PREDICTORS OF LEFT VENTRICULAR REMODELLING IN PATIENTS WITH DILATED CARDIOMYOPATHY- A CARDIOVASCULAR MAGNETIC RESONANCE STUDY

Improving Prediction of Left Ventricular Remodelling in Dilated Cardiomyopathy

TITLE PAGE

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ABSTRACT

Aims

There is an important need for better biomarkers to predict left ventricular (LV) remodelling in dilated cardiomyopathy (DCM). We undertook a comprehensive assessment of cardiac structure and myocardial composition to determine predictors of remodelling.

Methods and Results

Prospective study of patients with recent-onset DCM with cardiovascular magnetic resonance (CMR) assessment of ventricular structure and function, extra-cellular volume (T1 mapping), myocardial strain, myocardial scar (late gadolinium enhancement) and contractile reserve (dobutamine-stress). Regression analyses were used to evaluate predictors of change in LV ejection fraction (LVEF) over 12 months.

We evaluated 56 participants (34 DCM patients, median LVEF 43 (33-48)%; 22 controls). Absolute LV contractile reserve predicted change in LVEF (1% increase associated with 0.4% increase in LVEF at 12 months, p=0.02). Baseline myocardial strain (p=0.39 global longitudinal strain), interstitial myocardial fibrosis (p=0.41), replacement myocardial fibrosis (p=0.25), and right ventricular contractile reserve (p= 0.17) were not associated with LV reverse remodelling. There was a poor correlation between contractile reserve and either LV extra-cellular volume fraction (r= -0.22, p=0.23) or baseline LVEF (r=0.07, p=0.62). Men were more likely to experience adverse LV remodelling (p=0.01) but age (p=0.88) and 'disease-modifying' heart failure medication (beta blocker p= 0.28, ACE inhibitor p=0.92) did not predict follow-up LVEF.

Conclusions

Substantial recovery of LV function occurs within 12 months in most patients with recent-onset DCM. Women had the greatest improvement in LVEF. A low LV contractile reserve measured by dobutamine-stress CMR appears to identify patients whose LVEF is less likely to recover.

Keywords

Dilated cardiomyopathy; myocardial remodelling; recovery; dobutamine stress

ABBREVIATIONS

CMR; cardiovascular magnetic resonance
DCM; dilated cardiomyopathy
LVEF; left ventricular ejection fraction
HVOL; healthy volunteer
ECV; extracellular volume fraction
SAX; short axis
HLA; horizontal long axis
VLA; vertical long axis

INTRODUCTION

The prognosis of patients with dilated cardiomyopathy (DCM) is variable, with a 5 year mortality rate of ~20%[1, 2], yet a potential reverse remodelling rate of over 20% [3-6]. Unfortunately, clinical variables and indices of LV function measured at rest do not accurately predict the direction or extent of LV remodelling[6-8]. As highlighted by recent AHA guidelines[9] the identification of potential responders to therapy versus non responders remains a major unmet need.

We used cardiovascular magnetic resonance imaging (CMR) not only to provide accurate and reproducible measurements of cardiac structure and function but also to assess the myocardial substrate. The ability to predict whether or not LV function will improve, remain unchanged or deteriorate could inform management, helping some patients to avoid unnecessary device therapies and others to avoid false hope of recovery.

Contractile reserve, the ability of the impaired ventricle to respond to a stressor, portends a good prognosis[10, 11]. We therefore hypothesised that contractile reserve could predict LV remodelling, adverse or beneficial, in patients with recent onset DCM. In particular we sought to evaluate the relative contribution of ejection fraction, biventricular contractile reserve, myocardial strain and myocardial fibrosis as determinants of myocardial reverse remodelling.

METHODS

The study was a prospective observational study of patients with recent onset DCM assessed at baseline and 12 months.

Study cohort, inclusion and exclusion criteria

Dilated cardiomyopathy cohort

Patients with DCM diagnosed within the preceding 1 year who were aged >18 years, in sinus rhythm and with no contraindications to CMR or dobutamine stress (Supplementary materials) were recruited from local clinics, a regional network of cardiologists or self-referral from the Cardiomyopathy UK patient-association via its website.

Healthy volunteer cohort

A cohort of age and sex matched healthy volunteers (HVOL) was recruited to permit comparison of the baseline contractile reserve response in DCM patients and normal subjects. These individuals had no history of medical illness, were not taking regular medication, and did not have evidence of cardiac structural or functional impairment on CMR scanning.

All participants gave written informed consent and the study was approved by the regional research ethics committee.

CMR protocol

All participants underwent CMR at 3T (Siemens Skyra scanner). Typical imaging parameters for the CMR protocol are outlined in Supplementary materials.

Dobutamine assessment of contractile reserve

LV contractile reserve was defined as the absolute difference between baseline LVEF or baseline myocardial strain and maximum change after peak dobutamine stress.

All patients stopped beta blockers for 48 hours prior to the scan. A baseline ECG was performed. Dobutamine (concentration 1mg/mL) was administered via a peripheral intravenous cannula with long line extension to the infusion pump located in the control room. Heart rate and blood pressure was measured at baseline and then every 2 minutes during dobutamine infusion.

A short-axis (SAX) cine stack was acquired at baseline, and at two doses of dobutamine (5μg/kg/minute and 10μg/kg/minute; each stage continued for at least 5 minutes) [2]. Biventricular volumes, ejection fraction and LV mass were measured using a semiautomated threshold-based technique (CMRtools, Cardiovascular Imaging Solutions, London, UK). All volume and mass measurements were indexed to body surface area and referenced to age and gender based tables[12]. Left and right atrial area (LAA, RAA) and ventricular wall thickness were also measured (Supplementary materials).

