Brain, Behavior, and Immunity 26 (2012) 301–310

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Type D personality and course of health status over 18 months in outpatients with heart failure: Multiple mediating inflammatory biomarkers

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ARTICLE INFO

Article history:
Received 24 August 2011
Received in revised form 21 September 2011
Accepted 22 September 2011
Available online 29 September 2011

Keywords:
Biomarkers
Cytokines
Follow-up
Heart failure
Health status
Mediation
Latent growth models
Structural equation modeling
Type D personality

ABSTRACT

Background: The distressed (Type D) personality is associated with poor health status (HS) and increased inflammatory activation in heart failure (HF). We tested whether multiple inflammatory biomarkers mediated the association between Type D personality and the course of self-reported HS over 18 months.
Methods: HF outpatients (n = 228, 80% male, mean age 67.0 ± 8.7 years), filled out the Type D questionnaire (DS14) at inclusion and the Short Form-12 (SF12) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 0, 6, 12, and 18 months. Blood samples at inclusion were analyzed for high sensitive C-reactive protein (hsCRP), interleukin (IL)-6, tumor necrosis factor (TNF)-α, and its soluble receptors (sTNFr1, sTNFr2). A multiple mediation latent growth model was tested using structural equation modeling.
Results: Type D personality (prevalence = 21%) was associated with poorer HS (all scales $p < 0.001$), deterioration of mental HS ($p < 0.001$), and higher TNF-α and sTNFr2 levels in the full mediation model. A higher inflammatory burden was associated with a poorer baseline level and a deterioration of generic physical, mental and disease-specific HS. No mediating effects were found for the multiple inflammatory biomarkers on the association between Type D and *baseline* self-reported HS, whereas *change* in physical HS was significantly mediated by the group of five inflammatory biomarkers ($p = 0.026$).
Conclusions: Only the association between Type D personality and change in self-reported physical health status was significantly mediated by inflammatory biomarkers. Future research should investigate whether the association between Type D personality and poor health status may be explained by other biological or behavioral factors.

1. Introduction

Heart failure (HF) is a taxing condition, with frequent hospitalizations (Jhund et al., 2009), increased mortality (Curtis et al., 2008), and impaired health status (Juenger et al., 2002). Its prevalence continues to increase as a consequence of the aging population and improved survival after cardiac events (Murdoch et al., 1998; Senni et al., 2005).

Ample studies have linked psychological risk markers with health outcomes in HF, including poor health status (MacMahon and Lip, 2002; Pelle et al., 2008). Health status is defined as a self-reported assessment of patients' symptoms, function, and quality of life (Spertus, 2008), and poor self-reported physical health status is a predictor of adverse HF prognosis (Mommersteeg et al., 2009). One emerging psychological risk marker in this context is the 'distressed' (Type D) personality type. Type D personality is characterized by a general propensity to psychological distress as defined by high negative affectivity and social inhibition (Denollet, 2005; Denollet et al., 2010), and has been consistently associated with poor health status (Pedersen et al., 2010; Pelle et al., 2009; Schiffer et al., 2008).

Poor health behaviors and biological factors have been proposed as candidate mechanisms to explain the adverse health effects of psychological distress (Kop et al., 2011; van der Wal et al., 2010; York et al., 2009). Increased inflammation is a key characteristic of HF and is a plausible candidate mechanism (Bozkurt et al., 2010; Mann and Bristow, 2005). Inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and TNF-α's soluble receptors, and the acute phase protein hsCRP have been associated with both poor self-reported health status (Mommersteeg et al., 2010b; Parissis et al., 2009) and disease progression (Araujo

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doi:10.1016/j.bbi.2011.09.010

et al., 2009; Deswal et al., 2001; Rauchhaus et al., 2000). Further, Type D personality has been associated with increased levels of inflammatory biomarkers (Conraads et al., 2006; Denollet et al., 2003; Denollet et al., 2008) and unfavorable cytokine profiles (Denollet et al., 2009) in HF.

To date, no studies have focused on psychological risk markers, multiple markers of inflammation, and the course of self-reported health status in a longitudinal cohort study simultaneously. The aim of the current study was to prospectively examine whether the associations between Type D personality and baseline level and course of generic and disease-specific self-reported health status over 18 months, are mediated by increased levels of multiple inflammatory biomarkers in a sample of HF outpatients.

2. Methods

2.1. Participants and procedure

The sample comprised 252 consecutive CHF outpatients recruited between June 2006 and February 2009 from the St. Elisabeth Hospital, Tilburg, the Netherlands, participating in a longitudinal observational cohort study. Inclusion criteria consisted of age $\leqslant$80 years, left ventricular ejection fraction (LVEF) $\leqslant$40%, New York Heart Association (NYHA) functional class I-III, stable on oral medication during at least one month, and no hospital admissions in the month prior to inclusion. Exclusion criteria were signs of acute infection, active episodes of gout or arthritis, use of anti-inflammatory medication, evident cognitive impairments, other life-threatening comorbidities (e.g., cancer), psychiatric comorbidity (except for mood disorders), and/or insufficient understanding of Dutch language. Final analyses were based on 228 patients with blood samples available at baseline. The mean age of the sample was 67.0 ± 8.7 year; 175 patients (80%) were men.

