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Tumor Necrosis Factor-α Predicts Response to Cardiac Resynchronization Therapy in Patients With Chronic Heart Failure

Roberto Rordorf, MD; Simone Savastano, MD; Antonio Sanzo, MD; Carla Spazzolini, BSc; Mara De Amici, MD; Rita Camporotondo, MD; Stefano Ghio, MD; Alessandro Vicentini, MD; Barbara Petracci, MD; Valentina De Regibus, MD; Erika Taravelli, MD; Maurizio Landolina, MD; Peter J. Schwartz, MD

Background: Pro-inflammatory cytokines contribute to the pathophysiology of heart failure (HF) and are up-regulated in affected patients. We investigated whether pro-inflammatory cytokines might predict the response to cardiac resynchronization therapy (CRT).

Methods and Results: Plasma levels of tumor necrosis factor-α (TNF-α) and interleukin-6 were assessed in 91 patients before CRT. Response to CRT was defined as a decrease ≥15% in left ventricular end-systolic volume (LVESV) at 6 months. Baseline TNF-α did correlate with LVESV reduction (P=0.001) after CRT. The subject group was divided according to tertiles of TNF-α. From the lower to the upper tertile LVESV (–31±28%, –17±17%, –9±22%) and LV end-diastolic volume (–23±25%, –14±16%, –4±18%) were progressively less reduced after CRT (P<0.001). The proportion of responders to CRT was 70%, 42% and 33%, according to the lower, intermediate and upper tertile of TNF-α distribution (P=0.01). Serious cardiac events (cardiac death, HF hospitalization or urgent heart transplantation) occurred in 63% of patients in the upper tertile vs. 32% and 17% in the intermediate and lower tertiles, respectively, during a median follow-up of 47 months (P<0.001).

Conclusions: Circulating TNF-α predicts the degree of LV reverse remodeling after CRT and may contribute to the early identification of those patients at higher risk of events after device implantation. (*Circ J* 2014; **78:** 2232–2239)

Key Words: Brain natriuretic peptide; Cardiac resynchronization therapy; Reverse remodeling; Tumor necrosis factor-α

The levels of circulating cytokines are directly related to disease progression and prognosis in patients with chronic heart failure (HF).[1–4] Specifically, tumor necrosis factor-α (TNF-α) appears to exert a direct negative inotropic effect, to trigger apoptosis in cardiomyocytes and to affect myocardial remodeling.[5,6] Cardiac resynchronization therapy (CRT) plays a major role in the management of HF in as it induces left ventricular (LV) reverse remodeling, improves symptoms and reduces overall mortality in patients with drug-refractory HF.[7,8] Previous studies on the relationship between pro-inflammatory cytokines and CRT focused mainly on the potential anti-inflammatory effect of CRT.[9–11]

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The primary objective of the present study was to investigate whether a pre-implantation assessment of circulating pro-inflammatory cytokines might predict the response to CRT, which would facilitate early identification of patients less likely to derive a substantial benefit from CRT. A secondary endpoint was to assess whether baseline levels of pro-inflammatory cytokines might also forecast clinical outcome.

Methods

This was a single-center prospective study enrolling consecutive patients with HF referred for implantation of a biventricular device. Inclusion criteria were: symptomatic HF, LV ejection fraction (LVEF) ≤35% and QRS exhibiting left bundle branch block[12] with a duration ≥120 ms. Patients with atrial

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Department of Cardiology (R.R., S.S., A.S., R.C., S.G., A.V., B.P., V.D.R., E.T., M.L.), Department of Pediatrics (M.D.A.), IRCCS Fondazione Policlinico S. Matteo, Pavia; Department of Molecular Medicine, Cardiology Section, University of Pavia, Pavia (C.S.); and IRCCS Istituto Auxologico Italiano, Center for Cardiac Arrhythmias of Genetic Origin, Milan (C.S., P.J.S.), Italy

Mailing address: Roberto Rordorf, MD, Department of Cardiology, IRCCS Fondazione Policlinico S. Matteo, V.le Golgi 19, 27100, Pavia, Italy. E-mail: r.rordorf@smatteo.pv.it

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fibrillation, prior pacemakers or implantable cardioverter defibrillator, prosthetic valves or a recent (within 3 months) episode of acute decompensation, myocardial ischemia or revascularization were excluded. Also, patients with an ongoing or recent infectious or inflammatory disease were not enrolled. The protocol was approved by the local Ethics Committee and informed consent was obtained from each patient.