Assessment of interstitial fibrosis

T1-mapping was performed at basal and mid-ventricular short axis levels before and 15 minutes after a bolus of a gadolinium-based contrast agent (Gadovist, Bayer) (0.1mmol/kg)[13]. T1 measurements were taken before and, once heart rate had returned to baseline levels, after dobutamine. A shortened Modified Lock-Locker Imaging (MOLLI) sequence[14] was acquired in 11 cardiac-cycle breath-holds. Images were analysed using CMR tools. T1 values were measured in a well-defined region of interest in the septum avoiding replacement fibrosis, and a circular region in the blood pool. Haematocrit was measured on the day of the scan and extracellular volume fraction (ECV) calculated [15]. The mean of two ECV measurements was taken.

Assessment of myocardial strain using cine DENSE imaging

All patients underwent baseline assessment of myocardial strain using a modified cine spiral DENSE sequence [16, 17]. Images were acquired at the mid-ventricular SAX level and two long axis

planes (horizontal and vertical) at rest and during the 10μg/kg/min dobutamine dose. Images were analysed and myocardial strain was extracted from the DENSE data using semi-automated MATLAB (The Mathworks, Natick, MA, USA) post-processing software from the University of Virginia [18-20]. For long axis images line contour and for SAX images, both contour and region of interest (manually defined between endo- and epicardial borders) analysis was performed. Strain was then calculated in the segmented areas, generating regional polar-strain/time curves for radial and circumferential strain and contour strain/time curves for longitudinal strain in two planes and short axis strain.

As a post hoc analysis, CMR feature tracking was used as an alternative longitudinal strain analysis on baseline cine images. The methods and results are presented in Supplementary materials.

Assessment of replacement myocardial fibrosis

Provided eGFR was >30mL/min/1.73m^2, late-gadolinium enhancement (LGE) images were acquired using a breath hold inversion recovery sequence following 0.1mmol/kg of gadolinium contrast agent (Gadovist, Bayer), with inversion times optimised to null normal myocardium. Images were acquired in three long axis planes and short axis levels corresponding to the cine images. All LGE images were acquired after swapping of the phase encode direction. Mid-wall myocardial fibrosis was recorded as present if detected in both phase-encoding direction and in two orthogonal views. The borders of the myocardium were delineated in each short axis slice with LGE. The enhanced areas were then segmented using the full-width at half maximum technique and semi-automated software (CMR42, Circle Cardiovascular Imaging Inc).

Follow up imaging

Patients underwent follow up imaging with CMR at 12 months or focused 3D echocardiography (Phillips i33, 3d probe X5-1; analysis using the XCELERA software) if there was a contraindication

to CMR. Evaluation of follow-up imaging data including LVEF was performed blinded to baseline scan results (i.e. blinded to the time point of the scan).

Statistical analysis

The sample size calculation was based on the hypothesis that contractile reserve and change in LVEF from baseline to 12 months are associated. A sample size of 31 was required to achieve 80% power with a significance level of 5%, for a univariable regression assuming a 0.25% absolute increase in 12-month LVEF for each unit increase in LVEF during dobutamine infusion (contractile reserve). The effect size was calculated based on an R^2 of 0.2 for the relationship between absolute contractile reserve and LVEF at 12 months; a conservative estimate given that previous echocardiographic studies showed a stronger correlation between stress and follow-up LVEF (r =0.7-0.8)[21, 22]. Target recruitment was inflated from 31 to 34 to allow for an expected 10% drop-out rate. Sample size calculations were performed using the pwr.f2.test in R for linear regression models.

We used univariate and multivariate linear regression analysis to identify predictors of change in LVEF from baseline to 12 months. Our primary focus was on the capacity of absolute LV contractile reserve to predict change in LVEF from baseline to 12 months. Reflecting the biological response, a specific cut off for contractile reserve was not applied (to indicate the presence/absence of contractile reserve). We expected that change in LVEF would be related to baseline LVEF because of regression to the mean, therefore our main analyses were adjusted for baseline LVEF.

To establish the normal range for contractile reserve a healthy volunteer cohort was recruited. Target recruitment was set at 20 volunteers, which yields 80% power at a 5% significance level, to detect a 9% difference in baseline contractile reserve between patients and healthy volunteers.

At baseline continuous variables were compared using the Mann-Whitney test and categorical variables using the Fisher test. A p value of <0.05 was considered significant. All analyses were conducted in R (version 3.3.1).

RESULTS

Cohort size and loss to follow up

We recruited 34 patients with DCM and 32 completed the study. Two patients withdrew from the study; one developed bladder cancer and one had a family bereavement. In addition, 22 healthy volunteers were enrolled as control participants. The median time between presentation and baseline was 113 days (IQR 51-148 days).

Patient characteristics and comparison of DCM patients with healthy volunteers

Baseline demographics and CMR parameters of the cohort are shown in Table 1. The median age at enrolment was 52.5 years in DCM patients and 49.0 years in healthy volunteers. 25 (74%) DCM patients and 15 (68%) healthy volunteers were male. Median body surface area was similar in DCM patients and healthy volunteers (2.00 m^2 vs 1.89 m^2).

Most patients were in NYHA functional class I/II (n=33, 97%) and were prescribed beta-blockers (n=27, 79%), either ACE inhibitors or angiotensin 2 receptor blockers (n=30, 88%), diuretics (n=22, 65%) and a mineralo-corticoid receptor antagonist (n=19, 56%). Two patients had asthma and one had bradycardia, precluding the use of beta-blockers. Two patients were taking ivabradine, one due to a contraindication to beta-blockers. One patient was not on any medication due to personal choice.

As expected, patients had higher indexed LV end diastolic and end systolic volumes, higher indexed LV mass, and lower LVEF compared to healthy volunteers (Table 1). Whilst patients had a higher

overall ECV at LV basal and mid-ventricular levels (Table 1) there was considerable overlap in ECV between DCM patients and healthy volunteers (Supplementary Figure 3).

Safety of dobutamine

One patient did not complete the infusion protocol to 10 μg/kg/min due to an abnormal BP response, and only had a maximal dobutamine dose of 5 μg/kg/min. No other adverse incidents occurred during or after the administration of dobutamine in the remaining patients.

