Prediction of individual response to heart failure therapy

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This editorial refers to ‘Effects of myocardial fibrosis and ventricular dyssynchrony on response to therapy in new-presentation idiopathic dilated cardiomyopathy: insights from cardiovascular magnetic resonance and echocardiography’¹, by D.P. Leong et al., on page 640

Heart failure is associated with an adverse prognosis, and aggressive therapy is needed. In most patients, medical therapy is the cornerstone of treatment. Although the response to medical therapy is good in heart failure patients, benefit varies significantly among individual patients. This has been particularly demonstrated for beta-blocker therapy. Packer and colleagues evaluated 2000 heart failure patients, who were randomized to placebo or carvedilol.¹ The authors reported a 35% decrease in the risk of death with carvedilol as compared with placebo; moreover, a 24% decrease in the combined risk of death or hospitalization was observed. Other studies demonstrated that beta-blocker therapy in heart failure patients was associated with an improvement in left ventricular ejection fraction (LVEF).²,³ although a substantial percentage of individual patients did not exhibit a significant improvement in LVEF (defined as an increase ≥ 5%).² Data from the Carvedilol Hibernation Reversible Ischemia Trial: Marker of Success (CHRISTMAS) trial showed that the magnitude of improvement in LVEF after carvedilol therapy was related to the extent of viable tissue (on single photon emission computed tomography) in the left ventricle.⁴ Similarly, Bello et al. evaluated 45 heart failure patients who received beta-blocker therapy, with contrast-enhanced cardiovascular magnetic resonance (CMR) to assess the extent of scar tissue in the left ventricle.⁵ The authors demonstrated that significant improvement in LVEF (defined as ≥ 5%) after 6 months of beta-blocker therapy was not observed in 43% of the patients. Moreover, the extent of scar tissue on CMR was inversely related to the likelihood of improvement in LVEF. Another study in 43 heart failure patients demonstrated that the presence of contractile reserve on dobutamine echocardiography was associated with good response to beta-blocker therapy, and that the improvement in function occurred earlier after initiation of beta-blocker therapy in patients with idiopathic dilated cardiomyopathy as compared with patients with ischaemic cardiomyopathy.⁶ These findings provide some preliminary evidence for the possibility of identifying heart failure patients that may respond better or worse to beta-blocker therapy.

The varying response in heart failure patients has also been observed in device therapy, in particular cardiac resynchronization therapy (CRT). In the Cardiac Resynchronization-Heart Failure (CARE-HF) study, 813 heart failure patients [New York Heart Association (NYHA) class III–IV] were randomized to optimized medical therapy or CRT.⁷ Over a follow-up period of 29.4 months, mortality was significantly lower with CRT as compared with medical therapy (20% vs. 30%, P < 0.002). Moreover, the combined endpoint of all-cause mortality or unplanned cardiovascular hospitalization was reached in 39% of patients undergoing CRT as compared with 55% of patients receiving medical therapy (P < 0.001). Also, patients with CRT exhibited an improvement in LVEF, with a reduction in left ventricular (LV) end-systolic volume and mitral regurgitation, as well as a reduction in symptoms and an improvement in quality of life. Based on the CARE-HF trial and other studies, severe heart failure patients with wide QRS complex (≥ 120 ms) and depressed LVEF (≤ 35%) have a class I indication for CRT;⁷ more recently, these guidelines have been updated based on new evidence, now also including patients with less severe heart failure as candidates for CRT.⁸ Despite these selection criteria, the individual response to CRT varies significantly, with a relatively high percentage of non-responders, depending on the definition of non-response.¹⁰ In general, absence of reverse LV remodelling is observed more often than absence of improvement in heart failure symptoms. This has prompted an extensive search for prediction of response to CRT. Various variables have been proposed, e.g. the QRS duration, cardiac dyssynchrony, and the presence of extensive scar tissue. For example, patients with a QRS duration > 150 ms tend to respond better to CRT as compared with patients with a QRS duration between 120 and 150 ms.¹¹ Many studies have used cardiac dyssynchrony (predominantly assessed by
echocardiography) to predict response to resynchronization therapy, but a single dysynchrony parameter has not yet been defined. The use of sophisticated echocardiographic techniques including real-time three-dimensional echocardiography and strain imaging may provide superior measurements of cardiac dysynchrony. Finally, the extent and localization of scar tissue appear important in the response to resynchronization therapy; in particular, the presence of scar tissue on contrast-enhanced CMR was associated with non-response: the non-response rate was 81% in patients with transmural scar tissue in the posterior-lateral wall, the preferred site for the LV pacing lead.

