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Association between brain natriuretic peptide, markers of inflammation and the objective and subjective response to cardiac resynchronization therapy

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ABSTRACT

Introduction: Studies suggest that cardiac resynchronization therapy (CRT) can induce a decrease in brain natriuretic peptide (BNP) and systemic inflammation, which may be associated with CRT-response. However, the evidence is inconclusive. We examined levels of BNP and inflammatory markers from pre-CRT implantation to 14 months follow-up in CRT-responders and nonresponders, defined by two response criteria. *Methods:* We studied 105 heart failure patients implanted with a CRT-defibrillator (68% men; age = 65.4 ± 10.1 years). The objective CRT-response was defined as a reduction of $\geqslant$15% in left ventricular end systolic volume; subjective CRT-response was defined as an improvement of $\geqslant$10 points in patient-reported health status assessed with the Kansas City Cardiomyopathy Questionnaire. Plasma BNP and markers of inflammation (CRP, IL-6, TNFα, sTNFr1 and sTNFr2) were measured at three time points. *Results:* Pre-implantation concentrations of TNFα were significantly lower for subjective responders compared to nonresponders ($p = .05$), but there was no difference in BNP and the other inflammatory markers at baseline. Objective CRT-response was significantly associated with lower BNP levels over time ($F = 27.31$, $p < .001$), and subjective CRT-response with lower TNFα levels ($F = 5.67$, $p = .019$). *Conclusion:* Objective and subjective response to CRT was associated with lower levels of BNP and TNFα, respectively, but not with other markers of inflammation. This indicates that response to CRT is not automatically related to a stronger overall decrease in inflammation. Large-scale studies are warranted that further examine the relation between the clinical effects of CRT on inflammatory markers, as the latter have been associated with poor prognosis in heart failure.

1. Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with severe heart failure (HF) and ventricular conduction disturbances (Kamioka et al., 2012; Theodorakis et al., 2006). The biventricular pacing induced by CRT can help restore left ventricular (LV) systolic function by correcting the electro-mechanical dyssynchrony, which improves exercise capacity and reduces rehospitalization and mortality (Anand et al., 2009; Linde et al., 2008; McAlister et al., 2004; Young et al., 2003). CRT has also been associated with favorable changes in circulating levels of neurohormones and inflammatory cytokines in HF patients (Theodorakis et al., 2006; Glick et al., 2006; Erol-Yilmaz et al., 2005; Kubanek et al., 2006; Lappegard and Bjornstad, 2006; Seifert et al., 2007; Stanciu et al., 2013). The two most commonly examined neurohormones in relation to heart failure are B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP). Natriuretic peptides are secreted by

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cardiomyocytes when the heart is diseased or the load on any chamber is increased. Increased BNP levels have been shown to be strong indicators for poor prognosis, but also to be of value in guiding therapy to treat heart failure. Evidence suggest a strong link between the endocrine function of the heart and the immune system, in which cytokines upregulate BNP expression while BNP has immunomodulatory functions which can induce pro-inflammatory cytokines. (Ogawa and de Bold, 2012)

Many studies have shown that CRT induces a significant decrease in BNP (Glick et al., 2006; Erol-Yilmaz et al., 2005; Kubanek et al., 2006; Lappegard and Bjornstad, 2006; Seifert et al., 2007; Stanciu et al., 2013), but the evidence on inflammatory markers like C-reactive protein (CRP), IL-6, TNFα, and soluble TNF receptors 1 and 2 (sTNFr1, sTNFr2) is inconclusive. The majority of studies report a decrease in IL-6 (Theodorakis et al., 2006; Lappegard and Bjornstad, 2006; Stanciu et al., 2013; Michelucci et al., 2007; Przybyla et al., 2011) and CRP (Glick et al., 2006; Michelucci et al., 2007) 3 months to 1 year after CRT implantation, but only two studies showed a decrease in TNFα and the soluble TNF receptors (Theodorakis et al., 2006; Orrego et al., 2011). Tarquini et al. observed no reduction in any of the inflammatory markers after CRT implantation at 1 year follow-up (Tarquini et al., 2009). In addition, most of the evidence regarding these inflammatory markers is based on studies with a small number of patients, missing pre-implantation data, a short follow-up duration, and a lack of adjustment for pertinent clinical or socio-demographic covariates in the analyses.