Contractile reserve

Amongst DCM patients, the change (absolute units) in LVEF with dobutamine (contractile reserve) ranged from a fall of 9% to an increase of 23% with a median change of 11%. Amongst healthy volunteers, none had a fall in LVEF during stress and increase ranged from 1% to 20% with a median change of 10%. The contractile reserve was similar for patients with DCM and healthy volunteers (p=0.99) in both univariate or multivariate analyses (Supplementary materials). Among all study participants, there was no evidence that LV contractile reserve was associated with either baseline LVEF (Pearson's correlation r=0.07, p=0.62) or the change in systolic blood pressure (SBP) with dobutamine (r=0.10, p=0.49) (Supplementary materials).

LVEF increased to >35% during dobutamine infusion in seven of ten patients with a baseline LVEF <35%, although all ten subsequently improved LVEF to >35% by 12 months.

Amongst patients with DCM, the absolute change in RVEF with dobutamine ranged from a fall of 17 units to an increase of 24 units with a median change of 5%. Amongst healthy volunteers, the range was from a fall of 4% to an increase of 18% with a median of 10.5%. The RV contractile reserve was similar for patients with DCM and healthy volunteers (p=0.24). RV contractile reserve

was not correlated with baseline LVEF (r=0.15, p=0.28). However, RV and LV contractile reserves were highly correlated (r=0.81, p<0.00001).

Absolute changes in dobutamine-induced global circumferential and radial strain, short-axis contour strain, and long-axis strains were similar for patients and healthy volunteers (Table 1), with the exception of horizontal long-axis strain.

Mechanistic basis of contractile reserve: correlation between contractile reserve and ECV

The ability to assess interstitial fibrosis in-vivo using CMR provides an opportunity to explore the biological basis of contractile reserve. There was a strong correlation between native T1 measurements before and after dobutamine, both at basal (r=0.96, p<0.00001) and mid-ventricular (r=0.93, p<0.00001) levels, suggesting that dobutamine does not affect T1 measurements at 3T.

Contractile reserve was not associated with the amount of interstitial fibrosis in patients with DCM, measured as basal (r= -0.22, p=0.23) or mid LV ECV (r=-0.24, p=0.19). Whilst the individual with a very high ECV also had a fall in LVEF with dobutamine, for other patients, there was no clear relationship between higher ECV and lower contractile reserve, as would be expected if reduced contractile reserve was a consequence of interstitial fibrosis (Figure 1). Most notably, those with a fall in LVEF with dobutamine had similar ECV values to those in whom LVEF rose substantially. In healthy volunteers, despite little variation in ECV, there was wide variation in contractile reserve and no correlation between these two measures (basal LV ECV r= -0.16, p=0.49; mid LV ECV r=-0.21, p=0.37) (Figure 1).

Relationship between LVEF from baseline to 12 months

At 12 months, eight patients (25%) had received a CRT (n=3) and/or an ICD device contra-indicating CMR and therefore had 3D echocardiography assessment of LV function. The median

absolute change in LVEF between baseline and follow-up (Figure 2) was 13% (range -1% to 47%). Nineteen patients (59%) had an absolute increase in LVEF of >10%. LVEF improved from a baseline of 11% to 58% at 12 months in one patient. Only two patients had a fall in LVEF and only one other patient had no improvement by 12 months. All 10 patients with an initial LVEF <35% had an LVEF >50% at 12 months. Overall, most patients achieved an LVEF >50% and 5 an LVEF >60%.

The lack of association between LVEF at baseline and follow-up (r=0.10, p=0.58,) suggests that treatment is effective in restoring LVEF even in patients with very low LVEF at baseline. Of 13 patients with an LVEF <40% at baseline, 11 (85%) had at least a 10% improvement in LVEF by 12 months, compared to 8 of 18 (44%) amongst those with LVEF ≥40% at baseline.

Predictors of change in LVEF

After adjustment for baseline LVEF, contractile reserve was associated with change in resting LVEF at 12 months. Each percentage point increase in contractile reserve was associated a 0.4% increase in LVEF (p=0.02, Table 2; Figure 4). Upon inspection of this figure, it can be seen that the relationship between contractile reserve and LVEF at 12 months was driven to a substantial degree by a failure of LVEF to improve substantially in 3 of the 4 patients with a negative contractile reserve measurement (baseline LVEFs 36%, 39%, 44%).

The change in LVEF during infusion of dobutamine is partly load-dependent. Accordingly, we tried to assess myocardial strain contractile reserve, which is the change in peak strain induced by dobutamine. However, this could only be assessed for between 21 and 25 patients due to inadequate image quality during peak stress and failed to demonstrate a statistically significant relationship between strain contractile reserve and LVEF at 12 months (Table 2).

Several other baseline variables were not significantly associated with follow-up LVEF, including age, NYHA class, beta-blocker use, mid-wall LGE presence and extent, basal or mid ECV, native T1, baseline myocardial strain and RV contractile reserve (Table 2). However, LVEF improved substantially more in women than in men after adjustment for baseline LVEF (Table 2). Contractile reserve remained a significant predictor of change in LVEF after adjustment for both sex and baseline LVEF (p=0.044).

Sensitivity analysis

Findings were broadly similar after adjustment for baseline LVEF. In a model which included both sex and contractile reserve, both variables remained significantly associated with follow-up LVEF. Changes in heart rate and functional mitral regurgitation during dobutamine stress did not predict follow-up LVEF. Adjustment for the time since DCM diagnosis did not affect the association of LV contractile reserve with follow up LVEF. Finally, we evaluated whether the association between contractile reserve and follow up LVEF was affected by the presence of LBBB, as LVEF change may not reflect contractile reserve in patients with LBBB. When the analysis was restricted to the 9 patients with LBBB, contractile reserve was no longer associated with follow up LVEF. Amongst the remaining DCM patients without LBBB, contractile reserve remained associated with follow up LVEF (Supplementary Table 1).

