

Invited Editorial / Davetli Editöryal Yorum

Influences of cardiac resynchronization therapy on cardiac biomarkers in patients with chronic heart failure

Kronik kalp yetmezliği olan hastalarda kardiyak resenkronizasyon tedavisinin kardiyak biyobelirteçler üzerine etkisi

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Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure (HF) and reduced ejection fraction who have a significant left ventricular (LV) conduction delay, as it has been proven to reduce morbidity and mortality. However, one-third of patients don't respond favorably to CRT and therefore, the identification of patients who would be most likely to benefit from CRT has a special importance. Left bundle branch block (LBBB) QRS morphology, QRS duration >150 milliseconds, non-ischemic etiology, and female gender are referred as strong predictors for better outcomes of CRT. In addition, it should be emphasized that recent HF guidelines do not recommend CRT in patients with a QRS duration <130 milliseconds.^[1]

CRT not only reduces morbidity and mortality, but also improves symptoms and New York Heart Association (NYHA) class, increases LVEF, and reduces LV systolic and diastolic volumes in CRT responders. Biventricular, pacing-induced QRS shortening is a pretty good sign of favorable response to CRT and improvement of dyssynchronous ventricular contraction. Improvement in dyssynchrony results in a reduction in LV chamber size and reverses cardiac remodeling, and thereby improves cardiac performance. CRT has also been shown to reduce neurohormonal biomarkers by decreasing intracardiac pressures and myocardial wall stress.

In a study published in this issue of the Archives of the Turkish Society of Cardiology,^[2] in 41 HF patients with NYHA class II-III symptoms, LVEF ≤35%, LBBB, QRS duration ≥120 mil-

liseconds who underwent CRT implantation, the authors demonstrated that cardiac fibrosis markers, including galactin-3, growth differentiation factor 15 (GDF-15) and procollagen III N-terminal propeptide (P3NTP), were significantly decreased in patients with reverse electrical remodeling (n=16), defined as a decrease in intrinsic QRS duration by ≥20 milliseconds, after 12 months of CRT implantation, whereas no significant changes were observed in these biomarkers in patients who did not show reverse electrical remodeling (n=25). However LVEF, end-diastolic volume, end-systolic volume, and NYHA class were reported to significantly improve in both groups of patients, with and without reverse electrical remodeling. The authors concluded that electrical reverse remodeling after CRT is associated with a decrease in cardiac fibrosis.

These are important and interesting findings, though many of them are not really surprising. This is

Abbreviation:

CRT	Cardiac resynchronization therapy
GDF-15	Growth differentiation factor 15
HF	Heart failure
LBBB	Left bundle branch block
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NP	Natriuretic peptide
NYHA	New York Heart Association
P3NTP	Procollagen III N-terminal propeptide

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certainly not the first study to evaluate the long-term effects of CRT on biomarkers involved in the different pathophysiological processes of HF. In a very similar, recently published study by Turkish authors,^[3] it was determined that among 15 biomarkers evaluated in 44 HF patients with NYHA II-III symptoms, LVEF $\leq 35\%$, and QRS duration ≥ 120 milliseconds who underwent CRT implantation, cardiac fibrosis marker galectin-3 was significantly reduced in echocardiographic CRT responders, defined as a reduction in LV end-systolic volume by $\geq 15\%$, after 12 months of CRT implantation. No significant change was found in the galectin-3 level in echocardiographic CRT non-responders. In contrast to the present study,^[2] the P3NTP level was not decreased in either CRT responders or CRT non-responders at 12-month follow-up.^[3]

There are several studies evaluating the effects of CRT on biomarkers. However, different findings have been reported in these studies. In a substudy of the CARE-HF (Cardiac Resynchronization in Heart Failure) trial evaluating changes in biomarkers after CRT in 260 HF patients, the levels of fibrosis biomarkers, including galectin-3 and P3NTP did not change throughout the 18-month follow up-period.^[4] Furthermore, data from MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) examining the relationship between plasma galectin-3 concentration and CRT demonstrated that overall, there was a 1.3 ng/mL increase in mean galectin-3 level over 12 months after CRT ($p=0.054$).^[5] So, it can be said that the reported findings on changes in these novel biomarkers after CRT are inconsistent.

Despite the improvement in LVEF, LV end-systolic and end-diastolic volumes, and NYHA functional class, in the present study, natriuretic peptide (NP) levels were not found to significantly decrease with CRT in both groups of patients, with and without reverse electrical remodeling.^[2] In contrast to the present study, almost all studies have consistently shown a significant reduction in NP level after CRT implantation and the reduction in NP level is referred to as a simple sign for monitoring the effects of CRT.^[3,6,7] Furthermore, the reduction in NP level was reported to be correlated with the changes in LV volume or LVEF and also with the improvement in exercise capacity after CRT.^[8]

A group of biomarkers, including galectin-3, soluble ST2, P3NTP, and matrix metalloproteinase 1

and 2, are considered fibrosis biomarkers. GDF-15 is generally referred to as an inflammatory marker. Fibrosis biomarkers are consistently demonstrated to be associated with adverse long-term cardiovascular outcomes and to be useful surrogates of structural and functional abnormality of the myocardium. Although elevated levels of these biomarkers are thought to reflect the degree of myocardial fibrosis, it is unclear whether the reduction of these biomarkers reflects a decrease in myocardial fibrosis or it is just a consequence of hemodynamic improvements. Late gadolinium-enhanced cardiac magnetic resonance imaging would be the best method to assess changes in the degree of myocardial fibrosis.

Many confounders may affect the level of these biomarkers. For instance, galectin-3 has also been reported to be involved in renal dysfunction and could be a mediator of worsening renal function.^[9] Elevated concentrations of GDF-15 were not only associated with HF, but also with hypertrophy, atherosclerosis, stable coronary artery disease, and myocardial infarction, as well as hypertension, diabetes mellitus, abdominal obesity, chronic kidney disease, and malignancy. Furthermore, mineralocorticoid receptor antagonist and statin therapies have been reported to reduce P3NTP levels.^[10,11] Ivabradine treatment has also been shown to significantly reduce GDF-15 levels.^[12] Some studies suggest that HF therapies had no clear effect on galectin-3 levels.^[13] In the present study, there is no clear information about renal dysfunction, worsening renal function, or medication changes during follow-up period. So, it is very difficult to exclude all these factors for a precise interpretation of the study findings. Moreover, there is uncertainty about the cut-off point of these markers. How much of a decrease or increase in these parameters is clinically meaningful is unclear.

In conclusion, the present study represents a nice addition to a growing body of evidence surrounding novel biomarkers in HF. However, there are many questions to answer. It is very clear that these novel markers have been proven to be very useful in risk stratification and predicting long-term adverse clinical outcomes in HF. Yet, because of inconsistent findings from different studies, we need more data from well-designed studies for the potential use of these biomarkers in the prediction or assessment of treatment effectiveness for HF.

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