Factors predicting recovery of left ventricular dysfunction in non-ischaemic cardiomyopathy

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EDITORIAL COMMENT

Factors predicting recovery of left ventricular dysfunction in non-ischaemic cardiomyopathy

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This article refers to 'Predictors of left ventricular remodelling in patients with dilated cardiomyopathy – a cardiovascular magnetic resonance study' by U. Tayal *et al.*, published in this issue on pages xxx.

Patients with new-onset heart failure (HF) usually undergo rigorous testing to identify the underlying cause and correct modifiable conditions such as coronary artery disease. Often, these patients present with dilated left ventricles and reduced ejection fraction. A large proportion of these patients have no modifiable factors and are therefore coined to have idiopathic dilated cardiomyopathy (DCM). This group is still very heterogeneous with different aetiologies including genetic causes. Response to treatment and spontaneous recovery is variable and difficult to predict.

In this issue of the Journal, Tayal *et al.*[1] present their results employing cardiac magnetic resonance imaging (CMR) combined with dobutamine stress testing to improve prediction of left ventricular (LV) functional recovery. They included 34 patients with recent-onset DCM, most of which had substantial improvement of LV function after 12-month follow-up. In addition to female sex, the study demonstrates that contractile reserve measured by dobutamine stress CMR predicts functional recovery.

Is seems that there is spontaneous recovery in many patients presenting with new-onset LV dysfunction. All but a small subset of patients with unbearable side effects or unwillingness to adhere to pharmacological therapy, however, are treated with HF medication including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-adrenergic receptor blockers and mineralocorticoid receptor antagonists. A recent randomized study has investigated if it is safe to withdraw this medication after LV recovery in DCM patients. The TRED-HF study has demonstrated that removal of HF medication leads to recurrence of LV dysfunction in many patients and 'spontaneous' improvement is actually HF remission induced by medication and not recovery.[2] As reverse remodelling is not only closely related to exercise capacity and HF functional class but also reduction of HF hospitalizations and mortality, HF medication should not be removed in these patients. In patients that do not sufficiently respond to traditional HF medication, the option to add a neprilysin inhibitor, sacubitril/valsartan, can lead to further improvement in HF outcome. A recent study by Martens *et al.*[3] demonstrated in 151 HF with reduced ejection fraction (HFrEF) patients after switch to sacubitril/valsartan that an improvement in LV ejection fraction (LVEF) of >5% is related to reduction in ventricular arrhythmias.

There are subsets of patients with LV dysfunction that have recovery and may not need long-term HF medication. Patients with peripartum cardiomyopathy that have fully recovered were stable after 5-year follow-up but 70% of patients were still on at least one HF drug.[4] Another example are patients presenting with Takotsubo syndrome, but even in this population severely depressed LV function is at least a marker of adverse long-term outcome.[5]

In many cases DCM is caused by genetic mutations. It is unclear if these patients respond in the same way to pharmacological therapy as those without a different aetiology. They are treated in the same manner as patients without a documented genetic mutation. One of the few studies that investigated mutations and outcome after treatment involved patients with a truncating titin mutation that is associated with a mild form of DCM.[6] In this study, 46.9% patients with a titin mutation had an increase in LVEF of >10% while this occurred in only 6.5% of patients with a lamin A/C mutation and 18.5% of patients with idiopathic DCM, that is without any documented genetic mutations.

Recent evidence has shown that functional recovery can also depend on electrical factors. Broadening of QRS complex, especially in combination with left bundle branch morphology, adversely affects recovery of LV dysfunction by medical therapy.[7] On the other hand, these patients often respond to cardiac resynchronization therapy (CRT) with improvement to normalization of LV function, highlighting the concept of electrical dyssynchrony as the major aetiological factor in a subset of patients with HF. In the current study by Tayal *et al.*,[1] three patients have had a CRT device