Accordingly, the response to medical and device therapy in heart failure patients is variable, and sophisticated imaging techniques (advanced echocardiography, CMR) may help in selecting patients who have a higher likelihood of response to therapy. This was the topic of the study by Leong and co-workers, who report on the value of sophisticated echocardiography and contrast-enhanced CMR in patients presenting with new-onset dilated cardiomyopathy. The authors evaluated 68 patients presenting with dilated cardiomyopathy at a median of 12.5 days after the initial diagnosis. Coronary artery disease was excluded by invasive coronary angiography, and the LV function was depressed as indicated by the mean LVEF of 29 ± 8% and the global longitudinal strain score (derived from speckle tracking strain echocardiography) of –12 ± 2%. The LV was dilated, with a mean indexed LV end-systolic volume of 60 ± 22 ml/m². The patients were symptomatic, with a mean Minnesota Heart Failure score of 44 ± 22, a reduced 6 min walk distance of 420 ± 96 m, and a median N-terminal pro brain natriuretic peptide (NT-proBNP) value of 1183 ng/L. Of note, the mean QRS duration was 114 ± 29 ms.

The patients underwent contrast-enhanced CMR to detect the extent of LV fibrosis, pulsed-wave Doppler echocardiography to determine interventricular dysynchrony, and colour-coded tissue Doppler echocardiography to assess intra-LV dysynchrony. Of the 68 patients, 12 (24%) had fibrosis on contrast-enhanced CMR, with a mean mass of 2.2 ± 1.3 g, typically located in the mid-wall or at the right ventricular insertion. Both inter- (31 ± 24 ms) and intraventricular dysynchrony (41 ± 14 ms) were increased. Optimized medical therapy was started according to recent heart failure guidelines, and included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and aldosterone antagonists when tolerated.

At 5 months follow-up, the LV function had improved significantly (LVEF 43 ± 13%, P < 0.001 vs. baseline; LV global longitudinal strain score –16 ± 4%, P < 0.001 vs. baseline), and LV reverse remodelling had occurred (indexed LV end-systolic volume 44 ± 22 ml/m², P < 0.001 vs. baseline). Also, the symptoms and the 6 min walk distance improved significantly. In contrast, cardiac dysynchrony did not improve. As evidenced by the standard deviations of the follow-up measurements of cardiac structure and function (as well as symptoms), there was a significant variation in the individual responses. When an improvement in LVEF >5% was considered as a marker of therapeutic response, 19 patients (28%) failed to respond favourably. There was a significant difference in LV fibrosis on contrast-enhanced CMR between responders and non-responders (0.9 ± 0.9 g vs. 0.2 ± 0.6 g, P < 0.001). Other univariate predictors of LVEF improvement were NT-proBNP, intraventricular dysynchrony, and QRS duration. On multivariate analysis, LV fibrosis and intraventricular dysynchrony remained predictive of LVEF improvement.

The findings in the study of Leong et al. confirm that heart failure patients respond differently to medical therapy, with 28% of patients not exhibiting a significant improvement in LVEF. The results also indicate that advanced imaging may help in the prediction of individual response to therapy. Specific measurements of structure (fibrosis) and function (dysynchrony) may help in the identification of potential responders. The study included only a small number of patients, and was restricted to non-ischaemic heart failure patients. Moreover, the follow-up after medical therapy (5 months) was relatively short. Larger cohorts with longer follow-up are needed to confirm the current findings. It has become clear, however, that not every heart failure patient is the same, and response to therapy varies significantly. From a ‘personalized medicine point of view’ it will therefore become increasingly important to identify responders to therapy at an early stage and, ideally, predict the response before initiation of the therapy. This will be important not only in medical therapy but also in device therapy (CRT, implantable cardioverter-defibrillator). Eventually, this may translate into superior survival and reduction of cardiovascular events.

What is needed at the current stage is identification of the markers that may predict response, and this may require a better understanding of the role of these markers in the pathophysiology of heart failure. In particular, the presence of fibrosis appears to be important in (non-)response to therapy, with more extensive fibrosis limiting the response. Although the contrast-enhanced CMR technique allows adequate assessment of macroscopic fibrosis, it may be preferred eventually to detect the diffuse, microscopic fibrosis in the left ventricle. This may eventually permit prediction of response at an earlier stage in the disease process (the development of heart failure). In particular, T1-weighted imaging with CMR may help in this regard.

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References