In addition, it is not clear whether changes in the plasma levels of BNP and inflammatory markers are associated with *response* to CRT. The CRT-response can be assessed using various objective and subjective criteria. Objective response criteria are echocardiographic parameters that detect left ventricular reverse remodeling, indicating an improvement of the pump function of the heart. A subjective response criterion is patient-reported health status which has proven to be of important prognostic value in CRT patients (Fornwalt et al., 2010). Depending on the response criterion, 10–50% of patients are labeled as CRT-nonresponders. The few studies that examined BNP and inflammatory markers in relation to CRT-response have shown mixed results, (Kamioka et al., 2012; Tarquini et al., 2009; Aksoy et al., 2010; Boriani et al., 2006; Delgado et al., 2006; Dong et al., 2011; Galrinho et al., 2009; Magne et al., 2009; Menardi et al., 2008; Osmancik et al., 2013; Rubaj et al., 2013; Shinohara et al., 2011; Smit et al., 2011) and most of these studies defined CRT-response only using echocardiographic measures. As there is only a moderate association between the objective and subjective response criteria, it is possible that clinically relevant changes in health status can occur in the absence of changes in echocardiographic parameters (Fornwalt et al., 2010; Bleeker et al., 2006). Hence, the question is to which extent the results on inflammatory markers also relate to subjective CRT-response. No study to date has examined the association between changes in subjectively reported patient-reported health status after CRT and changes in levels of BNP or inflammatory markers, and compared these to response according to objective echocardiographic parameters. For both the objective and subjective CRT response criteria, the expectation is that responders will have a stronger decrease in BNP and cytokine levels compared to non-responders.

Hence, the aim of this study was to (1) further explore the profile of BNP and inflammatory markers from pre-CRT implantation until 14 months follow-up in CRT-responders and nonresponders, defined by echocardiography as well as patient-reported health status, and (2) to additionally explore the contribution of socio-demographic, clinical and lifestyle factors to the association between BNP or inflammatory markers and the response to CRT therapy.

2. Methods

2.1. Study design and participants

The sample comprised HF patients receiving a first-time CRT implantation according to the guidelines (NYHA functional class ⩾II despite optimal pharmacological therapy, LV ejection fraction (LVEF) ⩽35%, QRS ⩾120 ms) between January 2009 and August 2011 at the University Medical Center Utrecht, The Netherlands. All patients received a CRT device with defibrillator function (CRT-D). Patients participated in the 'The influence of **PSY**chological factors on health outcomes in **HEART** failure patients treated with **C**ardiac **R**esynchronisation **T**herapy: A prospective, single-center, observational study' (PSYHEART-CRT). PSYHEART-CRT was primarily designed to examine whether psychological factors moderate the effect of the objectively assessed response to CRT implantation in patients with HF. Patients were not eligible for inclusion when aged <18 or >85 years; having insufficient knowledge of the Dutch language; a history of psychiatric illness other than affective/anxiety disorders; cognitive impairments; or if they were on the waiting list for heart transplantation. Blood samples were drawn at baseline (i.e., one day prior to CRT implantation), 2, and 14 months after implantation. Patients were instructed not to smoke or drink coffee 2 h prior to the blood draws. The majority of the blood draws were performed during midday. In order to minimize burden to patients, follow-up assessments were scheduled at the same time as the regular follow-up visits to the outpatient clinic. Patients were also asked to complete a set of standardized and validated questionnaires at baseline, 2, 6, and 14 months after implantation. The questionnaires were returned in a stamped, pre-addressed envelope. If the questionnaire was not returned within two weeks, patients received a reminder telephone call or letter. The study protocol was approved by the Medical Ethics Committee of the University Medical Center Utrecht. The study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent.

3. Measures

3.1. Socio-demographic and clinical variables

Information on socio-demographic variables comprised sex, age, marital status, employment status, and educational level, and were obtained via purpose-designed questions at baseline. Information on clinical variables, including HF etiology (ischemic versus non-ischemic), history of sustained ventricular tachyarrhythmias, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), QRS duration, QRS morphology, left bundle branch block, diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal failure (GFR ml/minute/1.73 m^2 < 60), body mass index (BMI), smoking, and cardiac medication, were extracted from patients' medical records.

3.1.1. Objective CRT-response according to echocardiography

Prior to implantation and 6 months post-implantation, patients underwent an echocardiographic evaluation to assess their LV end systolic and diastolic volumes (LVESV and LVEDV, respectively) and consequently their LVEF. LVESV and LVEDV were defined as the smallest and largest ventricular volume within one RR cycle, respectively, with both mitral valve and aortic valve being closed. Subsequently, volume traces were set along the endocardial border. Papillary muscles were included in the LV cavity. Volumes were assessed according to Simpson's biplane method. Echocardiographic response to CRT was defined by a ⩾15% relative reduction in LVESV, indicating reverse remodeling. This cut-off of 15% was