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CONFIDENTIAL

**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- α (TNF- α) 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- α , 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- α measures ($p = .006$); i.e., circulating levels of TNF- α (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- α , 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- α (OR = 9.5, 95%CI 2.1-43.8, $p = .004$) and TNF- α 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.

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, Blumenthal & Kaplan, 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 adherence to treatment (Ziegelstein, Bush, Fauerbach, 1998), and more direct physiological mechanisms such as impaired platelet function, decreased heart rate variability, and triggering of myocardial ischemia (Krantz, Kop, Santiago & Gottdiener, 1996). Lately, immune activation has been proposed as a novel mechanism that may explain the link between emotional distress and acute coronary events (Appels, J. Bär, C. Bär, Bruggeman & de Baets, 2000; Ishihara, Nohara, Makita, Imai, Kubo & Hashimoto, 1999; Kop & 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 & Konstam, 1999). Each year, approximately 550,000 patients develop heart failure in the United States (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, Purcell, Henein & Coats, 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 (Gheorghiade & Bonow, 1998). There is also growing evidence that elevated concentrations of proinflammatory cytokines play an important role in the pathogenesis/ progression of CHF (Deswal, Petersen, Feldman, Young, White & Mann, 2001).

Tumor necrosis factor- α (TNF- α) is a proinflammatory cytokine that exerts local actions that facilitate the development of an inflammatory reaction at a lesion site (Maier & Watkins, 1998). TNF- α 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- α also plays a role in the instability of an atherosclerotic

plaque. Binding of membrane-bound TNF- α receptors with their ligand, TNF- α , results in shedding of the extracellular domain, referred to as soluble TNF- α receptor 1 and receptor 2 (sTNFR1 and sTNFR2). Plasma levels of sTNFR1 and sTNFR2 purportedly reflect exposure of the organism to TNF- α over longer periods of time. TNF- α , sTNFR1 and sTNFR2 have consistently emerged as predictors of mortality in patients with CHF (Deswal et al., 2001; Ferrari, Bachetti, Confortini, et al., 1995; Rauchhaus, Doehner, Francis, et al., 2000; Torre-Amione et al., 1996). The determinants of these increased levels of TNF- α in CHF patients are not well understood.

Negative emotions are associated with increased production of proinflammatory cytokines including TNF- α (Kiecolt-Glaser, McGuire, Robles & Glaser, 2002). Episodic psychological risk factors such as depression have been associated with a poor prognosis in CHF (Jiang, Alexander, Christopher, et al., 2001; Vaccarino, Kasl, Abramson, Krumholz, 2001; Faris, Purcell, Henein & Coats, 2002). 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, Cohen, Rabin, Skoner & Doyle, 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 were at risk for CHF (Denollet & Brutsaert, 1998). Therefore, the purpose of this study was to examine associations between Type D personality and TNF- α in patients with CHF.

METHODS

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, Conraads, 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.

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). Cronbach's α 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.

TNF- α , sTNFR1 and sTNFR2

An enzyme-linked immunosorbent assay (ELISA) was used to measure circulating plasma levels of TNF- α , sTNFR1 and sTNFR2. Fasting blood samples were collected between 8 and 9 AM into ethylenediaminetetraacetic (EDTA) tubes (Vacutainer®, Becton and Dickinson, Meylan, France) and plasma was separated by centrifugation and aliquots were stored at -20°C . A high sensitivity kit (Quantikine HS, R&D Systems, sensitivity 0.18 pg/ml) was used to measure TNF- α . The manufacturer's specifications were used to measure soluble TNF- α receptors (Quantikine, R&D Systems, sensitivity: 1.5 pg/ml for sTNFR1, 1 pg/ml for sTNFR2). All samples were run in duplicate. The investigators were blinded with regard to CHF etiology and Type D status.

Etiology and severity of CHF

Deswal et al. (2001) showed that circulating levels of cytokines and cytokine receptors were significantly greater in CHF patients with ischemic heart disease as compared to patients with idiopathic CHF. Therefore, ischemic cause of CHF was included to control for this major cardiological determinant of cytokine proliferation. LVEF and New York Heart Association [NYHA] class were included to control for disease severity as a determinant of TNF- α and its receptors.

Statistical analyses

A general linear model with Type D as between-subjects factors was used to examine the overall effect of personality on TNF- α , sTNFR1 and sTNFR2. To examine the clinical effect of Type D, effect sizes (ES) were calculated by taking the difference in mean cytokine levels between Type D/ non-Type D, and dividing this difference by the standard deviation of the patient population

as a whole. An $ES=0.2$ was considered to indicate a small effect, an $ES=0.5$ a moderate effect and an $ES=0.8$ a large effect (Cohen, 1988). A median split was used to dichotomize cytokine levels in order to stratify patients in high- and low-risk groups, respectively. Multiple logistic regression analyses (method= enter) were used to determine the risk associated with Type D after controlling for ischemic cause of CHF and disease severity as indicated by NYHA class. All analyses were conducted using the SPSS software package, release 11.0 (SPSS Inc., Chicago, IL).