Echocardiography

Standard echocardiography, including Doppler, was performed the day before and 6 months after device implantation. LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were measured using the area-length method. LVEF was calculated as [(LVEDV–LVESV/LVEDV)×100%]. Compared to baseline, the 6-month reduction in LVESV, in LVEDV and the increase in LVEF were calculated to estimate the degree of LV reverse remodeling. Response to CRT was defined as ≥15% reduction in LVESV at 6 months.

Biochemistry

The day before device implantation, fasting blood samples were collected after at least 15 min of rest. Samples were immediately centrifuged at 3,500 rpm for 5 min and the plasma was immediately frozen and kept at –20°C until cytokine assay analysis. The assay used for the quantitative determination of human interleukin-6 (IL-6) was based on the quantitative sandwich enzyme immunoassay (ELISA) technique, using a commercial kit (Quantikine™; R&D Systems, Milan, Italy). For the quantitative determination of human TNF-α, high-sensitivity quantitative sandwich enzyme immunoassay (ELISA; Quantikine™ HS; R&D Systems, Milan, Italy) was used. Sensitivity was expressed as pg/ml for the 2 cytokines considered. The minimum detectable doses (MDD) were determined by adding 2 SD to the mean optical density value of 20 zero standard and calculating the corresponding concentration. The MDD of IL-6 was <0.70 pg/ml; the MDD of TNF-α ranged from 0.038 to 0.191 pg/ml. We also measured brain natriuretic peptide (BNP) using an assay in EDTA plasma with an automated immunochemistry analyzer (Advia Centaur, Siemens Diagnostic Division, Erlangen, Germany).

Estimated glomerular filtration rate (eGFR) was calculated from baseline plasma creatinine level using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Patients with eGFR <60 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ were considered affected by chronic renal insufficiency.

Device Implantation

All patients underwent implantation of a biventricular-pacing device according to standard technique. A lead for LV pacing was successfully placed in a posterolateral or lateral tributary vein of the coronary sinus in all cases. A dedicated resynchronization device was used in all the patients and a device with defibrillation back-up (CRT-D) was implanted in 87% of cases.

Follow-up

All patients underwent electrocardiography and clinical assessment at baseline and at each scheduled visit during follow-up (1 month after device implantation and every 6 months thereafter). At each visit the New York Heart Association (NYHA) class was assessed and clinical events were recorded in a patient file. Hospitalization for acute HF was defined as the need for hospitalization due to worsening clinical status requiring i.v. therapy. The incidence of the composite of cardiac death, HF hospitalization and urgent heart transplantation was analyzed in order to assess clinical outcome. The first event was considered for each patient. If, however, an episode of acute HF decompensation was followed during the same hospitalization by death or urgent transplantation, only the last main outcome was recorded. Furthermore, patients were categorized according to a modified clinical composite score that combines changes in NYHA functional class and the documented occurrence of major cardiac events during follow-up.[13] Briefly, patients were "improved" if they had a favorable change in NYHA (1 class improvement) and did not experience any major adverse event by the time of the last visit; "worsened" if they had at least 1 major clinical event and/or an unfavorable change in NYHA (1 class deterioration); and "unchanged" if they neither improved nor worsened. All the physicians who adjudicated the clinical events, evaluated patient clinical status, and performed the echocardiographic evaluation were blinded to the results of pro-inflammatory cytokines analysis.

Statistical Analysis

Data for continuous variables are described as mean±SD or as median and interquartile range (IQR) whenever the distribution was skewed. The former presentation was applied also to cytokine data, although they were not normally distributed, in order to allow for comparisons with the results from other studies. According to normality and variance assumption, data were compared using parametric procedures (t-test for independent or paired samples and 1-way ANOVA) or by their non-parametric equivalents (Mann-Whitney U-test and Kruskal-Wallis test), as appropriate. Categorical variables are expressed as absolute and relative frequencies and were compared using Fisher's exact test or chi-square test. The relationship of the 2 cytokines evaluated during the study with the reduction of LVESV were analyzed using non-parametric Spearman correlation and their predictive role on LVESV % change (on a continuous scale) after CRT was assessed in a linear regression model on log-transformed data. To determine the association of circulating TNF-α with the probability of being a responder to CRT as evaluated at 6 months after device implantation, this continuous variable was divided into tertiles. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated with a multivariate logistic regression model used to predict the response to CRT while controlling for potential confounders. Kaplan-Meier analysis, with log-rank test for comparison, was used to estimate the cumulative event-free survival to any first adverse event among those comprising the pre-defined composite endpoint during follow-up. Incidence rates, with exact 95% CI, were calculated by dividing the number of patients with any first event by the total number of person-years. The Cox proportional-hazards model was used to evaluate the significant and independent contribution of TNF-α level to the risk of a first clinical event after adjustment for clinically relevant characteristics. Two-sided $P<0.05$ was considered statistically significant. All statistical analysis was done using IBM SPSS.

