictors of follow-up LVEF were systolic blood pressure (0.18 , $p = 0.001$), black race (-0.12 , $p = 0.02$), and NYHA class (-0.11 , $p = 0.04$).⁷ Interestingly, baseline LVEF did not predict follow-up LVEF ($p = 0.32$).⁷ The authors also noted differing recovery profiles stratified by gender and race, with recovery (LVEF $>50\%$) more likely in white women (38%) and least likely in black men (15%).⁷ Whilst 12% of subjects had an endomyocardial biopsy at baseline, a limitation of this study was that imaging with cardiovascular magnetic resonance (CMR) was not performed, which may have been able to identify a reversible inflammatory myocarditis, as well as evaluate the role of myocardial fibrosis in predicting recovery.

Role of CMR detected late gadolinium enhancement in predicting remodeling

A subsequent study of 44 patients with recent onset DCM evaluated CMR predictors of remodeling, together with serum biomarkers, endomyocardial biopsy, cardiopulmonary exercise testing, and echocardiography.⁵ In this study, patients had CMR at baseline and at 1-year follow up, and left ventricular reverse remodeling (LVRR) was defined as an absolute increase in LVEF of 10% to a final value $>35\%$, together with a reduction in LV end diastolic dimension at the 1-year mark.⁵ In total,

LVRR was observed in 45% of patients. Of all variables evaluated including serum biomarkers and myocarditis on biopsy, the independent predictors of LVRR were the extent of myocardial fibrosis assessed by late gadolinium enhancement (LGE) CMR (OR 0.67, (0.50–0.90), $p = 0.008$) and higher myocardial edema ratio (T2 index) assessed on CMR (OR 1.45, (1.04–2.02), $p = 0.027$).⁵ The authors also measured BNP at 3, 6, and 12 months. At 3 months (though not at baseline), plasma BNP was the most powerful predictor of LVRR. These data suggest that CMR predictors of remodeling were the earliest to identify the potential for recovery.

Another CMR-based study of remodeling in 68 DCM patients (disease onset <2 weeks) also identified that improvement in LVEF (at 5 months) was inversely correlated with the extent of LGE.²⁹ Notably, this study excluded patients with suspected myocarditis (abnormal troponin I or myocardial oedema on CMR), so may be a more accurate study of recovery in true idiopathic DCM, with estimates of recovery not conflated by inclusion of patients with myocarditis—a condition with a high degree of reversibility.

Not all studies agree with regards to CMR LGE predicting LVRR. In a Portuguese study of 113 DCM patients followed for 7 years, LVRR (defined as absolute LVEF increase of 10% and decrease in LV diastolic diameter) occurred in approximately one-third of patients.⁹ On multivariable analysis, only ACEi use was associated with LVRR. CMR-LGE was not a predictor on univariable analysis. However, only 38 patients had CMR and of these, over 50% had LGE, which is higher than conventional estimates, suggesting that their criteria for identification of mid-wall fibrosis (as opposed to all forms of LGE) were inadequate.⁹ Notably, and in line with other studies, baseline LVEF did not predict LVRR.

Similarly, in a separate study of 97 patients with DCM, LVRR (defined as an increase in LVEF of 5%) occurred in 71% ($n=69$) of patients after 1-year follow up.¹⁰ On multivariable analysis, only LV end-diastolic volume and the duration of symptoms on presentation were independent predictors of 1-year LVEF. Neither baseline LVEF nor the presence of CMR-LGE (performed in 88 patients) predicted LVRR.¹⁰ In another sub-study of 66 DCM patients who had CMR, LGE was detected both in the patients who did not experience LVRR as well as in patients with late LVRR (LVEF increase of 10% after 1 year), although the extent of LGE enhancement was lower in patients who responded compared to the non-responders.¹¹ This small study, subject to marked ascertainment bias (the original cohort was >200 patients), suggests that the association between CMR-LGE and LV remodeling may be more nuanced than previously imagined.

