Neurohormonal and inflammatory markers as predictors of short-term outcome in patients with heart failure and cardiac resynchronization therapy

Aharon Glick MD*, Yoav Michowitz MD*, Gad Keren MD and Jacob George MD

Department of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
Affiliated to Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: congestive heart failure, B-type natriuretic peptide, C-reactive protein, cardiac resynchronization therapy

Abstract

Background: Cardiac resynchronization therapy is a modality with proven morbidity and mortality benefit in advanced systolic heart failure. Nevertheless, not all patients respond favorably to CRT. Natriuretic peptides and inflammatory markers are elevated in congestive heart failure and reflect disease severity.

Objectives: To test whether an early change in neurohormonal and inflammatory markers after implantation can predict the clinical response to CRT.

Methods: The study group included 32 patients with advanced symptomatic systolic heart failure and a prolonged QRS complex who were assigned to undergo CRT. Baseline plasma levels of B-type natriuretic peptide and high sensitivity C-reactive protein were determined in the peripheral venous blood and coronary sinus. Post-implantation levels were determined 2 weeks post-procedure in the PVB. Baseline levels and their change in 2 weeks were correlated with all-cause mortality and hospitalization for congestive heart failure.

Results: At baseline, coronary sinus levels of BNP but not hsCRP were significanly elevated compared to the PVB. Compared to baseline levels, BNP and hsCRP decreased significantly within 2 weeks after the implantation (BNP mean difference 229.1 ± 102.5 pg/ml, 95% confidence interval 24.2–434, $P < 0.0001$; hsCRP mean difference 5.2 ± 2.4 mg/dl, 95% CI 0.3–10.1, $P = 0.001$). During a mean follow-up of 17.7 ± 8.2 months 6 patients died (18.7%) and 12 (37.5%) were hospitalized due to exacerbation of CHF. Baseline New York Heart Association and CSBNP levels predicted CHF-related hospitalizations. HsCRP levels or their change over 2 weeks did not predict all-cause mortality or hospitalizations.

Conclusions- BNP levels in the CS and peripheral venous blood during biventricular implantation and 2 weeks afterwards predict cilinical response and may guide patient management.

IMAJ 2006;8:391–395

Despite improved pharmacological management, congestive heart failure continues to be a prevalent syndrome with substantial morbidity and mortality. In recent years, cardiac resynchronization therapy was introduced as a new treatment modality for patients with systolic heart failure and New York Heart Association functional class III-IV and evidence of cardiac asynchrony [1]. Early studies have demonstrated an improvement in patients' performance status and left ventricular ejection fraction as well as in their quality of life [2-6]. The COMPANION trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) demonstrated a reduction in the composite endpoint of death from any cause and in hospitalizations of patients treated with CRT alone or in combination with implantable defibrillator as compared to medical therapy [7]. The recently published CARE-HF trial (Cardiac Resynchronization-Heart Failure) further validated the role of CRT treatment in these patients and its favorable clinical effects on morbidity and mortality [8].

In the CARE-HF trial CRT was shown to improve hemodynamic, echocardiographic and biochemical parameters. Accordingly, N-terminal pro-B-type natriuretic peptide levels were significantly reduced at 18 months follow-up in patients treated with CRT. Patients with congestive heart failure exhibit heightened inflammatory activity, as reflected by increased C-reactive protein levels [9]. However, whether these levels are influenced by CRT treatment was not addressed. It should be noted that not all patients benefit from CRT, therefore it is important to identify the non-responsive subjects [1,10].

The purpose of the current study was to examine whether CRT is associated with an early reduction of BNP and CRP levels and whether this reduction can predict patients' response to the treatment. Levels of these markers were assessed in both the coronary sinus and the peripheral venous blood.

Patients and Methods

Patients

The study included 32 consecutive patients eligible for CRT at the Tel Aviv Sourasky Medical Center, i.e., patients with systolic heart failure with left ventricular ejection fraction < 35%, NYHA functional class III-IV despite maximal medical treatment and QRS complex duration > 120 msec. Patients were also evaluated for their need of a defibrillator in combination with CRT.

