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## Cytokines and immune activation in systolic heart failure: the role of Type D personality

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### Abstract

The proinflammatory cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and its soluble receptors 1 (sTNFR1) and 2 (sTNFR2) are predictors of mortality in chronic heart failure (CHF) but the determinants of these increased levels of disease-promoting cytokines are largely unknown. Type D personality refers to the combination of the tendency to experience negative emotions (negative affectivity) and the tendency to inhibit the expression of emotions in social interaction (social inhibition). Type D is an independent predictor of cardiac events in coronary patients who are at risk for CHF. The present study examined the effect of Type D personality on TNF- $\alpha$ , sTNFR1, and sTNFR2 in 42 men with CHF (mean age = 57.9  $\pm$  10.5 years). There was a significant multivariate effect of Type D on TNF- $\alpha$  measures ( $p = .006$ ); i.e., circulating levels of TNF- $\alpha$  (4.8  $\pm$  0.9 versus 2.5  $\pm$  0.2 pg/ml,  $p = .003$ ), sTNFR1 (1814  $\pm$  314 versus 1134  $\pm$  78 pg/ml,  $p = .014$ ), and sTNFR2 (2465  $\pm$  243 versus 1874  $\pm$  118 pg/ml,  $p = .019$ ) were significantly higher in Type D patients as compared to non-Type D patients. The effect size (ES) of Type D personality ranged from rather large (sTNFR1, ES = 0.77; sTNFR2, ES = 0.73) to large (TNF- $\alpha$ , ES = 0.90). After controlling for ischemic etiology and severity of heart failure, Type D personality emerged as an independent predictor of increased circulating levels of both TNF- $\alpha$  (OR = 9.5, 95% CI 2.1–43.8,  $p = .004$ ) and TNF- $\alpha$  receptors (OR = 6.1, 95% CI 1.4–25.8,  $p = .014$ ). These findings are consistent with the prognostic power of Type D personality regarding long-term morbidity and mortality in patients with established coronary heart disease. This study suggests that individual differences in personality contribute to the psychoneuroimmunological aspects of heart failure.

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### 1. Introduction

“The impact of the immune system would be an interesting subject for future research in cardiovascular behavioral medicine, which might be of relevance for the onset of acute coronary syndromes...” - Willem Kop (1994)

This opening quotation is in fact the very last sentence of the closing chapter of Dr. Willem Kop's innovative work published in 1994. His conclusion was the harbinger for the integration of psychoneuroimmunology with psychosomatic cardiology. A number of reviews in primary journals (Kop, 1999; Rozanski et al., 1999; Ziegelstein, 2001) have provided abundant evidence suggesting that psychological factors may impact on the development and course of acute coronary syndromes. The underlying mechanisms explaining this association include indirect mechanisms such as poor

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adherence to treatment (Ziegelstein et al., 1998), and more direct physiological mechanisms such as impaired platelet function, decreased heart rate variability, and triggering of myocardial ischemia (Krantz et al., 1996). Lately, immune activation has been proposed as a novel mechanism that may explain the link between emotional distress and acute coronary events (Appels et al., 2000; Ishihara et al., 1999; Kop and Cohen, 2001).

Chronic heart failure (CHF) has emerged as an epidemic as a result of an aging population and improved survival after myocardial infarction (Goldberg and Konstam, 1999). Each year, approximately 550,000 patients develop heart failure in the US (Hellermann et al., 2002). CHF is a condition that carries a high mortality risk (Hellermann et al., 2002) and that calls for the further identification of risk factors for a poor prognosis (Faris et al., 2002). In the past two decades, there has been a shift in the etiology of CHF from hypertension or valvular disease to coronary heart disease (Gheorghiadu and Bonow, 1998). There is also growing evidence that elevated concentrations of proinflammatory cytokines play an important role in the pathogenesis/progression of CHF (Deswal et al., 2001).