DISCUSSION

Our study suggests that patients with a lower baseline LVEF, a higher contractile reserve and women have the largest improvement in LVEF by 12 months. Poor contractile reserve appears to be a promising marker to detect patients with DCM who are less likely to have favourable LV remodelling. Conversely, a large contractile reserve suggests that improvement in LVEF may be

likely. This is the first study to provide a comprehensive CMR assessment of DCM, including contractile reserve, cardiac structure and function and myocardial tissue characterisation, in order to evaluate imaging predictors of remodelling. LV contractile reserve was the only imaging marker that predicted 12-month LVEF in this cohort; resting measurements of LV structure or function and myocardial strain or fibrosis did not. Contractile reserve was poorly related to the amount of myocardial fibrosis, suggesting that the fundamental cause of a decline in contractile reserve is either a reduction in cardiac myocyte contractile function or in the connection between cardiac myocytes and the collagen infrastructure.

Previous work in the field of echocardiography has largely focussed on the prognostic capacity of contractile reserve[10, 11, 23-28] though some studies have also evaluated the ability of contractile reserve to predict LV remodelling in response to medical therapy[22, 29, 30] or CRT in heart failure patients[31]. In the latter meta-analysis, the presence of contractile reserve in heart failure patients was associated with a higher chance of CRT response (odds ratio 4.42, 95% confidence interval 2.15–9.07, $P < 0.001$). The authors concluded that these findings may indicate that patients with contractile reserve still have myocyte viability, despite decreased LV function, and as such could respond to CRT with restoration of myocardial function. However this and the preceding studies are distinct to the focus of this current study. The unique aspect of our study is that we evaluated CMR assessed contractile reserve in a DCM specific cohort. This is advantageous for a number of reasons. The overall response to therapies including CRT has been observed to differ between patients with ischaemic and non-ischaemic aetiologies[32]. Non ischaemic heart failure encompasses more than just DCM therefore studying a DCM only cohort enables the results to be more applicable to DCM patients, instead of extrapolating their management from a broad heart failure cohort. It is known that LV remodelling can occur either spontaneously, or in response to medical therapy or device therapy[21]. The purpose of our study was to evaluate whether contractile reserve response at baseline would be predictive of follow up LVEF, but the study was not designed to

evaluate response to specific treatments. Accordingly, our findings are applicable to a DCM patient in the early stages of their disease (within the first year), which is often a time at which patients are anxious for a better understanding of their likely disease course and an important time for decision making about device therapy. At present our predictors of changes in LVEF are limited. In contrast to many of the previously reported contractile reserve studies, CMR measurements of left ventricular function are more accurate and reproducible than echocardiography; this is of particular importance when it comes to the assessment of contractile reserve using LVEF. In addition, utilising CMR enabled the simultaneous interrogation of other potentially important imaging predictors of remodelling, in particular mid wall fibrosis. Furthermore, utilising CMR enabled advanced tissue characterisation of interstitial fibrosis which permitted a mechanistic study of the biological basis of contractile reserve.

Many patients had a remarkable improvement in LVEF and by one year, most patients had an LVEF >50% and 16% had an LVEF >60%, demonstrating a remarkable LV structural and functional plasticity even amongst patients with severe LV impairment due to DCM. How much of the observed recovery was spontaneous and how much reflected the effects of guideline-recommended therapy is unclear. Almost 60% of patients in this study showed an improvement of LVEF greater than 10%, which is towards the upper limit of previous findings (25-70%) [8, 33-38] perhaps reflecting advances in pharmacological and device therapy. Contractile reserve itself may not be the underlying mechanism for remodelling, but the presence of LV contractile reserve is at least a surrogate marker for the potential for ventricular remodelling. Predicting recovery in patients with recent onset DCM may be very useful for planning future management. All 10 patients with an initial LVEF <35% improved LV function to move out of current guideline criteria for ICD implantation. However, this may be very different from predicting recovery in patients with chronic disease who have been established on guideline-treatments for a year or more.

Control individuals and DCM patients did not statistically differ in their overall contractile reserve response. However, whilst both DCM patients and control individuals had a wide range of positive contractile reserve responses, a negative contractile reserve (fall in LVEF with dobutamine) was unique to the DCM patients. Our results were highly influenced by the failure of LVEF to improve in DCM patients with a negative contractile reserve. Therefore a negative contractile reserve may be the most informative response and warrants further investigation.

This study shows that imaging predictors of outcome in DCM, such as mid-wall replacement fibrosis (both presence and extent) and RV contractile reserve[11], are not strongly related to LV remodelling, indicating that such measurements are not interchangeable. This suggests that contractile reserve may reflect the global capacity of the myocardium to remodel whereas LGE mid-wall fibrosis is a focal insult that does not affect remote myocardial remodelling. However, as the study was powered to evaluate the association between contractile reserve and left ventricular functional recovery, we may remain underpowered to detect an association between these other imaging parameters and functional recovery. For example, though we did not see a consistent association between global longitudinal strain (GLS) and follow up LVEF in our cohort, there is limited evidence that GLS can predict a future deterioration in LVEF in patients with apparently recovered LVEF[39].

Medications that improve prognosis also failed to predict recovery of LVEF, although this may have been confounded by the duration of therapy, the high prescription of beta-blockers, and the fact that not all patients had indications to be on guideline directed medical therapy. Once baseline LVEF was taken into account, men were less likely to demonstrate recovery in LV function.