RESULTS

- Table 1 -

Type D and characteristics of CHF

The diagnosis of Type D personality was not significantly associated with age ($p= .63$), ischemic etiology of CHF ($p= .23$), or severity of CHF as indicated by mean LVEF ($p= .79$) or proportion of CHF patients with a LVEF < 25% (Table 1). There was a tendency for Type D patients to be more often classified in NYHA class III/IV than non-Type D patients, but this difference was not statistically significant ($p= .13$). Type D patients did not differ from non-Type Ds in terms of medical treatment, including use of ACE-inhibitors, diuretics, spironolactone, or beta-adrenergic blocking agents.

- Figure 1 -

Type D and mean levels of TNF- α

A general linear multivariate model of TNF- α , sTNFR1 and sTNFR2 with Type D as between-subjects factor indicated a significant overall effect of Type D personality [main effect: $F(1,40)= 8.42$, $p=.006$]. Post-hoc analyses revealed that Type D patients displayed significantly increased circulating plasma levels of (a) TNF- α [$F(1,40)= 9.66$, $p=.003$] and (b) both sTNFR1 [$F(1,40)= 6.64$, $p=.014$] and sTNFR2 [$F(1,40)= 5.94$, $p=.019$], as compared to non-Type D patients (Figure 1). Ischemic etiology of heart failure was also associated with significantly increased plasma levels of TNF- α (4.1 ± 2.9 pg/ml versus 2.4 ± 1.1 pg/ml, $p=.03$) but not sTNFR1 ($p=.25$) or sTNFR2 ($p=.14$).

In order to estimate the clinical significance of the association between Type D and TNF- α , ES values of Type D were calculated using Cohen's (1988) criteria (i.e., $ES=0.2$ represents a small Type D effect, an $ES=0.5$ a moderate effect, and an $ES=0.8$ a large effect). The effect of Type D personality ranged from rather large (sTNFR1, $ES=0.77$; sTNFR2, $ES= 0.73$) to large (TNF- α ,

ES=0.90). In comparison, the effect of ischemic etiology –an important cardiological determinant of immune activation in CHF patients (Deswal et al., 2001)- ranged from rather small (sTNFR1, ES=0.37) and moderate (sTNFR2, ES= 0.46) to rather large (TNF- α , ES=0.66). These findings suggest that Type D was as important as ischemic etiology with reference to immune activation.

Type D and high levels of TNF- α

A median split was used to classify patients as displaying high versus low levels of TNF- α (mean= 4.8 ± 2.7 pg/ ml versus 1.9 ± 0.7 pg/ ml). An aggregate index was used to contrast patients with high levels of both TNF-receptors (mean sTNFR1= 1794 ± 930 pg/ ml and sTNFR2= 2737 ± 504 pg/ ml) with patients scoring below the median on at least one of these two receptors (mean sTNFR1= 844 ± 193 pg/ ml and sTNFR2= 1468 ± 351 pg/ ml). Type D men were significantly more likely to display high levels of TNF- α (75%versus 23% OR=10.0 [95%CI 2.3-42.8], $p=.002$) and its receptors (69%versus 23% OR=7.3 [95%CI 1.8-29.6], $p=.005$) as compared with non-Type D men.

- Table 2 -

Type D as independent predictor

Apart from Type D personality, ischemic etiology and NYHA class were included in a multiple logistic regression model in order to control for etiology and severity of CHF. This model retained Type D personality ($p=.004$) as an independent predictor of high TNF- α levels (Table 2, top). Accordingly, Type D personality was also an independent predictor of high TNF- α receptor levels ($p=.014$) after controlling for both the etiology and severity of CHF (Table 2, bottom).

DISCUSSION

These findings need to be interpreted with caution, given the small number of subjects, the cross-sectional nature of the study, and the wide range of estimated odds ratios in logistic regression analyses. Proinflammatory cytokines can incite symptoms such as fatigue, insomnia or weight loss, that are very similar to those observed in clinical depression (Kronfol & Remick, 2000) or heart failure (Skotzko et al., 2000). This further complicates the interpretation of this cross-sectional study. Finally, the exclusion of female patients also limits generalization of the present findings. Recent evidence indicates that elderly women with CHF frequently have a preserved systolic function (Masoudi et al., 2003), suggesting that the patients from the present study are not entirely representative of the “typical” patient with CHF (Jessup, 2003).

