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Prediction of left ventricular reverse remodelling. Mini review on clinical aspects

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Improvement of left ventricular ejection fraction (LVEF) in patients after the first manifestation of heart failure with reduced ejection (HFrEF) is currently observed more frequently than years ago. This appears to be due to the early initiation of comprehensive HF therapy. According to these observations a new HF syndrome category – heart failure with improved ejection fraction (HFimpEF) – was introduced. The morphological and functional myocardial changes seen in patients with HFimpEF are referred to as reverse remodelling (RR).

Despite the lack of guidelines and recommendations there is a consensus among experts on the following RR criteria (1):

- Documented reduced LVEF < 40%,
- An increase in LVEF of at least 10% from baseline value,
- An increase in LVEF to >40%.

The average RR incidence is 22.64% according to a recent meta-analysis (2). In clinical practice, reverse remodelling is associated with improved functional capacity and reduced hospitalisation and mortality rate (2). According to these characteristics, the induction of reverse remodelling becomes a major therapeutic target in patients with HFrEF. The predictive factors of reverse remodelling have today been partially described, but both detailed knowledge of them, as well as accurate RR prediction, are important for a therapeutic strategy decision, especially when expensive device therapy is being considered.

Predictors of reverse remodelling (Figure 1)

Aetiology and clinical parameters

In general, patients with an ischemic cause of HFrEF are less likely to achieve RR than patients without ischemic myocardial damage.

Dilated cardiomyopathy dominates among the non-ischemic causes of HFrEF, with non-familial forms of DCMP having more favourable prognoses and higher probability of RR induction. DCMP associated with truncating titin mutations usually responds well to drug treatment, and RR is more likely to develop compared to DCMP associated with laminin A/C and other sarcomere proteins gene mutations. The estimated probability of RR induction due to proper treatment in patients with idiopathic DCMP is approximately 40% (3).

Higher BMI (4), female sex (5, 6), shorter disease duration (7) as well as higher blood pressure (8, 9) were identified as predictors of RR derived from medical history and the patient´s clinical profile.

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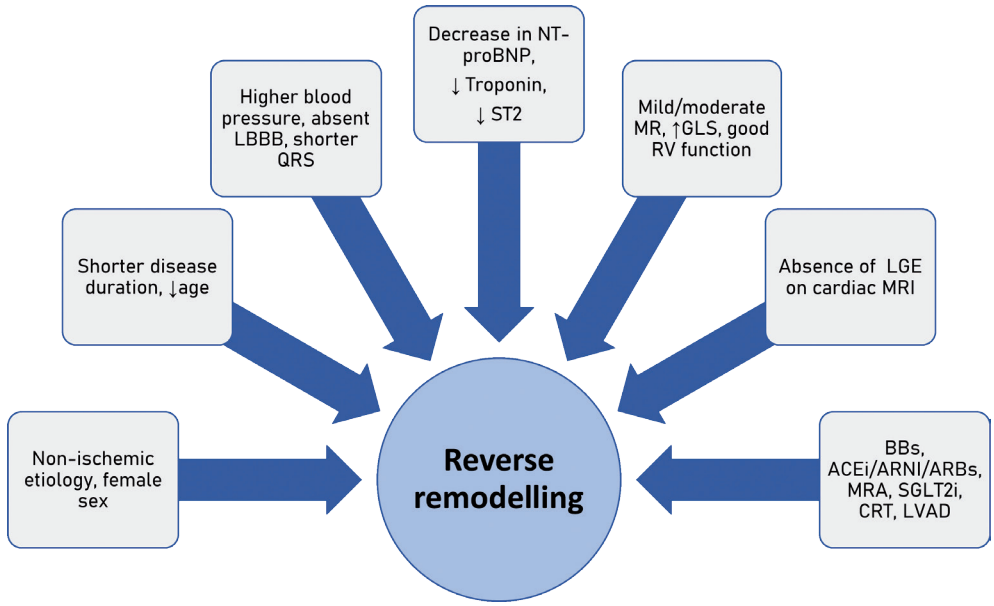

