Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Biological Markers to Predict Cardiac Resynchronization Therapy Effect

– Old Means to Meet New Ends? –

François Regoli, MD, PhD; Domenico Regoli, MD, PhD; Tiziano Moccetti, MD

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.

Article p2232

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.[1] 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[2] and transthoracic echocardiography[3,4] 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[5] 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.[6] 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 (≥2.19 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

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

Neurohormones and peptides
ANP
BNP
N-terminal brain natriuretic peptide
END
Inflammation cytokines and related circulating receptors
TNF-α
IL-6
hsCRP
Transforming growth factor β
CT-1
Epigenetic factors
Messenger ribonucleic acid
miRNA

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; CT-1, cardiotrophin-1; END, endothelin; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; miRNA, tiny regulatory non-coding RNAs; TNF, tumor necrosis factor.

Received July 16, 2014; accepted July 16, 2014; released online August 6, 2014
Fondazione Cardiocentro Ticino, Lugano (F.R., T.M.), Switzerland; Department of Experimental and Clinical Medicine, University of Ferrara, Ferrara (D.R.), Italy
Mailing address: François Regoli, MD, PhD, Fondazione Cardiocentro Ticino, Via Tesserete 48, CH-6900 Lugano, Switzerland. E-mail: francois.regoli@cardiocentro.org
ISSN-1346-9843 doi:10.1253/circj.CJ-14-0771

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

Author (year)	Study design	No. of patients	Biological markers	Follow-up (months)	Main results
Boriani et al (2006)[7]	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 remodelling
Pitzalis et al (2006)[8]	Prospective Single-center	50	BNP	1	· High plasma BNP levels after CRT related with events · BNP >91.5 pg/ml after CRT identifies patients with progressive HF at 12 months
Seifert et al (2007)[9]	Prospective Multicenter	22	BNP, NE	12	· At 12 months significant reductions in plasma levels of BNP and NE
Lellouche et al (2007)[10]	Retrospective 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)[11]	Prospective Single-center	120	BNP, END, big-END, E, TNF-α	12	· BNP and big-END significantly reduced after CRT
Kamioka et al (2012)[12]	Prospective Single-center	65	hsCRP, BNP	6	· Higher pre-implant hsCRP in CRT non-responders · hsCRP independent predictor of non-response · Increased mortality risk when hsCRP >3.0 mg/L
Osmancik et al (2013)[13]	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)[14]	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
Marfella et al (2013)[15]	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.

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**)[7–15] 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.[5,15] 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.[7] On the other hand, short-term reductions of hsCRP in the first months after CRT imply a CRT-induced anti-inflammatory effect.[12] 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[15] 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.

From the important work by Rordorf et al,[5] 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

1. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA). *Europace* 2013; **15:** 1070–1118.
2. Takaya Y, Noda T, Nakajima I, Yamada Y, Miyamoto K, Okamura H, et al. Electrocardiographic predictors of response to cardiac resynchronization therapy in patients with intraventricular conduction delay. *Circ J* 2013; **78:** 71–77.
3. Chan PS, Khumri T, Chung ES, Ghio S, Reid KJ, Gerritse B, et al. Echocardiographic dyssynchrony and health status outcomes from cardiac resynchronization therapy: Insights from the PROSPECT trial. *JACC Cardiovasc Imaging* 2010; **3:** 451–460.
4. Sakamaki F, Seo Y, Ishizu T, Yanaka S, Atsumi A, Yamamoto M, et al. Tissue Doppler imaging dyssynchrony parameter derived from the myocardial active wall motion improves prediction of responders for cardiac resynchronization therapy. *Circ J* 2012; **76:** 689–697.
5. Rordorf R, Savastano S, Sanzo A, Spazzolini C, De Amici M, Camporotondo R, et al. Tumor necrosis factor-α predicts response to cardiac resynchronization therapy in patients with chronic heart failure. *Circ J* 2014; **78:** 2232–2239.
6. Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol* 2000; **35:** 537–544.
7. Boriani G, Regoli F, Saporito D, Martignani C, Toselli T, Biffi M, et al. Neurohormones and inflammatory mediators in patients with heart failure undergoing cardiac resynchronization therapy: Time courses and prediction of response. *Peptides* 2006; **27:** 1776–1786.
8. Pitzalis MV, Iacoviello M, Di Serio F, Romito R, Guida P, De Tommasi E, et al. Prognostic value of brain natriuretic peptide in the management of patients receiving cardiac resynchronization therapy. *Eur J Heart Fail* 2006; **8:** 509–514.
9. Seifert M, Schlegl M, Hoersch W, Fleck E, Doelger A, Stockburger M, et al. Functional capacity and changes in the neurohormonal and cytokine status after long-term CRT in heart failure patients. *Int J Cardiol* 2007; **121:** 68–73.
10. Lellouche N, De Diego C, Cesario DA, Vaseghi M, Horowitz BN, Mahajan A, et al. Usefulness of preimplantation B-type natriuretic peptide level for predicting response to cardiac resynchronization therapy. *Am J Cardiol* 2007; **99:** 242–246.
11. Menardi E, Vado A, Rossetti G, Racca E, Conte E, Deorsola A, et al. Cardiac resynchronization therapy modifies the neurohormonal profile, hemodynamic and functional capacity in heart failure patients. *Arch Med Res* 2008; **39:** 702–708.
12. Kamioka M, Suzuki H, Yamada S, Kamiyama Y, Saitoh S, Takeishi Y. High sensitivity C-reactive protein predicts nonresponders and cardiac deaths in severe heart failure patients after CRT implantation. *Int Heart J* 2012; **53:** 306–312.
13. Osmancik P, Herman D, Stros P, Linkova H, Vondrak K, Paskova E. Changes and prognostic impact of apoptotic and inflammatory cytokines in patients treated with cardiac resynchronization therapy. *Cardiology* 2013; **124:** 190–198.
14. Limongelli G, Roselli T, Pacileo G, Calabró P, Maddaloni V, Masarone D, et al. Effect of cardiac resynchronization therapy on cardiotrophin-1 circulating levels in patients with heart failure. *Intern Emerg Med* 2014; **9:** 43–50.
15. Marfella R, Di Filippo C, Potenza N, Sardu C, Rizzo MR, Siniscalchi M, et al. Circulating microRNA changes in heart failure patients treated with cardiac resynchronization therapy: Responders vs. non-responders. *Eur J Heart Fail* 2013; **15:** 1277–1288.