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a proinflammatory cytokine that exerts local actions that facilitate the development of an inflammatory reaction at a lesion site (Maier and Watkins, 1998). TNF- $\alpha$  stimulates adhesion and migration of leukocytes into the coronary endothelium, and regulates the interaction between the endothelium and blood platelets as well as clotting and fibrinolytic factors. Hence, TNF- $\alpha$  also plays a role in the instability of an atherosclerotic plaque. Binding of membrane-bound TNF- $\alpha$  receptors with their ligand, TNF- $\alpha$ , results in shedding of the extracellular domain, referred to as soluble TNF- $\alpha$  receptor 1 and receptor 2 (sTNFR1 and sTNFR2). Plasma levels of sTNFR1 and sTNFR2 purportedly reflect exposure of the organism to TNF- $\alpha$  over longer periods of time. TNF- $\alpha$ , sTNFR1, and sTNFR2 have consistently emerged as predictors of mortality in patients with CHF (Deswal et al., 2001; Ferrari et al., 1995; Rauchhaus et al., 2000; Torre-Amione et al., 1996). The determinants of these increased levels of TNF- $\alpha$  in CHF patients are not well understood.

Negative emotions are associated with increased production of proinflammatory cytokines including TNF- $\alpha$  (Kiecolt-Glaser et al., 2002). Episodic psychological risk factors such as depression have been associated with a poor prognosis in CHF (Faris et al., 2002; Jiang et al., 2001; Vaccarino et al., 2001). Chronic psychological risk factors may also affect clinical manifestations of heart disease (Kop, 1999), but individual difference variables like personality traits have received little attention to date in behavioral immunology research (Miller et al., 1999).

Type D personality is an individual difference variable that may play a role in the prognosis of CHF. Type-D

refers to the combination of the tendency to experience negative emotions (i.e., negative affectivity) and the tendency to inhibit self-expression (i.e., social inhibition). This personality predisposes to chronic emotional stress in coronary patients. In a 6–10 year follow-up study, Type D was associated with a 4-fold increased risk for mortality (Denollet et al., 1996). A 5-year prospective follow-up study confirmed that Type D patients were at an increased risk of cardiac events (Denollet et al., 2000). Type D is also predictive of the clinical course of coronary patients who are at risk for CHF (Denollet and Brutsaert, 1998). Therefore, the purpose of this study was to examine associations between Type D personality and TNF- $\alpha$  in patients with CHF.

## 2. Methods

### 2.1. Subjects

This study included 42 men with CHF (mean age =  $57.9 \pm 10.5$  years) from the Department of Cardiology, University Hospital of Antwerp (January 2000–November 2001). Preliminary analyses have been reported elsewhere (Denollet et al., 2002). Mean LVEF was  $25.3\% \pm 7.4\%$ , etiology of CHF was coronary heart disease ( $n = 24$ , 57%) or idiopathic dilated cardiomyopathy ( $n = 18$ , 43%). Only patients with stable CHF were included in the study. CHF stability was inferred if patients were free of hospitalization and stable with regard to symptoms and medical therapy (ACE-inhibitors 90% of patients, diuretics–spironolactone  $\geq 83\%$ ; beta-blockers 54%; digoxin 39%, aspirin–amiodarone 24%) for at least one month. Patients with active infection, allergy, rheumatoid disease, cancer, or taking anti-inflammatory medications were excluded. The study was approved by the Local Ethical Committee and all patients gave written informed consent.

### 2.2. Type D personality

Personality was assessed using the Type D Scale-14 or DS14 (Denollet, 2002) comprising a 7-item subscale measuring negative affectivity (the first personality component of Type D) and a 7-item subscale measuring social inhibition (the second personality component of Type D). Cronbachs'  $\alpha$  of these subscales is 0.88 and 0.86, respectively. A cut-off of 10 on both DS14 subscales was used to classify patients as Type D, resulting in 16 Type D patients and 26 non-Type D patients.

### 2.3. TNF- $\alpha$ , sTNFR1, and sTNFR2

An enzyme-linked immunosorbent assay (ELISA) was used to measure circulating plasma levels of TNF- $\alpha$ , sTNFR1, and sTNFR2. Fasting blood samples were

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