Even though cardiac resynchronization therapy (CRT) confers improvements of symptoms and left ventricular (LV) function in selected heart failure (HF) patients, approximately 30% of patients implanted with CRT devices do not present the awaited clinical benefits during follow-up. CRT non-response remains a major clinical problem.

The most recent randomized clinical trials, REVERSE, MADIT-CRT, and RAFT, have consistently observed that the magnitude of the CRT effect is more manifest in certain patient subgroups with respect to others. Based on the evidence of these trials, the latest CRT guidelines have issued more stringent recommendations where the strength of the indication is weighed on the basis of QRS morphology and duration. In HF patients with LV systolic dysfunction who present with non-LBBB ventricular delay or LBBB-block with QRS <150 ms, the magnitude of the CRT response remains uncertain. In this context, the clinical utility of both electrocardiography and transthoracic echocardiography to improve patient selection for CRT remains limited. Therefore, renewed interest in identifying means to predict CRT outcome has emerged. In the past, determinations of circulating plasma levels of natriuretic peptides, neurohormones, and cytokines have played a central role in understanding the underlying pathophysiologic mechanisms of cardiac insufficiency and to establish the basis of current pharmacologic strategies to manage chronic HF syndrome.

In this issue of the Journal, Rordorf et al investigate the effects of baseline pre-implantation circulating tumor necrosis factor (TNF) α and interleukin (IL)-6 levels on CRT-induced LV reverse remodeling and cardiac outcome. Circulating TNF-α is a mature protein derived from a 233 amino acid prohormone precursor anchored in the cell membrane. In response to a wide variety of infectious or inflammatory stimuli, both transcription and translation of the TNF precursor is increased, and large amounts of mature protein are rapidly released into the circulation. TNF regulates the expression of a variety of peptide regulatory factors, including platelet-derived growth factor and transforming growth factor-β, as well as a group of eicosanoids and hormones that includes platelet-activating factor and adrenaline. IL-6 is also a peptide regulatory factor that depends on circulating TNF. In HF, TNF-α exerts a direct negative inotropic effect, triggers apoptosis of cardiomyocytes and negatively affects myocardial remodeling, through activation of metalloproteinase and reduced expression of metalloproteinase inhibitors.

The well-designed, observational, single-center study by Rordorf et al demonstrated, primarily, that baseline TNF-α levels, and not circulating levels of IL-6, correlated with LV end-systolic volume (LVESV) reduction after CRT. Second, by stratification of the patient cohort according to tertiles of baseline TNF-α level, patients with higher levels (≥22.19 pg/dl) were less likely to respond to CRT (defined as >15% reduction of LVESV) and presented a worse outcome in terms of cardiac events (>60%, at 5 years). Compared with the tertile group with lower TNF-α circulating levels, the upper group presented a 4-fold increased risk of having a major cardiac event during follow-up. In this context, determination of baseline circulating TNFα activity and activation of metalloproteinase inhibitors may play a central role in understanding the pathophysiologic mechanisms of cardiac insufficiency and to establish the basis of current pharmacologic strategies to manage chronic HF syndrome.

**Table 1. Classification of Biological Markers Used to Predict CRT Effects**

<table>
<thead>
<tr>
<th>Neurohormones and peptides</th>
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<tbody>
<tr>
<td>ANP</td>
<td>Brain natriuretic peptide</td>
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<tr>
<td>BNP</td>
<td>Endothelin</td>
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<tr>
<td>N-terminal brain natriuretic peptide</td>
<td>hsCRP</td>
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<td></td>
<td>Transforming growth factor β</td>
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<td></td>
<td>CT-1</td>
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<tr>
<td>Inflammation cytokines and related circulating receptors</td>
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<td></td>
<td>CT-1</td>
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<tr>
<td>Epigenetic factors</td>
<td>Epigenetic factors</td>
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<tr>
<td>Messenger ribonucleic acid</td>
<td>miRNA</td>
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Biological Markers and CRT

The follow-up. In the multivariate analysis, baseline circulating TNF-α levels between the upper and lower tertiles were an independent predictor of cardiac adverse events.