Results

Subjects

Demographic and baseline clinical characteristics of the 91 study patients are listed in Table 1. All patients were on maximum tolerated medical therapy for at least 3 months.

LV Reverse Remodeling and TNF-α

Compared to baseline, on echocardiographic evaluation 6 months after CRT there was a significant ($P<0.001$ for all tests) reduction of both LVESV (222±81 vs. 177±79 ml) and LVEDV

Table 1. Baseline Characteristics of the Overall Study Population and of Patients Stratified According to TNF-α Tertiles

Variable	All patients (n=91)	TNF-α (pg/ml)			P-value
		≤0.66 (n=30)	0.67–2.19 (n=31)	>2.19 (n=30)	
Age (years)	63±10	61±11	64±8	64±10	0.38
Male	74 (81)	20 (67)	27 (87)	27 (90)	0.04
Ischemic etiology	30 (33)	5 (17)	13 (42)	12 (40)	0.067
Duration of disease (years)	5 (1–9)	2 (1–7)	3 (1–8)	8 (2–11)	0.049
Resting heart rate (beats/min)	68±13	68±12	69±16	68±12	0.77
QRS duration (ms)	163±28	164±24	163±28	161±33	0.90
QRS duration ≥150 ms	67 (75)	22 (73)	26 (84)	19 (68)	0.35
NYHA class					0.19
II	37 (41)	13 (43)	10 (32)	14 (46.7)	
III	52 (57)	17 (57)	21 (68)	14 (46.7)	
IV	2 (2)	0	0	2 (6.7)	
IL-6 (pg/ml)	13±15	12±18	13±11	12±15	0.23
BNP (pg/ml)	383±389	281±244	397±496	464±357	0.1
TNF-α (pg/ml)	1.83±1.88	0.26±0.19	1.27±0.42	3.98±1.77	
LVEF (%)	25±7	24±5	26±7	25±7	0.40
LVEDV (ml)	294±93	296±77	303±103	282±98	0.67
LVESV (ml)	222±81	227±68	227±90	213±85	0.74
MR moderate-severe	19 (23)	3 (12)	6 (21)	10 (35)	0.14
RSVP (mmHg)	31±15	29±16	32±14	31±15	0.75
eGFR (ml·min^{-1}·1.73 m^{-2})	64±22	73±19	60±23	58±22	0.02
β-blockers	79 (87)	26 (87)	28 (90)	25 (83)	0.72
ACEI/AT II receptor blockers	85 (93)	26 (87)	30 (97)	29 (97)	0.19
Furosemide	87 (96)	27 (90)	30 (97)	30 (100)	0.15
K$^+$ sparing diuretics	58 (64)	17 (57)	21 (68)	20 (67)	0.61
Statins	39 (43)	15 (50)	12 (39)	12 (41)	0.65

Data given as n (%)†, mean±SD or median (IQR). †Patients with available data for each variable.
ACEI, angiotensin-converting-enzyme inhibitor; AT II, angiotensin II; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TNF-α, tumor necrosis factor-α.

