Exercise and heart failure: Improve your functional status and your biomarker profile

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This article refers to ‘Effects of a cardiac rehabilitation programme on plasma cardiac biomarkers in patients with chronic heart failure’, by G Billebeau et al.1

In the last decade, it has become very clear that inactivity should be regarded as a major cardiovascular risk factor.2 On the other hand, evidence in favour of (cardiovascular) exercise is mounting, and has already been incorporated into a World Health Organization statement and in the International Society and Federation of Cardiology position paper of 1994.3 However, despite striking effects on exercise performance, on slowing disease progression,4 on improving symptoms,5 quality of life and outcomes6 of chronic heart failure (CHF) patients,7 the effects on biomarker levels are less clear.

In the current issue of the journal, Billebeau et al. describe these effects.7 They included 107 stable CHF patients with reduced left ventricular ejection fraction (<45%) and New York Heart Association (NYHA) functional class between II and IV. The study duration was 4–6 months, in which a total of 40 supervised exercise sessions were planned. Echocardiography and blood sampling were performed at enrolment and after completion of the study. Cardio-pulmonary exercise test was conducted at enrolment only. Biomarkers, including B-type Natriuretic Peptide (BNP), mid-regional atrial natriuretic peptide (MR-proANP), MR-pro adrenomedullin (MR-proADM), creatinine, galectin-3 and soluble Suppressor of Tumorigenicity (sST-2) were measured in samples before and after the exercise programme.

The cardiac exercise programme in this study was generally successful, reflected by an increase of 14.5% in peak VO2 and an improvement in NYHA functional class in 54% of the patients.

The main outcomes show that a decrease of 6.3%, 7.4%, 6.4%, 16% and 46% was observed for galectin-3, sST-2, MR-proADM, MR-proANP and BNP, respectively. Creatinine levels increased by 7.1%. The control group, which was not participating in the programme, showed no change in any biomarker value. In a sub-group of patients with the most benefit from cardiac exercise, the largest differences in biomarkers were observed.

The two most widely studied biomarkers in heart failure are (NT-pro)BNP and troponin. In a sub-study of the HF-ACTION trial consisting of 928 subjects these biomarkers along with high-sensitivity C-reactive protein were analysed.8 The HF-ACTION study, a randomized clinical trial of exercise training versus usual care in 2331 CHF patients with reduced left ventricular ejection fraction (<35%), demonstrated no clear benefit from additional training regarding all-cause mortality and heart failure rehospitalization after one year. In line with this, in different sub-analyses no clear reductions of biomarker levels were observed. However, the authors observed a clear association with improvement of NT-proBNP levels and improvement of exercise capacity. Another, much smaller, study of 95 CHF patients, who underwent either a nine-months training programme at 60% of the maximal oxygen uptake or no training, also assessed natriuretic peptide levels.9 Peak VO2 was improved by 13%, and BNP and NT-proBNP were both significantly reduced, by 34% and 32% respectively. Again, increases in peak VO2 with training correlated significantly with the decreases in both BNP and NT-proBNP levels. Patients who did not undergo training showed no changes. Finally, it was recently observed that levels of pro-inflammatory and fibrosis biomarkers may predict the individual patient’s response to exercise training.10

Why would one measure serial biomarkers to assess the effects of cardiovascular exercise training and rehabilitation? First, the same intensity of exercise may provoke very beneficial effects in one patient, while it may not be intense enough for others. So individual
dosing of exercise is notoriously difficult. Second, subjective improvements are difficult to quantify, so that there is a need for objective measures to monitor the effects of such costly and time consuming programmes. After 3–6 months of exercise training, exercise tolerance may have improved but the patient may be dissatisfied, or, vice versa, the patient feels better but the exercise capacity may not have changed. In such cases, it may be useful to use biomarkers to persuade the patients (or oneself) that something was achieved – or not.

There are a few considerations for this approach. First, assessing whether serial measures of biomarkers present significant and clinically relevant differences is difficult. In the study of Billebeau et al. no individual data is available and only changes of the complete group are provided. The latter makes it even more difficult to comment on each individual. As suggested previously, clinicians should make use of the reference change values (RCVs) derived from variability studies, which could help to initiate a more tailored clinical approach. The RCV tells what change is necessary to move from the biological variation within an individual, and only when this threshold is reached, should changes be interpreted as clinically relevant.

Second, it may be difficult to position a biomarker outcome amidst other subjective, clinical and functional parameters as the direction of changes may be disparate. We would therefore not advocate to always use (serial) biomarker assessment, but in order to be able to use biomarkers it is advised to take a baseline sample and either do the assays or store the sample. We would also advocate assaying several markers from different heart failure domains. If, after a certain time period, the outcome of the programme is different from the expectations, measuring the markers again could be considered. This would give clinicians a better grasp as to whether the exercise programme results in improvement, which might be remaining under the surface clinically, but is associated with biomarker differences. Mostly, the current study by Billebeau et al. reminds us that exercise programmes are not just to make the patient feel better, but that they help to optimize cardiovascular condition and improve outcomes. All tools that help us to realize this should be considered.

**Author contribution**

The authors indicate this is original work and they both contributed equally to the article.

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