* The two first authors contributed equally to the manuscript

CRT = cardiac resynchronization therapy
PVB = peripheral venous blood
BNP = B-type natriuretic peptide
hs-CRP = high sensitivity C-reactive protein
CI = confidence interval
CHF = congestive heart failure
CS = coronary sinus
CRP = C-reactive protein
NYHA = New York Heart Association

Biventricular device implantation (with or without defibrillator)

All leads were implanted transvenously; the left ventricular pacing lead was inserted into either the lateral or posterolateral cardiac veins. The leads were connected to a biventricular pacemaker in 5 patients or implantable cardioverter defibrillator in 27 patients (Guidant in 28 patients, Medtronic in 3 patients, and Saint Jude in 1 patient). The atrioventricular delay was optimized echocardiographically.

Study design and follow-up

Blood samples from the peripheral venous blood and coronary sinus (in 18 patients) were collected during the implantation procedure. Patients were followed in the outpatient clinic for 2 weeks after the procedure at which time another peripheral venous blood sample was drawn. Sera were separated and frozen at -80°C until performance of the laboratory assays.

The extent of improvement according to the NYHA was assessed 1 month after the implantation. Thereafter, patients were followed every 3–6 months or at higher frequency as dictated by the patients' clinical status. During follow-up, an interrogation of the defibrillator for episodes of ventricular arrhythmias was conducted. The study endpoints were all-cause mortality and hospitalization due to heart failure. The local ethics committee approved the study.

BNP assay

BNP levels were measured by a chemiluminescent technique with the Bayer ADVIA Centaur BNP assay, according to the manufacturer's instructions (Bayer HealthCare LLC).

High sensitivity CRP concentrations

The assay for hsCRP was conducted according to the manufacturer's instructions (Dade Behring Inc.). Briefly, the principle of the method is the use of polystyrene particles coated with monoclonal antibodies to CRP. These particles agglutinate with CRP. CRP level was determined according to the intensity of the scattered light in the nephelometer, compared with standards of a known concentration.

Statistical analysis

Comparison between baseline levels of the different parameters and their change following the implantation were examined using Student's *t*-test for paired samples. The same test was used for evaluating the differences between baseline levels of BNP and hsCRP in the coronary sinus compared to PVB. Associations between the various parameters were assessed by Pearson's correlation coefficient.

Cox proportional hazard model was applied to study the effect of each one of the different parameters at baseline and the change in parameters (Δ) on survival and time to hospitalization, and to determine hazard ratios. Receiver operating characteristic analysis was used to define cutoffs of baseline and Δ levels of the different parameters with the greater sensitivity and specificity for event prediction.

Event rates were compared by Kaplan-Meier curves. The statistical significance level was set to 0.05 and the SPSS software version 12 was used for the analysis.

Results

Baseline clinical characteristics of our cohort are shown in Table 1. All patients except one were male and according to the inclusion criteria had NYHA III-IV (mean 3.4 ± 0.56) and LVEF 21.5 ± 5.9%. CRT-D was implanted in 27 patients (84%). The indication for CRT-D was an episode of sustained monomorphic ventricular tachycardia in 16 patients (59%), ventricular fibrillation in 6 patients (22%), induction of monomorphic VT during electrophysiologic studies in 4 patients (15%) and an episode of non-sustained VT coupled with low LVEF in 1 patient (4%).

Patients were followed for a minimum of 3.5 months and up to 34 months, mean 17.7 ± 8.2 months. During follow-up, there were 6 mortality events (18.7%) and 12 patients were hospitalized due to exacerbation of CHF (37.5%). Four patients had an episode of sustained monomorphic VT, which was terminated in three by anti-tachycardia pacing and necessitated automated cardioversion in one. None of these patients died during follow-up.

Levels of BNP and hsCRP decreased significantly 2 weeks after the implantation (BNP mean difference 229.1 ± 102.5 pg/ml, 95% CI 24.2–434, $P < 0.0001$; hsCRP mean difference 5.2 ± 2.4 mg/dl, 95% CI 0.3–10.1, $P = 0.001$) [Figure 1]. Levels of BNP were significantly higher in the CS compared to the peripheral

Table 1. Clinical characteristics of the patient cohort (n=32)

Age (mean ± SD)	68.6 ± 11.6 yrs
Males (%)	31 (96.8)
NYHA (mean ± SD)	3.4 ± 0.56
LVEF (mean ± SD)	21.5 ± 5.9%
QRS (mean ± SD)	165.5 ± 32.3 msec
Ischemic cardiomyopathy	19 (59.3)
Dilated cardiomyopathy	13 (40.6)
Hyperlipidemia	17 (53.1)
Smoking	2 (6.2)
Past smoker	14 (43.7)
Hypertension	13 (40.6)
Diabetes mellitus	11 (34.3)
Chronic atrial fibrillation	3 (9.3)
Transient ischemic attacks/cerbrovascular accidents	4 (12.5)
Percutaneous transluminal coronary angioplasty	12 (37.5)
Coronary artery bypass surgery	12 (37.5)
ACE inhibitors/ARBs	28 (87.5)
Spironolactone	12 (37.5)
Beta blockers	19 (59.3)
Statins	18 (56.2)
Digoxin	11 (34.3)
Diuretics	32 (100)
Anticoagulants	13 (40.6)