Figure 1 Factors associated with reverse remodelling
ACEi – angiotensin converting enzyme inhibitors; ARBs – angiotensin receptor blockers; ARNI – angiotensin receptor-neprilysin inhibitor; BBs – beta blockers; CRT – cardiac resynchronisation therapy; LBBB – left bundle branch block; GLS – global longitudinal strain; LGE – late gadolinium enhancement; LVAD – left ventricle assist device; MR – mitral regurgitation; MRA – mineralocorticoid receptor antagonist; MRI – magnetic resonance; NTproBNP – N-terminal prohormone of brain natriuretic peptide; RV – right ventricle; SGLT2i – sodium-glucose co-transporter-2 inhibitors; ST2 – ST2 cardiac biomarker

Imaging

When using echocardiography in RR prediction it is also necessary to evaluate, in addition to basic morphological and functional parameters, the deformation characteristics of the myocardium using speckle-tracking echocardiography: it reflects contractility and left ventricular systolic function more reliably and seems to predict RR better. Several studies have confirmed that left ventricular global longitudinal strain (GLS) is a reliable RR predictor (10). Left ventricular GLS also appears to be a suitable predictor of the further clinical course in patients with HFimpEF.

In addition to echocardiography, magnetic resonance imaging of the heart also plays an important role in RR prediction. Late gadolinium enhancement represents the main parameter predicting RR. Patients with low degree of LGE or no LGE at all are more likely to achieve RR (11, 12).

Biomarkers

Biomarkers are used routinely for heart failure diagnosis, prognosis assessment and response to treatment monitoring. Nowadays, it is possible to evaluate the degree and severity of some pathophysiological processes accompanying the onset and progression of heart failure by using biomarkers (13). Identification of biomarkers as RR predictors seems to be a useful step for clinical practice.

The contribution of NT-proBNP in RR prediction has been demonstrated in several studies that evaluated its dynamic changes. A significant NT-proBNP decrease was associated with LVEF improvement.

Troponin T as a myocardial damage marker appears to be a promising RR predictor. A study on a heterogenous group of HFrEF patients showed a higher incidence of RR in patients with the initial high-sensitive troponin T value < 11 ng/l compared to patients with higher troponin T levels (14).

One study including 304 outpatients with HFrEF identified ST2 (suppression of tumorigenicity 2) as the only biomarker associated with RR in a multivariate analysis. The authors also proposed using the ST2-R2 score to predict reverse remodelling, which consists of the following variables: ST2 < 48 ng/ml, non-ischemic aetiology,

absence of LBBB, disease duration < 12 months, baseline LVEF < 24% and a history of beta blocker treatment (7).

Management of patients with HFimpEF

After definition of a new group of patients with heart failure, new questions regarding their management have arisen. Due to the incomplete understanding of various mechanisms of reverse remodelling and a lack of large randomised clinical trials, no official guidelines for management of patients with HFimpEF have yet been published, and only the consensus of experts is being followed.

Patients with HFimpEF should be monitored regularly on an outpatient basis for the risk of repeated progression of systolic dysfunction. The frequency of check-ups should be every 6 months during the first three years. The regular outpatient check-up should include clinical examination focused on signs of congestion, physical capacity evaluation, an electrocardiogram, NT-proBNP level measurement and echocardiography. In patients with cardiomyopathy with a higher risk of atrial arrhythmias, an ECG Holter of at least once every two years is recommended.

Conclusion and further perspective

Studies evaluating clinical outcomes of patients with HFimpEF have consistently shown a reduction in mortality and hospitalisation rate as well as better quality of life compared to patients with HFrEF, HFmrEF (heart failure with mild reduced ejection fraction) and also HFpEF (15 – 17). In patients with heart failure, RR prediction is very important for determining a treatment strategy. We do not yet have an effective model for RR prediction, but it should consist of a wide range of information, including history data, clinical, laboratory and imaging parameters. However, development of such a model requires more scrupulous research of this heart failure phenotype. The results of studies focused on RR may, in addition to more accurate RR prediction, also identify new therapeutic targets for patients with HFrEF.

In conclusion, early identification of heart failure, accurate aetiological diagnosis (including genetic testing) and proper treatment with adequate dose titration are key factors for predicting and achieving RR in patients with HFrEF. In-depth study and knowledge of the molecular mechanisms involved in reverse remodelling may lead to the identification of new individualized therapeutic approaches for HFrEF.

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