Role of left atrial and right ventricular assessment

Many of the studies described limit evaluation of imaging predictors to indices of LV structure and function only. However, other cardiac structures such as the left atrium³⁰ and right ventricle may be important predictors of remodeling, as they reflect broader pathological involvement. A study of 44 patients with DCM without evidence of myocardial LGE who had CMR assessment of LA volume showed that LA volume was the only independent predictor of LVRR with a hazard ratio of 0.93 (0.88–0.99, $p=0.024$) (14 patients had LVRR defined as an increase in LVEF to >50% and a net increase of >20%).¹² This was a small study, the upper confidence interval approaches 1, and the results whilst interesting, are by no means definitive. Right ventricular function at baseline has recently been shown to predict LV remodeling at follow up in peripartum cardiomyopathy patients.³¹ This remains unexplored in DCM.

Predictors of sustained recovery

The Trieste Heart Muscle Disease Registry is a long running established database of cardiomyopathy patients at a tertiary referral centre. Study of this cohort has permitted the evaluation of both predictors of recovery overall,⁸ as well as predictors of sustained recovery, implying potential myocardial “healing”.⁶

In the first study from this group, LVRR (defined as LVEF >50% or absolute LVEF increase by 10%) was found in 89 of 242 (37%) patients with DCM. Only systolic blood pressure (OR 1.23 per 10 mmHg systolic blood pressure, $p=0.047$) and the absence of left bundle branch block (OR 2.47, $p=0.009$) predicted

LVRR.⁸ In the second study, published 4 years later with longer term follow up, in total 15% ($n=63$) of 408 DCM patients demonstrated “apparent healing”, defined as LVEF >50% and normal indexed LV end diastolic diameter, with 38 of the 63 patients (60%) demonstrating “persistent healing” at long-term follow up (mean 103 months). Amongst those patients who did not demonstrate sustained recovery, LVEF appeared to deteriorate after approximately 2 years of recovery, but with no clear discriminators of why this subgroup should have a different clinical course. On univariate analysis, no clinical or echocardiography imaging parameters predicted LV improvement either at mid-term (approx. 2 years follow up) or long-term follow up (over 8 years follow up).⁶

Interestingly, even amongst the group of patients with persistent apparent healing, 2 of the 38 (5%) patients died or underwent heart transplant at very long-term follow up, despite normalization of LVEF. Whilst speculative, this suggests that LVRR represents myocardial remission, but not true healing. In line with this, it has been suggested that in the presence of normalization of molecular, cellular, myocardial, and LV geometric changes permitting the heart to maintain preserved LV structure or function, the term “myocardial recovery” should only be used to describe situations associated with freedom from future heart failure events¹⁵ and the term “myocardial remission” should be used to describe preserved LV structure or function that is not associated with freedom from adverse events.¹⁵ Further support for this notion comes from a study evaluating outcomes in a cohort of 538 patients with heart failure with repeated LVEF assessments after primary prevention ICD implantation, in which 40% of patients had some improvement in LVEF over a mean follow up of 4.9 years (including 25% with LVEF improvement to >35%) but they remained at risk for appropriate shock therapy,³² suggesting that the myocardial substrate had not normalized.

Conclusion

In summary, it is clear that there is a distinct subgroup of DCM patients who can undergo reverse remodeling, either spontaneously or after therapy, and whose clinical course is associated with reduced adverse events. Identifying which patients may not remodel and therefore benefit from early referral for device therapy or advanced heart failure management is of great clinical importance. However, resting LV indices and clinical parameters have been shown to be inadequate predictors of this LV remodeling and/or recovery. Consensus is required regarding a universal definition of left ventricular reverse remodeling, and future studies should evaluate dynamic predictors of this process as well as

prospectively evaluate the long-term prognostic importance of a remodeled myocardial substrate.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: UT was funded by a Clinical Research Training Fellowship from the Medical Research Council (UK).

Ethical approval

None.

Guarantor

Sanjay K Prasad

Contributorship

UT designed the review, performed the literature search, and wrote the manuscript. SKP critically reviewed the manuscript. Both authors take full responsibility of its content.

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