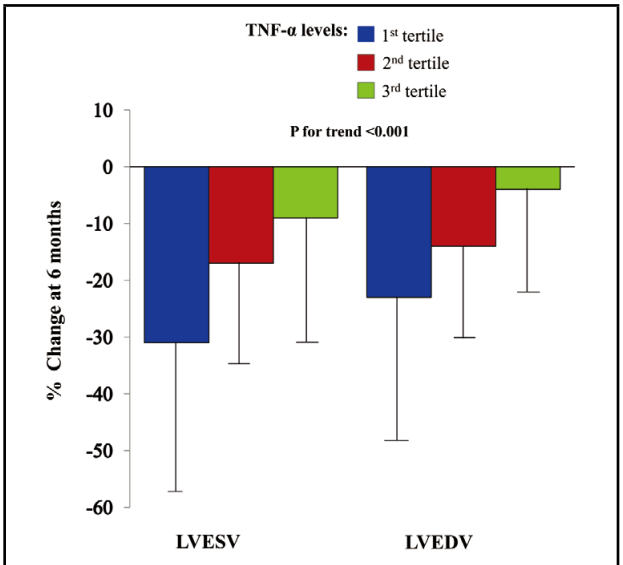

Figure 1. Relative reduction in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) after cardiac resynchronization therapy according to level of circulating tumor necrosis factor (TNF)-α: 1st tertile, ≤0.66 pg/ml (n=30); 2nd tertile, 0.67–2.19 pg/ml (n=31); 3rd tertile, >2.19 pg/ml (n=30).

(294±93 vs. 249±91 ml) and an absolute increase in LVEF of 5±8% (from 25±7 to 30±8%).

We used the relative (%) reduction from baseline of LVESV as a critical marker of LV reverse remodeling, and multivariate linear regression analysis to test the ability of the 2 cytokines to predict the amount of LV reversibility 6 months after CRT. While baseline circulating IL-6 was not correlated with reverse remodeling, TNF-α was significantly predictive of LVESV reduction (P<0.001) and, consequently, it became the focus of all following analyses. In order to evaluate the association between baseline circulating TNF-α and the parameters of LV remodeling after CRT, the subjects were retrospectively divided into 3 subgroups corresponding to tertiles of TNF-α.

The baseline patient clinical characteristics were similar across the 3 tertile-defined groups (Table 1), except for a marginally significant lower prevalence of male gender and of ischemic etiology in the lower tertile, and a longer duration of disease prior to device implantation and a higher prevalence of renal insufficiency among patients in the upper tertile. As shown in Figure 1, a significant difference was observed after CRT in the change in LVESV from baseline across the 3 tertiles (–31±28%, –17±17%, –9±22%, respectively; P for trend <0.001). A similar difference was observed in the change of LVEDV (–23±25%, –14±16%, –4±18%, respectively; P for trend <0.001), thus confirming the existence of an inverse relationship between baseline TNF-α and the likelihood of LV

reverse remodeling after CRT. Despite the lack of a linear trend, a significant change at 6-month evaluation was evident also for LVEF that increased by 9±8%, 3±6% and 4±9%, respectively, from the lower to the upper tertile (P=0.005).

We also explored the association between TNF-α and the response to CRT. According to our pre-defined classification of response to CRT, 44 patients were responders and 47 were non-responders. Although the 2 subgroups were similar for all other baseline clinical characteristics, responders had significantly lower mean TNF-α than non-responders (1.36±1.56 vs. 2.28±2.06 pg/ml, P=0.003). Also the rate of response to CRT was significantly different according to baseline circulating TNF-α. Indeed, there was a linearly decreasing proportion of patients with LVESV reduction ≥15% from the lower (70%) through the intermediate (42%) to the upper tertile (33%) of TNF-α level, representing a decreasing probability of being a responder (OR, 0.46; 95% CI: 0.27–0.80, P=0.006, **Figure 2**).

The contribution of TNF-α level to predicting response to CRT maintained its significant independence (P=0.03) and magnitude (OR, 0.50; 95% CI: 0.27–0.92) in a multivariate model while controlling for potential confounders (**Table 2**). Although gender was not significantly associated with response to CRT, female subjects had a greater reduction of LVESV compared to male subjects (–33±28% vs. –16±22%, P=0.006).

In contrast to TNF-α, neither baseline circulating IL-6 nor BNP significantly predicted response to CRT, and also, their means were not significantly different between responders and non-responders (IL-6, 12.3±17.2 vs. 12.8±12.4 pg/ml, respectively, P=0.41; BNP, 347±336 vs. 417±432 pg/ml, respectively, P=0.17).