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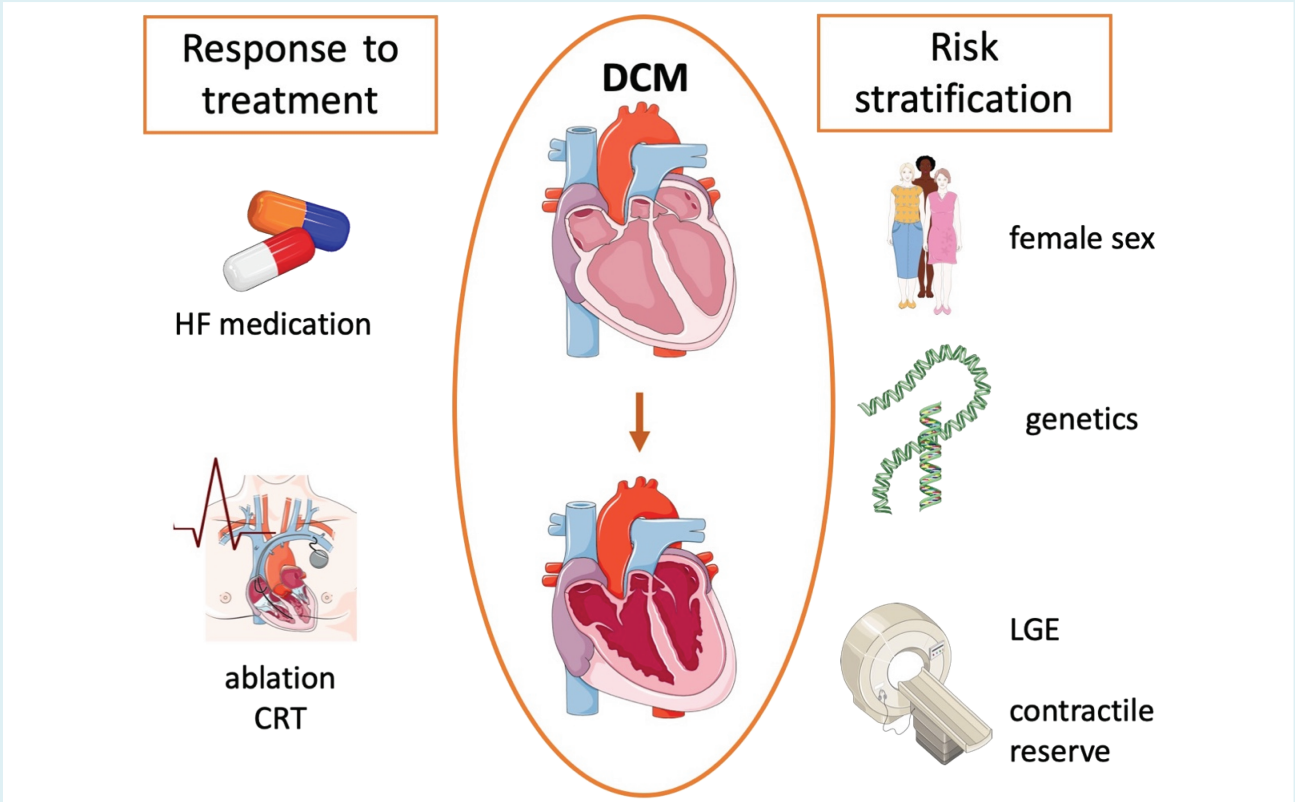

Figure 1 Schematic showing factors predicting response to treatment of dilated cardiomyopathy (DCM). CRT, cardiac resynchronization therapy; HF, heart failure; LGE, late gadolinium enhancement demonstrating cardiac fibrosis on cardiac magnetic resonance imaging.

implanted and all showed a large improvement in LVEF. In addition to dyssynchronopathy, frequent premature ventricular contractions can lead to cardiac dysfunction, especially in patients with high arrhythmia burden and epicardial origin of the extra beats.[8] Ablation therapy can be a beneficial addition to pharmacologic therapy in these patients leading to improvement of LV function especially in patients with more severely depressed LVEF[9] (*Figure 1*).

Although women are often underrepresented in clinical trials and cohort studies, sex differences in improvement of LVEF in patients with HFrEF have been reported increasingly over the last years. In the IMPROVE HF trial (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting), which included 3994 patients (70% male) with HFrEF, female sex was associated with a >10% improvement in LVEF at 24 months.[10] Additionally, a Canadian retrospective study on 3124 HFrEF patients (71% male) reported that female sex was independently associated with LVEF improvement of >10% at 6-month follow up.[11] Several studies have also found female sex to be an independent predictor in response to CRT.[12] These findings on sex differences in improvement of LVEF in HFrEF are in line with the finding in the study by Tayal *et al.* They reported that LVEF, evaluated by CMR at 12 months, had improved substantially more in women than in men with DCM after adjustment for baseline LVEF.[1] Female sex, compared to male sex, was associated with a 7.5% (1.7–13.3) increase in LVEF at 12 months ($P = 0.012$). This is of particular interest as it has recently been suggested that an improvement in outcome in female HFrEF patients may be achieved by administering lower doses of guideline-directed medical treatment, compared to male HFrEF patients.[13] Unfortunately, data on the use and doses of guideline-directed medical treatment have not been provided in this study.

The current study by Tayal *et al.*[1] has highlighted the importance of imaging studies not only in diagnosis of HF aetiology but also in improving prediction of LV recovery. CMR cannot only show the extent of connective tissue deposition but also functional parameters including contractile reserve by dobutamine stress imaging. Contractile reserve seems to be a good predictor of recoverability of LV dysfunction as it identifies the potential of the myocardium to improve contractile function if needed. It had earlier been demonstrated that contractile reserve can be utilized to predict response to CRT.[14] Tayal *et al.*[1] demonstrate that in their population the presence or amount of fibrosis does not predict LV recovery. Contractile reserve, however, was predictive for LV recovery. Interestingly, the response to dobutamine was similar in DCM patients and healthy controls (11% increase in LVEF vs. 10%). The amount of increase of LV function upon dobutamine infusion was related with improvement of LVEF at follow-up.

In conclusion, new-onset HF still needs rigorous work-up to identify underlying causally treatable conditions. In the absence of modifiable disease, patients may be scheduled for dobutamine

stress imaging to identify patients that might not respond favourably to standard HF therapy. These patients may be candidates for early additional medication such as sacubitril/valsartan or in case of severe HF can become candidates for advanced HF treatment such as implantation of an LV assist device. Patients without contractile reserve might also derive less benefit from electrical therapies such as CRT. We urgently need a better understanding of the pathophysiology of myocardial recovery to identify possible new therapeutic targets. Furthermore, research is necessary to identify patients that can safely stop HF medication after recovery.

Conflict of interest: none declared.

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