There is great interest in exploring the biological basis of recovery of myocardial function[40]. As contractile reserve predicts recovery of LV function, its biological basis could provide insights into

the mechanism of myocardial recovery. Interstitial fibrosis on endomyocardial biopsy has been inversely linked to the extent of LV contractile reserve[41] and myocardial recovery is thought to be possible if there is both a sufficient mass of viable myocytes and an absence of extensive fibrosis[42, 43]. Accordingly, we hypothesized that patients with a high ECV (an in vivo estimate of interstitial fibrosis assessed through CMR T1 mapping) would have diminished contractile reserve. However, the amount of interstitial fibrosis was poorly related to contractile reserve or recovery of LV function. This may reflect differing patient populations in previous studies in terms of aetiology or severity of fibrosis. The lack of correlation with long-term recovery may reflect that interstitial fibrosis is also a dynamic process that may be reversed with therapy. The biological basis for contractile reserve is likely to reside in multiple molecular pathways.

One of the main strengths of this CMR study is the depth of phenotyping with assessment of cardiac function, interstitial fibrosis, replacement myocardial fibrosis, and myocardial strain in one study, enabling a comprehensive, state of the art imaging evaluation of potential predictors of LV remodelling. Another key strength is its prospective study design, with the inclusion of patients with recent onset DCM (an 'inception cohort'[44]). This means that there is no survival bias that can occur in retrospective cohort studies of LV remodelling, whereby only patients who survived to remodel have repeated estimates of LV function. This therefore ensures that the estimate of the proportion of patients who exhibited LV reverse remodelling is also not biased.

A further important strength in this study is the statistical design and analysis. The study was adequately powered and no single, arbitrary threshold for left ventricular reverse remodelling (LVRR) was used. Previous studies have had different definitions of LVRR, with several using an arbitrary threshold for defining success. Whilst it might aid study design, defining an improvement in LVEF <10% as failure and >10% as success is less biologically meaningful.

Study Limitations

We evaluated contractile reserve using dobutamine; others have used exercise stress [45] and invasive methods[46]. Exercise stress depends on the voluntary effort of the patient. Both exercise and invasive measurements are challenging during CMR.

Patients with a lower baseline LVEF might be expected to have a greater increase in LVEF because of regression to the mean. However, the strength of this association was much stronger than might be expected. Moreover, regression to the mean is driven partly by the variability of a measurement but LVEF by CMR is highly reproducible. The relationship between contractile reserve and change in LVEF at 12 months was to a large extent driven by the failure of LVEF to improve greatly in three patients whose LVEF declined during dobutamine infusion. In addition, it is important to highlight that contractile reserve assessed by change in LVEF did not predict follow up LVEF amongst patients with LBBB and another marker of contractile reserve may need to be identified in these patients. We were not powered to detect whether LBBB is a significant modifier of the association of contractile reserve with change in LVEF.

Future directions

The study was not designed to evaluate either the prognostic role of contractile reserve in DCM, or whether the observed recovery was dependent on continuing pharmacological therapy (remission) or whether treatment could be withdrawn without further relapse (cure)[47]. A crucial unanswered question is whether recovery of LV function indicates a normal prognosis for a patient who has been diagnosed with DCM or whether, once someone has been diagnosed with DCM the prognosis remains impaired even if LV function appears to have normalised. The value of assessing contractile reserve after patients have received months or years of guideline-recommended therapy, with or without recovery of LVEF also needs to be considered; should it be used to select patients for more intense pharmacological interventions or novel therapies. Also, restoration of LVEF may

be an inadequate test for true normalisation of LV function which may require more sophisticated assessments, such as evaluation of myocardial strain or diffusion tensor imaging.

Conclusion

In this cohort of patients with recent-onset DCM, substantial recovery of LV function within 12 months was observed in the majority of cases. LVEF had risen to >50% for most patients by 12 months. The lack of association between LVEF at baseline and follow-up suggests that treatment is effective in restoring LVEF even in patients with very low LVEF at baseline. A low LV contractile reserve measured by dobutamine-stress CMR may have additional value in identifying patients whose LVEF is less likely to recover.

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TABLES AND FIGURES

FIGURES

Central Illustration Legend: LVEF change at 1 year. Figure shows baseline LVEF (blue dots) and follow up LVEF (red dots) after 1 year for each of the 32 DCM patients. Most patients showed improvement in LVEF, with only 2 patients showing a deterioration in LVEF on follow up imaging. Dotted lines show the LVEF 35%, 45%, 50%, and 60% cut offs. 'CRT' indicates which patients had CRT during follow up. 'F' indicates female patients. Left ventricular contractile reserve assessed through low dose dobutamine stress CMR was the only imaging predictor of ventricular remodelling in this cohort, suggesting it could be used to identify patients whose LVEF is less likely to recover and who may be candidates for early intervention with advanced therapies