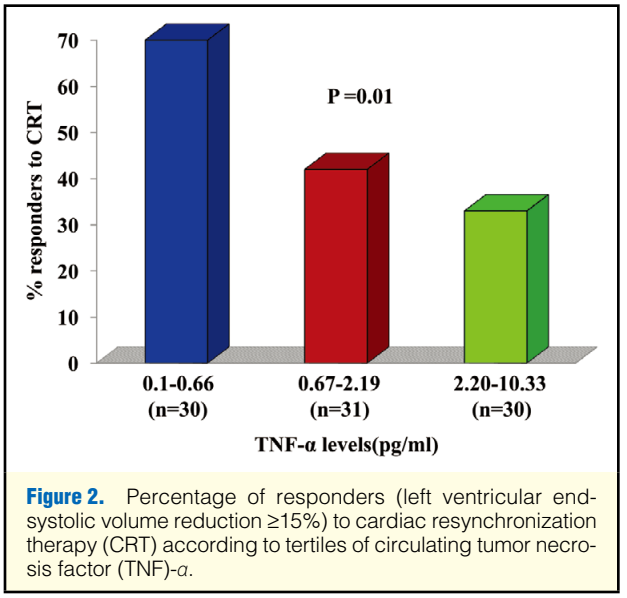

Figure 2. Percentage of responders (left ventricular end-systolic volume reduction ≥15%) to cardiac resynchronization therapy (CRT) according to tertiles of circulating tumor necrosis factor (TNF)-α.

Outcome

During a median follow-up of 47 months (IQR, 36–62 months), 29 patients were hospitalized for acute HF, 4 patients underwent urgent heart transplantation and 5 died due to cardiac reasons. Overall, 34 patients (37%) suffered a first adverse cardiac event during follow-up, with a 5.5% total cardiac mortality.

In patients with adverse events there was a higher proportion of NYHA class III/IV (74% vs. 51%, P<0.05) and of ischemic etiology (47% vs. 25%, P<0.05), a significantly shorter baseline QRS duration (152±30 vs. 169±26 ms, P=0.006) and higher baseline circulating TNF-α (2.7±2.1 vs. 1.3±1.5 pg/ml, P<0.001) compared to patients without adverse events. Patients with events also had a trend toward a higher prevalence of renal insufficiency, although the difference did not reach statistical significance (56% vs. 38%). All other baseline variables were similar in patients with and without clinical events. Of note, patients with clinical events also had a significantly smaller reduction of echocardiographic parameters of LV reverse remodeling after CRT (LVESV, –6±18% vs. –27±25%; LVEDV, –2.5±16% vs. –20±21%; P<0.001). Patients with the

Table 2. Predictors of Response to CRT

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
TNF-α (lower:intermediate:higher tertile)†	0.46 (0.27–0.80)	0.006	0.50 (0.27–0.92)	0.03
Gender				
Male vs. Female	0.44 (0.15–1.31)	0.14	0.55 (0.16–1.9)	0.35
Age (years)				
≥65 vs. <65	1.24 (0.55–2.84)	0.60	1.27 (0.47–3.42)	0.63
Etiology				
Ischemic vs. non-ischemic	0.74 (0.31–1.78)	0.50	0.89 (0.33–2.42)	0.82
NYHA class				
III/IV vs. II	0.82 (0.35–1.89)	0.64	0.84 (0.34–2.11)	0.71
QRS duration				
≥150 vs. <150 ms	2.0 (0.75–5.5)	0.16	1.75 (0.59–5.14)	0.31
eGFR				
<60 vs. ≥60 ml·min^{-1}·1.73 m^{-2}	0.79 (0.34–1.80)	0.57	1.14 (0.41–3.13)	0.81
LVEF				
<25 vs. ≥25%	1.6 (0.70–3.71)	0.26	1.63 (0.65–4.11)	0.30

†The variable coding for the three tertiles TNF-α was treated as a continuous variable following assessment by likelihood ratio test of the linear effect of TNF-α level on the probability of being a responder to CRT. The OR of 0.50 on multivariate analysis corresponds to a 50% reduction of this probability for TNF-α increase from the lower tertile to the intermediate tertile and also from the intermediate to the higher tertile. No significant interactions.
CI, confidence interval; CRT, cardiac resynchronization therapy; OR, odds ratio. Other abbreviations as in Table 1.

