It’s the metabolism, stupid! Why electrophysiologists should be interested in biomarkers of heart failure

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This editorial refers to ‘Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony’ by F.M. Fruhwald et al., on page 1592

Cardiac resynchronization therapy (CRT) has emerged as a new standard in the treatment of patients with moderate-to-advanced heart failure and ventricular dyssynchrony. The recently actualized ESC/AHA/ACC heart failure guidelines have classified CRT as a class I indication in patients with reduced ejection fraction and ventricular dyssynchrony (QRS width ≥120 ms) who remain symptomatic (NYHA III–IV) despite optimal medical therapy to improve symptoms, hospitalizations, and mortality. These criteria have been derived mainly from data of the COMPANION2 and CARE-HF3 trials. So far, so good. Why should we be interested in biomarkers of heart failure such as brain natriuretic peptide (BNP)? BNP is a hormone co-secreted with the inactive aminoterminal pro-BNP, i.e. NT-pro-BNP, from the ventricles in response to increase of left ventricular wall stress. Thus, levels of BNP or NT-pro-BNP in the serum are elevated in patients with both systolic and diastolic heart failure. At first sight, it seems rather self-evident that a treatment such as CRT which has been shown to lead to long-term reduction in left ventricular volumes in many patients should also lead to a reduction in NT-pro-BNP serum levels. Some previous, smaller trials have indicated that this may be indeed the case.4 But the data provided by Fruhwald et al.5 in this issue of the European Heart Journal are the first to demonstrate a significant and sustained reduction in NT-pro-BNP levels with CRT in a large, randomized, controlled clinical trial. What are the clinical implications of this finding?

The truth is that there is a lot about CRT that we do not know. Using the clinical criteria of the implantation guidelines results in a lack of clinically significant response to CRT in 30–40% of patients. Therefore, better criteria for identification of the optimal CRT candidate are urgently warranted. However, despite previous data indicating that elevated BNP or NT-pro-BNP levels may be markers of a poor prognosis,6 the biological variability of serum levels precludes its use for deciding which patient should be implanted or not. The data by Fruhwald and colleagues in this issue of the European Heart Journal therefore do not provide any evidence that this serum parameter may be used as a predictor for CRT response in the individual case despite the fact that higher baseline NT-pro-BNP levels indicated a worse prognosis in this trial. It still seems that modern imaging modalities such as echocardiographic tissue Doppler imaging or magnetic resonance tomography analysing the degree of baseline dyssynchrony and myocardial viability may be the future tools for selecting CRT responders.

However, there may still be an important role for this biomarker in the setting of CRT as can be derived from the data presented by Fruhwald et al. Despite the encouraging results with CRT including an improvement in left ventricular remodelling, NYHA functional status, quality of life, and, ultimately, mortality, all these data pertain to relatively short follow-up durations of usually not more than 2 years. Now that CRT is here to stay in the treatment of our heart failure patients we need to realize that we will see an increasing number of patients that have a resynchronization device implanted for much longer periods. Realizing that the heart responds to CRT not only acutely but that, in addition to the electrical activation changes and their direct haemodynamic consequences, there are distinct morphological adaptations7 as well as changes in expression of different contractile proteins8 after CRT, we have to ask ourselves if we really believe that the settings of such a device, programmed before discharge after the initial implantation are the optimal settings once and for all. Of course, this is unlikely, especially in the good responder showing the most intense reverse remodelling. Therefore, the cardiologist will need a diagnostic test that will provide an early information about changes in the patient’s haemodynamic status during long-term follow-up after CRT device implantation. This may be the future place for cardiac biomarkers such as NT-pro-BNP in the setting of CRT. The study nicely demonstrates that changes in biomarkers may precede the changes in heart volumes that can be observed by...
echocardiography. Therefore, measuring NT-pro-BNP may be a useful method to detect haemodynamic alterations very early in the process and thus to guide adjunctive medical therapy, prevent episodes of cardiac decompensation, or to recognize ineffective delivery of CRT, e.g. by intermittent loss of capture. Cardiac biomarkers may thus in the future represent another cornerstone in the care of CRT patients apart from other methods, which are mostly device-based such as thoracic impedance measurements, heart rate variability analysis, or telemetric device surveillance.

Follow-up investigations of implanted devices are often performed by cardiologists specialized in cardiac pacing and/or electrophysiology. They should realize that CRT is different from other pacing devices because resynchronization therapy has important metabolic effects on the heart. We are just beginning to unravel the mystery of these metabolic effects of cardiac pacing. But even now, these can already be utilized for optimizing care of our CRT patients. Thus, electricity may give the initiating spark but it’s the metabolism that eventually counts when treating heart failure by CRT.

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References