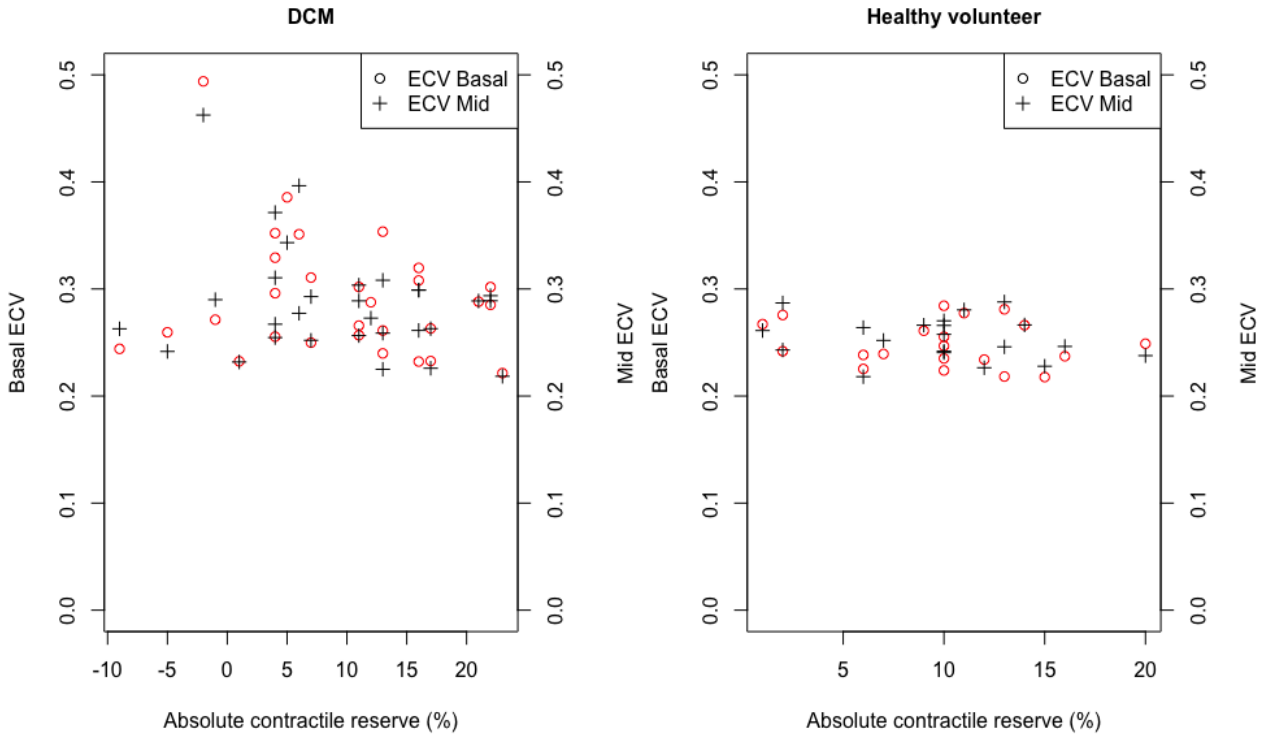

Figure 1: Contractile reserve and ECV. The graph shows that there is no clear relationship between ECV (left y axis for basal and right y axis for mid LV levels) and absolute contractile reserve (% unit change in LVEF after peak dobutamine infusion, x axis) in either DCM patients (left plot) or healthy volunteers (right plot).

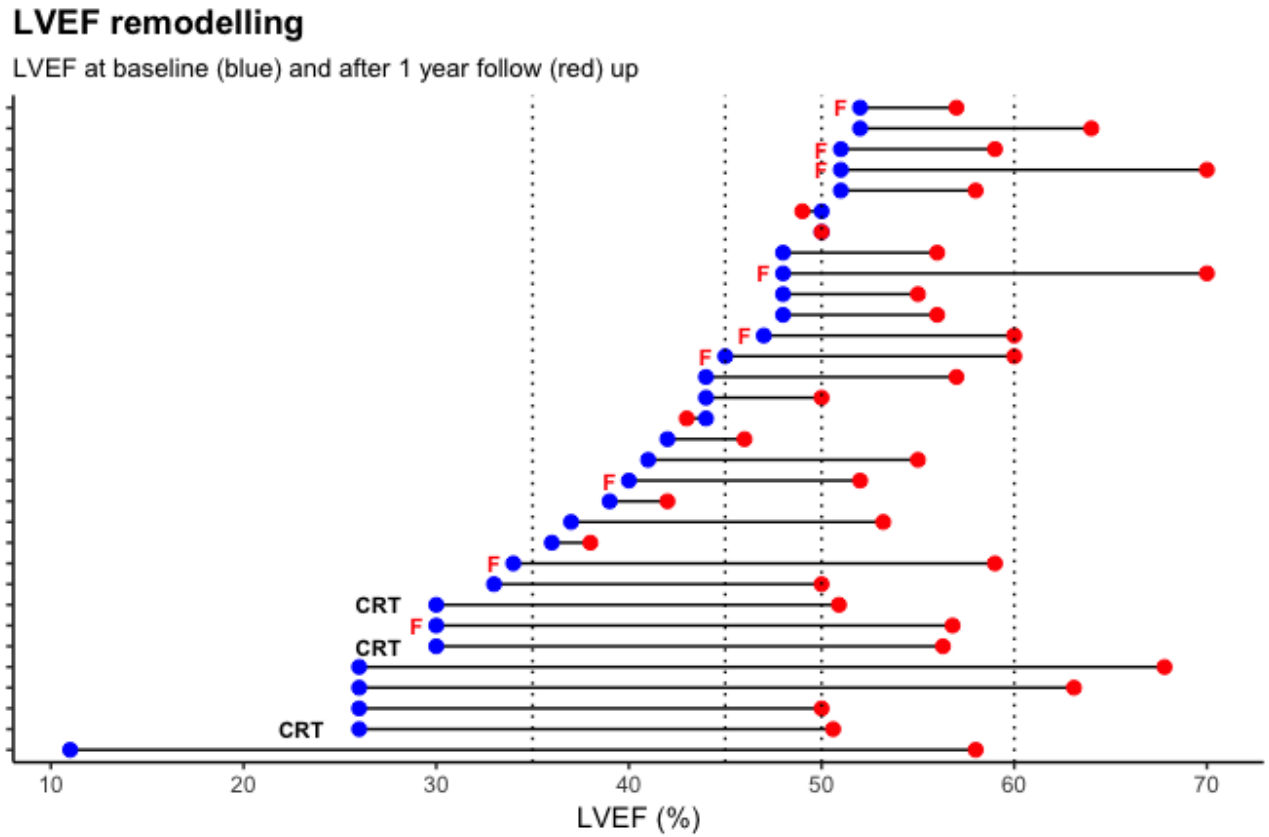

Figure 2: LVEF change at 1 year. Figure shows baseline LVEF (blue dots) and follow up LVEF (red dots) after 1 year for each of the 32 DCM patients. Most patients showed improvement in LVEF, with only 2 patients showing a deterioration in LVEF on follow up imaging. Dotted lines show the LVEF 35%, 45%, 50%, and 60% cut offs. 'CRT' indicates which patients had CRT during follow up. 'F' indicates female patients.