ACE = angiotensin converting enzyme, ARB = angiotensinogen receptor blockers

LVEF = left ventricular ejection fraction
CRT-D = defibrillator in combination with CRT
VT = ventricular tachycardia

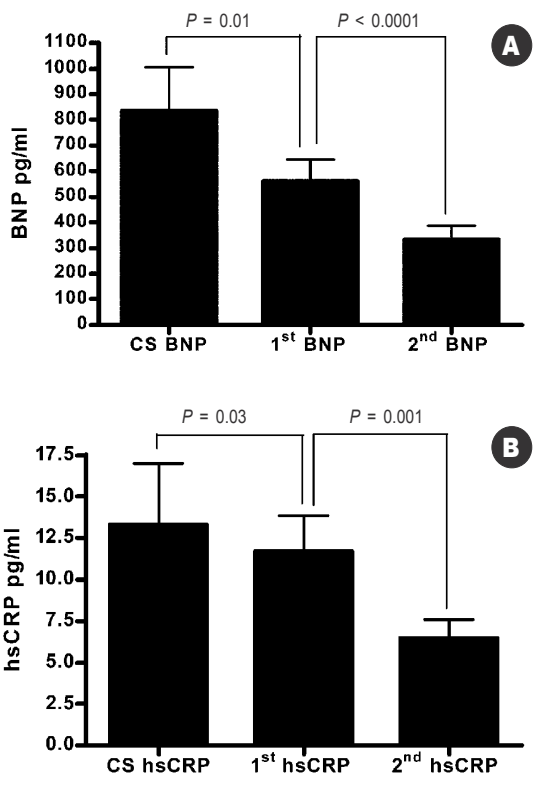

Figure 1. Levels of BNP **[A]** and hsCRP **[B]** at baseline in the coronary sinus (CS) and peripheral venous blood (1st) and in the peripheral venous blood 2 weeks after biventricular pacemaker implantation (2nd).

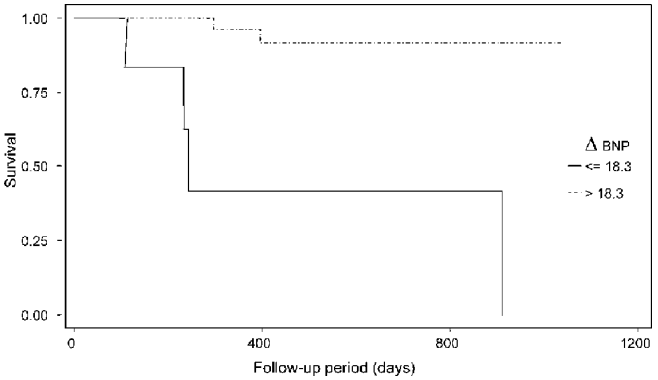

Figure 2. Survival curve according to Δ BNP. Relationship between the reduction in BNP levels 2 weeks after the implantation (Δ BNP) and survival based on a cutoff of 18.3 pg/ml. Dotted line = patients with Δ BNP > 18.3 pg/ml, continuous line = Δ BNP < 18.3 pg/ml

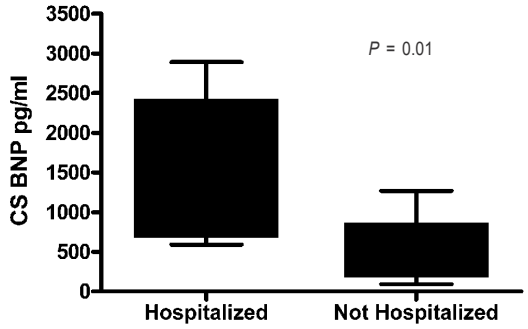

Figure 3. Baseline CS BNP in patients hospitlalized or not hospitalized after CRT. Levels of CS-BNP were determined by enzyme-linked immunosorbent assay as described in the Methods. A comparison was made between levels of CS BNP in patients hosptialized or not hospitalized subsequent to implantation of biventicular pacemaker.

venous blood (835 ± 704 pg/ml compared to 561 ± 483 pg/ml, $P = 0.01$). However, there was no significant difference in hsCRP levels between the CS and the PVB (13.3 ± 15.4 compared to 11.7 ± 11.9, P = 0.3). NYHA and QRS duration also decreased significantly (NYHA decreased from a mean of 3.4 ± 0.6 to 2.1 ± 0.4, $P < 0.0001$); QRS duration was reduced from 165.5 ± 32.3 to 113.1 ± 22 msec ($P < 0.0001$).