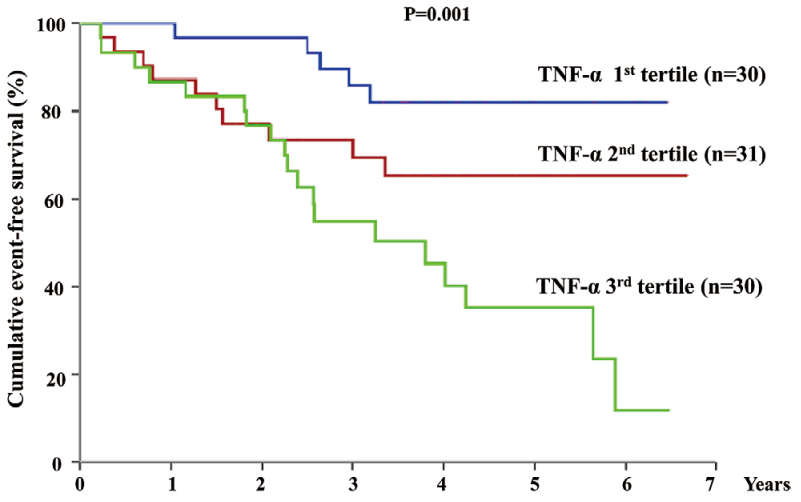

Figure 3. Kaplan-Meier event-free survival according to tertiles of circulating tumor necrosis factor (TNF)-*α*.

Table 3. Multivariate Risk Factors for Poor Outcome†

	HR (95% CI)	P-value
TNF-*α*		
Upper vs. lower tertile	4.3 (1.2–15.3)	0.02
Intermediate vs. lower tertile	1.9 (0.5–6.8)	0.34
Etiology		
Ischemic vs. non-ischemic etiology	3.2 (1.3–8.0)	0.01
NYHA class		
III/IV vs. II	3.9 (1.4–11.0)	0.01
QRS duration		
≥150 vs. <150 ms	0.3 (0.1–0.8)	0.01
eGFR		
<60 vs. ≥60 ml·min^{-1}·1.73 m^{-2}	2.9 (1.1–7.6)	0.02

†Cardiac death, heart failure, hospitalization or urgent heart transplantation. Findings were further adjusted for gender, age, BNP, IL-6 and baseline LVEF.
HR, hazard ratio; IL, interleukin. Other abbreviations as in Tables 1,2.

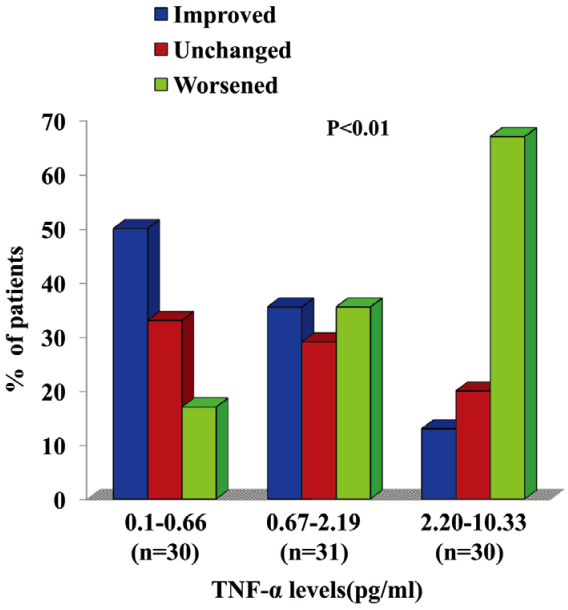

Figure 4. Composite clinical score according to tertiles of circulating tumor necrosis factor (TNF)-*α*.

higher baseline circulating TNF-*α* had the worst clinical outcome. The composite endpoint of cardiac death, HF hospitalization and urgent heart transplant, was reached by 19/30 (63%) patients with TNF-*α* >2.19 pg/ml (upper tertile), compared to 10/31 (32%) and to 5/30 (17%) of patients in the intermediate and lower tertiles, respectively (P for trend <0.001). The event rates per 100 person-years according to TNF-*α* level were, respectively, 20.8 (95% CI: 12.5–32.5), 10.1 (95% CI: 4.8–18.5) and 4.2 (95% CI: 1.4–9.9). As shown in Figure 3, there was a significant difference in the cumulative survival to adverse events during follow-up according to level of circulating TNF-*α* (P=0.001; Kaplan-Meier analysis). Consistently, in a multivariate Cox regression model, high TNF-*α* played a significant and independent prognostic role in event-free survival even after adjustment for clinically relevant characteristics. As shown in Table 3, compared to patients with TNF-*α* in the lower tertile, those having the highest level were at a significantly greater risk for adverse clinical events (hazard ratio, 4.3; 95% CI: 1.2–15.3, P=0.02). Also, ischemic etiology, NYHA class III/IV and renal insufficiency were found to be significantly associated with poorer outcome at multivariate analysis, while QRS duration ≥150 ms was an independent predictor of a reduction in the event rate. Neither IL-6 nor BNP baseline circulating levels significantly contributed to the prediction of the risk of cardiac events during long-term follow-up.