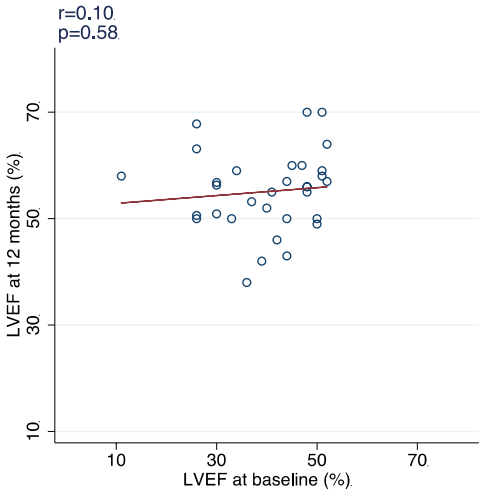

Figure 3: Scatter diagram showing relationship between baseline LVEF and LVEF at 12 months

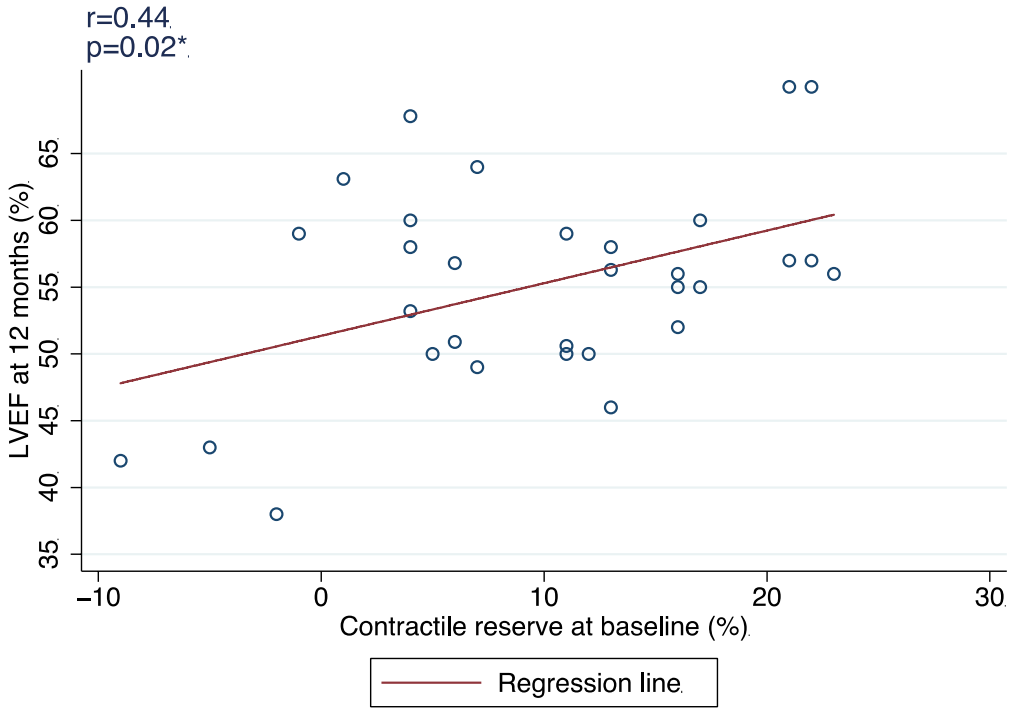

Figure 4: Scatter diagram showing relationship between contractile reserve at baseline and LVEF at 12 months. *Adjusted for baseline LVEF

TABLES

Table 1: Baseline demographics and CMR findings in cohort stratified by diagnosis. Continuous data are shown as median (interquartile range) and compared using the Mann-Whitney test, categorical data are shown as count (percentages) and compared using Fisher's exact test. LV/RV=left/right ventricular; EF=ejection fraction; EDVi/ESVi=indexed end diastolic/end systolic volume; LVMi=indexed LV mass; LAA/RAA=left/right atrial area; ECV=extracellular volume fraction, LGE= late gadolinium enhancement.

	DCM patients N=34	**Healthy volunteers N=22**	**P-value**
Age at baseline	52.5 (45.0 to 60.0)	49.0 (36.0 to 55.0)	0.097
Sex			0.77
F	9 (26.5%)	7 (31.8%)	
M	25 (73.5%)	15 (68.2%)	
Body surface area, m2	2.00 (1.78 to 2.21)	1.89 (1.77 to 2.09)	0.28
Body mass index (kg/m2)	28.0 [23.9, 32.6]	25.1 [24.1, 26.1]	0.036
Haematocrit	0.41 [0.39, 0.45]	0.43 [0.41, 0.44]	0.24
LBBB	9 (26.5%)	0 (0.0%)	0.0084
Systolic BP, mmHg	122.0 (110.0 to 134.0)	111.5 (102.0 to 118.0)	0.0047
Resting heart rate, bpm	62.5 (57.0 to 73.0)	62.0 (54.0 to 68.0)	0.37
NYHA class			<0.0001
I	16 (47.1%)	22 (100.0%)	
II	17 (50.0%)	0 (0.0%)	
III	1 (2.9%)	0 (0.0%)	
LVEDVi, mL/m2	119.6 (108.5 to 143.2)	85.0 (76.7 to 90.0)	<0.0001
LVESVi, mL/m2	65.0 (57.0 to 92.0)	27.5 (23.0 to 33.0)	<0.0001
LVMi, g/m2	82.5 (65.0 to 90.0)	61.5 (47.0 to 71.0)	0.0008
LVEF at baseline (%)	43.0 (33.0 to 48.0)	67.0 (62.0 to 70.0)	<0.0001
RVEDVi, mL/m2	92.6 (81.8 to 106.6)	91.1 (82.2 to 100.5)	0.48
RVESVi, mL/m2	45.4 (39.8 to 57.5)	36.6 (29.4 to 44.8)	0.0015
RVEF, %	49.0 (46.0 to 53.0)	58.5 (53.0 to 63.0)	<0.0001
Presence of midwall LGE	16 (48.5%)	0 (0.0%)	<0.0001
LAA, cm2	26.3 (21.0 to 29.9)	22.5 (20.4 to 26.7)	0.11