Baseline levels of PVB BNP and CS BNP correlated closely with each other ($r = 0.92$, P < 0.0001). PVB BNP also correlated with baseline NYHA ($r = 0.46$, $P = 0.007$). Due to smaller groups of patients tested for CS BNP, the correlation between CS BNP and baseline NYHA was only close to statistical significance ($r = 0.46$, $P = 0.06$). There was no correlation between baseline PVB BNP or CS BNP and LVEF or QRS duration.

There was a significant correlation between the decrease in BNP and hsCRP from baseline levels to the level 2 weeks post-transplantation ($r = 0.39$, $P = 0.02$). However, neither correlated with the difference in NYHA (Δ NYHA) or QRS duration (Δ QRS).

In order to study the clinical significance of the different baseline values and their change (Δ) after the implantation, a Cox regression model was used. Δ BNP was the only independent factor that predicted mortality ($P = 0.029$, hazard ratio 0.993, 95% CI 0.986–0.999), while CS BNP and baseline NYHA were the only independent predictors of the time to admission due to heart failure exacerbation (CS BNP: HR 1.001, 95% CI 1–1.002, $P = 0.024$; baseline NYHA: HR 5.47, 95% CI 1.2–25, $P = 0.028$).

Using ROC analysis we identified that a cutoff of 18.3 pg/ml in Δ BNP discriminated patients' response to CRT with regard to survival. A Kaplan-Meier survival curve [Figure 2] shows a significantly better outcome for patients with Δ BNP above this cutoff ($P < 0.001$). A cutoff of 812 pg/ml of CS BNP with regard to hospitalizations was identified, but it did not reach statistical significance due to the small sample group. Patients hospitalized due to CHF exacerbation had CS BNP of 1473 ± 938 pg/ml compared to 569 ± 373 of non-hospitalized patients (P = 0.01) [Figure 3].

Discussion

We demonstrated that within 2 weeks after CRT, patients in whom BNP level does not fall by more than 18.3 pg/ml are at increased

HR = hazard ratio
ROC = receiver operating characteristic

risk of mortality. Secondly, BNP levels in the CS are increased compared to PVB and can predict risk of CHF-related hospitalization after CRT. In addition, we demonstrated for the first time that CRT could reduce the activation of the inflammatory axis in patients with advanced CHF, as reflected by a drop in peripheral hsCRP levels. However, levels of hsCRP or their drop after 2 weeks of CRT did not correlate with clinical outcome.

CRT is now indicated for patients with systolic heart failure, wide QRS and NYHA ≥ III despite medical therapy [1]. However, adoption of these criteria results in a favorable response in only two-thirds of patients [10]. Several prospective and retrospective trials sought to identify better criteria for predicting adequate response to CRT [11-14]. These criteria include electrocardiographic [11] and echocardiographic findings [12], including tissue Doppler imaging [13] and parameters of ventricular asynchrony. These parameters are useful for choosing suitable patients prior to the implantation. Our finding that an early drop in BNP level predicts favorable response to CRT can guide clinicians in the follow-up of patients after implantation. Thus, a lack of early drop in BNP level post-implantation may warrant repositioning of the ventricular lead, intensifying patients' follow-up, or drug therapy. Similar reports of reduced NT-proBNP and BNP levels post-CRT were published previously [15]. Our results emphasize the usefulness of an early assessment of BNP levels. Also, our patient group differs in the high percentage of patients with implantable defibrillator.

An ongoing debate followed the COMPANION trial regarding whether CRT alone prolongs survival or whether the beneficial effect is related to the defibrillator. The CARE-HF trial supported a role for CRT as being beneficial in reducing mortality. Our results, that a drop in BNP level predicted favorable response in terms of mortality in patients with CRT, suggest that assessment of the neurohormonal axis could be employed for early assessment of patient response.