The strength of the contribution by Rordorf et al is that a clear relation is demonstrated between baseline circulating levels of TNF-α and LV reverse remodeling after CRT. Previous studies that investigated biological markers and CRT effect (Tables 1,2) were more concerned with CRT effects on the patterns of neurohormonal or inflammatory changes. As shown in Table 2, the data on biological markers and CRT effect are heterogeneous. Most of the studies were single-center, enrolled few patients, and assessed changes of different biological markers after CRT. Variables assessing CRT effect and patient response also varied considerably between the studies and included either functional evaluations (NYHA functional class, peak oxygen consumption), LV echocardiographic parameters (ejection fraction, reduction of LVESV) or sometimes, both. Furthermore, most biological markers, particularly the natriuretic peptides, presented mean circulating level values with a wide standard deviation interval, suggesting that circulating levels of these plasma markers are influenced by changing hemodynamic and clinical extracardiac (eg, obesity, chronic lung disease, renal impairment) conditions. On the basis of these data, the biological marker of choice for the clinical follow-up of CRT patients remains to be identified.

Despite these limitations, some clinical perspective may be derived from the previous contributions and may be integrated with more recently published data. First, reductions in the plasma levels of natriuretic peptides appear to be a short-term effect occurring within the first 3 months after CRT. Reduction of plasma levels of these markers supposes a beneficial hemodynamic effect of reduced volume overload and pressures in the cardiac chambers. On the other hand, short-term reductions of hsCRP in the first months after CRT imply a CRT-induced anti-inflammatory effect. If the circulating TNF-α levels are part of the HF inflammatory cascade, this complex molecule is not a simple marker of inflammation, but rather acts as a complex mediator of the “inflammatory reflex” that is unleashed during progressive HF syndrome caused by the profound and complex disruptions between the immune and autonomic nervous systems. As already mentioned earlier, at the level of the heart increased circulating TNF-α levels determine cardiac remodeling.

Another contribution has recently described the relation between changes in circulating levels of tiny regulatory non-coding RNAs (miRNAs) and CRT-induced LV reverse remodeling. The genetic profile of CRT responders (defined as LVESV reduction ≥15%) showed upregulation of some microRNAs, which underlies the reversion of cardiomyocyte apoptosis and fibrosis processes involved in LV remodeling. How this “genetic shift”, demonstrated in the CRT responder, is related to changes in the extracellular biochemical “milieu” of circulating neurohormones and cytokines, such as TNF-α, has never been investigated thus far.

Table 2. Principal Studies Investigating Biological Markers and Their Prediction of CRT Effect

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Biological markers</th>
<th>Follow-up (months)</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Boriani et al (2006) | Prospective Two centers 32       | ANP, BNP, E, NE, aldosterone, PRA, IL-6, TNF, TNF receptors 1 and 2, chromagranin A | 3                  | - Reduction of ANP and BNP plasma levels after 3 months of CRT  
- Pre-implant ANP ≤150 pg/ml predictive of symptomatic improvement and LV reverse remodeling |
- BNP >91.5 pg/ml after CRT identifies patients with progressive HF at 12 months |
| Seifert et al (2007) | Prospective Multicenter 22      | BNP, NE          | 12                 | - At 12 months significant reductions in plasma levels of BNP and NE |
| Lellouche et al (2007) | Prospective Single-center 164    | BNP              | 6                  | - CRT responders exhibited higher pre-implant BNP plasma levels (≥447 pg/ml good predictive value for CRT response) |
| Menardi et al (2008) | Prospective Single-center 120    | BNP, END, big-END, E, TNF-α | 12                 | - BNP and big-END significantly reduced after CRT |
- hsCRP independent predictor of non-response  
- Increased mortality risk when hsCRP >3.0 mg/L |
| Osmancik et al (2013) | Prospective Single-center 81     | IL-6, TNF-α, TGF-β | 6                  | - Significant reduction of TGF-β, IL-6, TNF-α  
- TGF-β independently predicts poor prognosis |
| Limongelli et al (2014) | Prospective Single-center 52     | CT-1             | ±6                 | - CT-1 levels reduction are correlated with LV reverse remodeling  
- Higher CT-1 levels after CRT independent predictor of cardiac events |
| Martella et al (2013) | Prospective Single-center 81     | miRNA            | 12                 | - CRT responder (LV reverse remodelling)  
- upregulation of miRNA  
- Some miRNA associated with CRT response |

E, epinephrine; LV, left ventricular; NE, norepinephrine; PRA, plasma renin activity; TGF-β, Transforming growth factor β. Other abbreviations as in Table 1.
From the important work by Rordorf et al., these and other insights surface and may offer new perspectives into the pathophysiology of HF progression. Contributions such as these may establish the basis for future genetic-based (miRNA-based therapeutics) or device-based (autonomic nervous system stimulators) therapies for HF, thus bringing new hopes to light the path of the hopeless CRT non-responder.

References