	DCM patients N=34	**Healthy volunteers N=22**	**P-value**
RAA, cm2	22.9 (20.4 to 26.6)	25.6 (21.2 to 29.4)	0.21
Maximum LV wall thickness, mm	11.5 (10.0 to 13.0)	9.0 (8.0 to 10.0)	0.0008
Lateral wall thickness, mm	7.0 (5.0 to 8.0)	6.0 (5.0 to 6.0)	0.066
Septal wall thickness, mm	9.0 (8.0 to 10.0)	7.3 (6.0 to 8.0)	<0.0001
Septal native T1, ms	1345 (1321 to 1379)	1278 (1261 to 1300)	<0.001
Basal ECV	0.29 (0.26 to 0.31)	0.24 (0.23 to 0.26)	0.0004
Mid septal ECV	0.28 (0.26 to 0.31)	0.25 (0.24 to 0.27)	0.0042
SAX contour strain	-0.09 (-0.12 to -0.07)	-0.16 (-0.18 to -0.14)	<0.0001
HLA contour strain	-0.09 (-0.11 to -0.07)	-0.16 (-0.16 to -0.14)	<0.0001
VLA contour strain	-0.09 (-0.11 to -0.08)	-0.15 (-0.16 to -0.14)	<0.0001
Radial strain	0.17 (0.09 to 0.25)	0.41 (0.37 to 0.50)	<0.0001
Circumferential strain	-0.10 (-0.12 to -0.08)	-0.17 (-0.19 to -0.17)	<0.0001
Strain reserve:			
SAX contour response	-0.01 (-0.02 to 0.01)	-0.01 (-0.04 to -0.00)	0.11
HLA contour response	0.01 (-0.01 to 0.02)	-0.02 (-0.03 to -0.01)	0.0008
VLA contour response	0.00 (-0.02 to 0.01)	-0.01 (-0.02 to -0.00)	0.16
Radial response	0.01 (-0.03 to 0.13)	0.10 (-0.02 to 0.21)	0.23
Circumferential response	-0.01 (-0.03 to 0.00)	-0.02 (-0.05 to -0.00)	0.35

Table 2: Association of patient characteristics with change in LVEF from baseline to 12 months, adjusted for baseline LVEF

Variable	Comparison	Number of patients with measurement	Estimated effect on LVEF (%)	P-value
Baseline variables				
Age	Per decade older	32	-0.2 (-2.8 to 2.4)	0.88
Female sex	Vs. male	32	7.5 (1.7 to 13.3)	0.012
Beta-blocker use	Vs. no use	32	3.8 (-3.3 to 10.9)	0.28
Beta-blocker dose	Per 1 unit higher	26	-0.1 (-1.8 to 1.6)	0.89
ACE inhibitor	Vs. no use	32	-0.4 (-7.3 to 6.6)	0.92
ACE inhibitor dose	Per 1 unit higher	24	0.3 (-0.4 to 1.0)	0.44
Aldosterone antagonist use	Vs. no use	31	1.4 (-4.7 to 7.6)	0.64
Aldosterone antagonist dose	Per 1 unit higher	19	0.1 (-0.5 to 0.6)	0.83
LBBB	Presence vs absence	32	-1.0 (-7.6 to 5.7)	0.77
NYHA class	Class II Vs class I		2.7 (-3.0 to 8.3)	0.069
	Class III Vs class I		16.0 (0.7 to 31.3)	
Presence of midwall LGE	Vs absence	31	-3.2 (-8.9 to 2.4)	0.25
Extent of LGE % (5 Standard Deviations)	Per 1% higher	16	0.0 (-1.0 to 1.1)	0.96
Extent of LGE % (FWHM – full width at half maximum)	Per 1% higher	16	0.2 (-0.6 to 1.0)	0.61
Mid ECV	Per 0.1 higher	31	-2.3 (-8.0 to 3.4)	0.42
Basal ECV	Per 0.1 higher	30	-3.0 (-8.3 to 2.2)	0.24
Basal native T1 (pre dobutamine)	Per 10ms higher	32	0.0 (-0.3 to 0.3)	0.87
Mid native T1 (pre dobutamine)	Per 10ms higher	31	-0.0 (-0.4 to 0.4)	0.87
SAX contour strain	Per 0.1 higher	28	-3.8 (-12.5 to 4.9)	0.38
HLA strain	Per 0.1 higher	29	-2.2 (-7.3 to 3.0)	0.39
VLA strain	Per 0.1 higher	27	3.1 (-7.4 to 13.6)	0.54
Radial strain	Per 0.1 higher	26	1.0 (-0.9 to 2.9)	0.29
Circumferential strain	Per 0.1 higher	26	-3.7 (-20.6 to 13.1)	0.65
Response under max dobutamine stress				
LV contractile reserve	Per 1% higher	31	0.4 (0.1 to 0.7)	0.020

Variable	Comparison	Number of patients with measurement	Estimated effect on LVEF (%)	P-value
RV contractile reserve	Per 1% higher	31	0.2 (-0.1 to 0.5)	0.17
SAX contour strain reserve	Per 0.1 higher	25	-2.7 (-6.8 to 1.4)	0.19
HLA contour strain reserve	Per 0.1 higher	21	-3.2 (-8.7 to 2.3)	0.24
VLA contour strain reserve	Per 0.1 higher	22	-6.3 (-12.8 to 0.1)	0.054
Radial strain reserve	Per 0.1 higher	22	-0.6 (-3.1 to 1.8)	0.59
Circumferential strain reserve	Per 0.1 higher	22	2.2 (-9.5 to 13.8)	0.70

‘Take home figure’

Figure 2

One –Sentence summary

A low LV contractile reserve measured by dobutamine-stress CMR may have additional value in identifying dilated cardiomyopathy patients whose LVEF is less likely to recover.