In accordance with a previous trial, BNP concentration in the CS was higher compared to the PVD [16]. We found that levels of BNP in the CS are better predictors of CHF-related hospitalizations after CRT. BNP is a 32 amino acid peptide generated through the enzymatic cleavage of its precursor proBNP. BNP is continuously released from ventricular myocytes in response to stretch and pressure overload in patients with CHF. It is cleared from the circulation by two main pathways: enzymatic degradation through neutral endopeptidases and receptor-mediated endocytosis followed by lysosomal degradation. Renal function also influences its level [17]. Therefore, peripheral blood BNP levels are influenced by other factors apart from myocardial wall stress, and it may be less correlated with heart failure severity than BNP levels in the CS. Our results that CS BNP is a better predictor of CHF-related hospitalization were obtained in a small group of patients and need further validation.

CRP, a non-specific "acute-phase" protein, is a known marker of inflammation. It was found to predict the clinical course in patients with CHF [9]. However, its role in patients treated with CRT was not tested. We found that similar to BNP, levels of hsCRP decreased already 2 weeks after the implantation, yet the magnitude of decrease did not correlate with clinical outcome. Whether this is related to the small study group or reflects inferiority of the predictive value of CRP compared to BNP in heart failure patients needs further testing. Nevertheless, we could demonstrate that CRT lessens the activation of the inflammatory axis in patients with CHF in a pattern similar to the effect on BNP.

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Conclusions

We demonstrated that in CHF patients treated with CRT, an early decrease in the levels of BNP and hsCRP is generally observed and patients who do not exhibit a decrease in BNP level have an increased mortality risk. We also demonstrated that CS levels of BNP are increased compared to the PVB levels and correlate better with CHF-related hospitalizations. Measuring BNP level during biventricular pacemaker implantation and 2 weeks afterwards may predict patient response to treatment and guide clinical management.

References

1. Strickberger SA, Conti J, Daoud EG, et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation* 2005;111:2146–50.
2. Rogers JE, Cain ME. Electromechanical associations. N E*ngl* J M*ed* 2004;350:2193–5.
3. Cazeau S, Leclercq C, Lavergne T, et al., for the Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N E*ngl* J M*ed* 2001; 344:873–80.
4. Abraham WT, Fisher WG, Smith AL, et al., for the MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N E*ngl* J M*ed* 2002;346:1845–53.
5. Young JB, Abraham WT, Smith AL, et al., for the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;289:2685–94.
6. Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. J A*m Coll Cardiol* 2003;42:1454–9.
7. Bristow MR, Saxon LA, Boehmer J, et al., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N E*ngl* J M*ed* 2004;350:2140–50.
8. Cleland JG, Daubert JC, Erdmann E, et al., for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N E*ngl* J M*ed* 2005;352:1539–49.
9. Alonso-Martinez JL, Llorente-Diez B, Echegaray-Agara M, Olaz-Preciado F, Urbieta-Echezarreta M, Gonzalez-Arencibia C. C-reactive protein as a predictor of improvement and readmission in heart failure. E*ur* J H*eart Fail* 2002;4:331–6.

10. Yu CM, Abraham WT, Bax J, et al., for the PROSPECT Investigators. Predictors of response to cardiac resynchronization therapy (PROSPECT) study design. *Am Heart J* 2005;149:600–5.
11. Lecoq G, Leclercq C, Leray E, et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J* 2005;26:1094–100.
12. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;40:1615–22.
13. Penicka M, Bartunek J, De Bruyne B, et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. *Circulation* 2004;109:978–83.
14. Fox DJ, Fitzpatrick AP, Davidson NC. Optimisation of cardiac resynchronisation therapy: addressing the problem of "non-responders." *Heart* 2005;91:1000–2.
15. Yu CM, Fung JW, Zhang Q, et al. Improvement of serum NT-ProBNP predicts improvement in cardiac function and favorable prognosis after cardiac resynchronization therapy for heart failure. *J Card Fail* 2005;11:42–6.
16. Goetze JP, Rehfeld JF, Videbaek R, Friis-Hansen L, Kastrup J. B-type natriuretic peptide and its precursor in cardiac venous blood from failing hearts. *Eur J Heart Fail* 2005;7:69–74.
17. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail* 2004;6:261–8.

Correspondence: Dr. J. George, Dept. of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv 64329, Israel.
Phone: (972-3) 697-3311
Fax: (972-3) 546-9832
email: jacobg@post.tau.ac.il

One of the hardest things in life is having words in your heart that you can't utter

James Earl Jones (1931-), U.S. actor