Patients were approached for participation by their treating cardiologist during a visit to the outpatient clinic. The psychologist (AP) contacted patients by telephone within 2 weeks after this visit to provide information about aims and study design. Participants completed a questionnaire at home to assess demographic variables, Type D personality and health status at inclusion (0 months) and at 6, 12 and 18 months, which was returned in a stamped and pre-addressed envelope. If the questionnaire was not returned within 2 weeks, patients received a reminder telephone call or letter. Blood samples were drawn at inclusion within one week after receipt of the questionnaire. The study was approved by the medical ethics committee of the St. Elisabeth hospital, and was conducted according to the Helsinki Declaration (2008). All patients provided written informed consent.

2.2. Measures

2.2.1. Demographic and clinical variables

The questionnaire assessed demographics and included age, gender, educational level, current smoking, and marital status. Clinical variables were obtained from patients' medical records and included left ventricular ejection fraction (LVEF), NYHA class (class I/II, and class III), etiology (ischemic versus non-ischemic), time since diagnosis, history of myocardial infarction, stroke, transient ischemic attack, coronary artery bypass grafting, or percutaneous coronary intervention, implantation of implantable cardioverter defibrillator or pacemaker, chronic obstructive pulmonary disease, diabetes, hypercholesterolemia, hypertension, peripheral arterial disease, and gastro-intestinal comorbidities, and body mass index (BMI). Information on prescribed medications was collected from patients' medical records (i.e. angiotensin-II receptor blockers, ACE-inhibitors, aspirin, beta-blockers, calcium-antagonists, diuretics, nitrates, statins, and psychotropic medication).

2.2.2. Inflammatory biomarkers

Inflammatory biomarkers were selected because of their relation with HF pathology. TNF-α may induce dysfunction of the cardiac muscle (Mann and Young, 1994). Soluble TNF receptors are endogenous modulators of TNF-α and may be responsible for prolonging the bioactivity of TNF-α (Aderka et al., 1992); both receptors (sTNFR1 and sTNFR2) were included in this study. We also analyzed IL-6 and hsCRP, both involved in the acute phase response and development of ventricular hypertrophy (Aukrust et al., 1999).

Venous blood samples were drawn and centrifuged at inclusion. Prior to centrifugation, blood was allowed to clot at room temperature for at least 20 min. Aliquoted serum samples were stored at -80 °C in anticipation of further processing. Concentrations of IL-6 (analytical sensitivity: 2 pg/ml) and TNF-α (analytical sensitivity: 1.7 pg/ml) were analyzed using a solid-phase, enzyme labeled, chemiluminescent immunometric assay (Immulite 1000, Siemens Healthcare Diagnostics, Breda, The Netherlands). Concentrations of sTNFR1 and sTNFR2 (analytical sensitivity for both: 15.6 pg/ml) were analyzed using a quantitative enzyme-linked immunosorbent assay (Hycult Biotechnology, Uden, The Netherlands). hsCRP was analysed on a Cobas C501 using a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Almere, The Netherlands). All tests were measured in accordance with the manufacturer's recommendations. The analytical sensitivity of all tests was calculated as the mean of six zero-values plus three SDs extrapolated on the standard curve. The intra-assay variation was <10%, and the inter-assay variation <11%.

2.2.3. Type D personality

The 14-item Type D Scale (DS14) was administered at inclusion to assess Type D personality (Denollet, 2005). The DS14 consists of two subscales, negative affectivity (NA) and social inhibition (SI), both comprising 7 items. A standardized cut-off score $\geqslant$10 on both subscales is used to classify Type D personality (Denollet, 2005). Scores on the DS14 are internally consistent (Cronbach's α = 0.88 and 0.86, respectively), and independent of mood and health status (Denollet, 2005). Type D personality has been shown to be stable over an 18-month period in cardiac patients (Martens et al., 2007) and over a 9-year period in the general population (Kupper et al., 2011).

2.2.4. Generic and disease-specific self-reported health status

The Dutch version of the Short-Form Health Survey 12 (SF-12) was administered at inclusion and at 6, 12, and 18 months follow-up to assess generic health status (Ware et al., 1996). The SF-12 measures overall physical and mental health status, as indicated by the physical component scale summary (PCS) and the mental component summary (MCS) scores. Scale scores were standardized, with higher scores indicating better health status. The SF-12 is a reliable and valid instrument (Mols et al., 2009; Ware et al., 1996).

Patients also filled out the 23-item Kansas City Cardiomyopathy Questionnaire to assess disease-specific health status at inclusion and at 6, 12 and 18-month follow-up (Green et al., 2000). The Overall Summary Score summarizes information from the physical limitation, social limitations, symptom and quality of life scales. Scores range from 0 to 100, with higher scores indicating better health status.