Finally, when the global clinical outcome after CRT was evaluated by means of the composite score,[13] the proportion of improved patients decreased significantly from 50% in the first tertile through 35% in the second to 13% in the third tertile of TNF-*α* levels (P<0.01; Figure 4).

Discussion

The present study provides the first evidence that circulating TNF-*α* correlates with the degree of LV reverse remodeling after CRT. We found a significant difference in the reduction

of LV volumes and in the improvement of LVEF after CRT among patients stratified according to baseline TNF-α. Also, baseline circulating TNF-α was associated with a differential risk for major clinical events during follow-up, thus suggesting a potential role of TNF-α in predicting the long-term clinical outcome after CRT. These findings raise clinically relevant issues pertaining to the pathophysiology of HF with implications for management.

TNF-α and LV Reverse Remodeling After CRT

Clinical trials and community-based studies have demonstrated that TNF-α is a prognostic marker for HF.[2,3] Whether TNF-α directly contributes to the progression of HF rather than being a simple marker of disease severity is still unclear, and the present study was not designed to address this issue. Nevertheless, the present results provide meaningful insights into the intriguing relationship between inflammatory markers and HF pathophysiology, as we have demonstrated a significant association between baseline circulating TNF-α levels and the degree of LV reverse remodeling observed after CRT. The patients in the upper tertile of circulating TNF-α had a negligible degree of LV reverse remodeling after CRT and also the percentage of non-responders was as high as 70% in this subgroup of patients. Conversely, patients with intermediate and low TNF-α had significantly more favorable LV reverse remodeling after CRT and were more likely to be responders to therapy.

A similar relationship between TNF-α level and regression in LV volumes had been previously observed in patients with chronic mitral regurgitation treated with valve repair surgery.[14] Experimentally, TNF-α activates metalloproteinase and reduces the expression of metalloproteinase inhibitors, thus favoring extracellular matrix degradation and remodeling.[15] Also, TNF-α is thought to trigger the apoptotic cascade and to have a negative inotropic effect at the cellular level.[5,6,15]

Considering these experimental findings together with our clinical observations it appears that the assessment of TNF-α is likely to provide information on the degree of remodeling in individual patients. Elevated circulating TNF-α seems to indicate a more advanced degree of remodeling at the cellular and extracellular levels, unlikely to be reversed by therapy.

The criteria used to define response to CRT is an important issue:[16] as the main objective of the present study was to assess the correlation between pro-inflammatory cytokines and LV reverse remodeling after therapy, we used a strict definition of response to CRT based on echocardiographic criteria only. As in previous studies, we used the arbitrary cut-off of LVESV reduction ≥15% to define response to therapy.[17–19] According to this criterion almost 50% of the patients were found to be responders, a proportion consistent with the 50–60% response rate reported by others.[17–19] Noteworthy, the present results were not strictly dependent on the use of a pre-specified cut-off to define responders, given that we demonstrated a significant correlation of baseline TNF-α with both the rate of response to CRT and with the degree of LVESV reduction, the latter considered as a continuous variable.

As the Department of Cardiology at the "Policlinco S. Matteo" Foundation is a referral center for non-ischemic cardiomyopathy, the percentage of ischemic patients enrolled was relatively low (33%). This could explain in part why we did not observe a significant association between HF etiology and the probability of being responder to CRT. In contrast to the literature,[20,21] gender did not predict response to CRT in the present subjects, although we observed a significantly greater reduction in LVESV after CRT in female. Because female gender and non-ischemic cardiomyopathy were slightly more represented in the lower tertile of TNF-α distribution, this could be considered as a potential confounder; the independent predictive role of TNF-α, however, was confirmed in a multivariate model, corrected for both gender and HF etiology. Similarly, TNF-α maintained its independent predictive value also when corrected for baseline renal function.

TNF-α and Clinical Outcome After CRT

Besides being an early marker of the chance of LV reverse remodeling after CRT, TNF-α was also associated with the long-term incidence of clinical events: during >3 years follow-up, patients with high vs. low circulating TNF-α had a significantly higher risk of major clinical events.

A role for circulating TNF-α in predicting major cardiovascular events during follow-up after CRT is supported by several pathophysiological considerations even though the present study did not have sufficient power to address this point thoroughly. The occurrence of LV reverse remodeling, which we have shown to be anticipated by circulating TNF-α level, is an established predictor of long-term clinical outcome in patients treated with CRT.[17]

Besides providing insights into the extent of remodeling, TNF-α is an accepted marker of the degree of neurohumoral activation in patients with HF. The immune and the autonomic nervous systems interact through the "inflammatory reflex",[22,23] according to which deleterious inflammatory reactions can be modulated favorably by vagal activation and adversely by sympathetic activation. Indeed, an imbalance in the autonomic nervous system with a reduction in vagal activity and an increase in sympathetic activity is present in HF patients with significant implications for both prognosis and management.[24–26]

Along these lines, reduced heart rate variability and down-regulation of adrenoreceptors in patients with HF identify patients at higher risk of clinical events after CRT.[27–30] Largely based on concepts resulting from the combination of experimental and clinical data,[24] interest in the interplay among the potential modulatory role of the autonomic nervous system, inflammation and LV remodeling in HF patients is rapidly growing. The initial and recent clinical experiences with autonomic modulation have focused on chronic vagal stimulation in HF patients, and very encouraging results have been reported.[31–33] Of special interest is the evidence that chronic vagal stimulation can induce, clinically, significant LV reverse remodeling[31,32] and, experimentally, a reduction in the inflammatory and apoptotic response following coronary occlusion.[34] The inhibitory effect of acetylcholine on inflammation and TNF-α synthesis is a possible mechanism that can explain the favorable effect of vagal stimulation.[35] The previous considerations provide support for the concept that TNF-α could play a pivotal role in the pathophysiological triangle constituted by immune activation, autonomic imbalance and LV remodeling. This critical role may help to explain why patients with elevated baseline circulating TNF-α had a poor response to CRT and an unfavorable prognosis in the present study.

TNF-α, IL-6 and BNP

Previous studies reported conflicting results on the usefulness of pre-implantation assessment of BNP in patients undergoing CRT.[36,37] In the present study pre-implantation BNP level predicted neither the response to CRT nor the outcome. The greater prognostic value of TNF-α compared to BNP may depend on the different within-patient biological variability of these 2 biomarkers.[38,39] In contrast to TNF-α, BNP level is more likely to be affected by short-duration fluctuations in health

status; this could explain the greater prognostic value of TNF-α compared to BNP in the present study. A similar difference in intra-individual biological variability could also explain the lack of prognostic value observed for IL-6 in the present study.[38]

Study Limitations

As the main objective of this study was to assess the role of baseline pro-inflammatory cytokines in the prediction of response to CRT, a re-quantification of circulating cytokines after device implantation was not scheduled. This prevented quantification of a potential anti-inflammatory effect of resynchronization therapy. Nonetheless, because the patients who benefited from therapy were those with low baseline TNF-α, a further significant reduction after CRT would not be expected.

Being a single-center experience, the sample size of the present study was limited. Although the number of endpoint events during follow-up was consistent with most other studies, it was relatively small. Thus, the present study was underpowered to validate the prognostic role of TNF-α for long-term clinical outcome with an appropriate adjustment for all potential confounders. The strong association between TNF-α and reverse remodeling after therapy, however, together with the pathophysiological links between TNF-α and HF progression, support a true prognostic role of TNF-α in the setting of CRT patients.

Conclusions

TNF-α is a significant predictor of the degree of LV reverse remodeling in HF patients treated with CRT. Pre-implantation assessment of TNF-α may contribute to the early identification of those patients who have a low probability of long-term benefits from CRT. The hypothesis, supported by the present data, that TNF-α might be an early marker of the chance of LV reverse remodeling after CRT and of clinical prognosis, is intriguing and warrants further studies.

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Disclosures

R. Rordorf has received speaking fees from Medtronic. M. Landolina has a speakers' bureau appointment with St. Jude Medical, Medtronic and Boston Scientific, and an advisory board relationship with St. Jude Medical and Medtronic. The other authors have nothing to disclose.

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