Yet, in light of the prognostic power of (1) TNF- α in patients with CHF (Deswal et al., 2001) and (2) Type D personality in patients at risk for CHF (Denollet & Brutsaert, 1998), they also do warrant further research in the complex domain of personality, immune activation and CHF. There has been a shift in the etiology of CHF from hypertension or valvular disease to coronary heart disease (Gheorghide & Bonow, 1998). The etiology of coronary heart disease, in turn, includes dynamic, pathophysiological factors such as immune factors (Ross, 1999). TNF- α may play a role in each of three pathogenic stages at the site of a vulnerable atherosclerotic plaque: (1) plaque instability, (2) plaque rupture, and (3) thrombosis (Gidron et al. 2002; Kop, 1994).

First, TNF- α stimulates adhesion and migration of leukocytes into the coronary endothelium and activation of macrophages, causing migration of smooth muscle cells and subsequent plaque instability. Second, TNF- α has been thought to stimulate vasoconstriction and elevated blood pressure; i.e., two extra-cellular factors that may induce plaque rupture. Third, proinflammatory cytokines regulate the interaction between the endothelium and blood platelets as well as clotting and fibrinolytic factors, causing enhanced platelet aggregation and subsequent thrombosis at the ruptured plaque. In addition, persistence of immune processes thought to be critical in the etiology of the coronary events may result from an imbalance between neuroendocrine factors that enhance and factors that inhibit immune responses.

Depression (Maes, Bosmans, Meltzer, Scharpe & Suy, 1993), acute stress (Maes, Song, Lin et al., 1998; Steptoe, Willemsen, Owen, Flower & Mohamed-Ali, 2001), and exhaustion (Appels et al., 2000) have also been related to elevations of pro-inflammatory cytokines. On the one hand, this chain of pathophysiological processes may endure due to lack of neuroendocrine-to-immune negative feedback stemming from 'cortisol resistance' (Chrousos, 1995). This condition of insufficient cortisol-induced immune suppression may account for this persistence of PNI processes potentially leading to an acute coronary event. On the other hand, activation of the sympathetic nervous system may also promote pro-inflammatory cytokines such as TNF- α .

Apart from negative emotions, social inhibition may also impact on the immune system. In patients with coronary heart disease, being introverted was associated with decreased natural killer cell activity, while high natural killer cell activity was associated with optimal emotional expression (Ishihara et al., 1999). Evidence linking social inhibition with altered cellular immune response has also been provided by research on human immunodeficiency virus (HIV) infection. Cole, Kemeny, Taylor, Visscher & Fahey (1996) documented a significantly accelerated HIV

progression in gay men who concealed their homosexual identity as compared to those who did not. Their description of these high-risk HIV patients (Cole, Kemeny & Taylor, 1997) matches remarkably well with our description of coronary patients with Type D (Denollet et al., 1996).

The present findings indicated that Type D personality was an independent predictors of higher values for TNF- α in men with CHF. The presence of chronic inflammation in these patients has been widely recognized, and circulating levels of sTNFR1 proved to be better predictor of mortality than standard risk factors such as NYHA class or impaired LVEF (Deswal et al., 2001; Rauchhaues et al. 2000). Of note, CHF patients with a Type D personality displayed significantly higher plasma levels of this TNF- α receptor as compared to non-Type D patients. Hence, chronic psychoimmunological dysregulation may be a mechanism that mediates the relation between Type D and poor prognosis in patients with ischemic heart disease (Denollet et al., 1996).

The co-occurrence of emotional distress and coronary heart disease may lead to higher morbidity and mortality (Rozanski et al., 1999). Depression is relatively common in patients with CHF (Skotzko, Krichten, Zietowski et al., 2000). Not only depression but other psychological factors may as well impact on morbidity and mortality in CHF. The findings of the present study highlight the importance of individual difference variables such as broad and stable personality traits that may modify circulating levels of disease-promoting proinflammatory cytokines. Kiecolt-Glaser et al. (2002) have argued that distress-related immune dysregulation may be one core mechanism behind a large and diverse set of health risks associated with negative emotions. The findings of the present study suggest that these distress-related health risks may also include cardiac complications in CHF as a function of individual differences in personality.

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Table 1 Baseline characteristics as a function of Type D personality.

	Personality Type		<i>p</i>
	Non-Type D (n = 26)	Type D (n = 16)	
Age	58.5 (10.7)	56.9 (10.5)	<i>p</i> = .63
Severity & Etiology of CHF			
LVEF (%)	25.0 (7.8)	25.7 (6.9)	<i>p</i> = .79
LVEF < 25%	10 (39%)	7 (44%)	<i>p</i> = .74
NYHA class III/ IV	10 (39%)	10 (62%)	<i>p</i> = .13
Ischemic etiology	13 (50%)	11 (69%)	<i>p</i> = .23
Medical treatment			
ACE-inhibitors	24 (92%)	14 (87%)	<i>p</i> = .62
Diuretics	24 (92%)	13 (81%)	<i>p</i> = .34
Spironolactone	22 (85%)	13 (81%)	<i>p</i> = .69
Beta-blockers	15 (58%)	8 (50%)	<i>p</i> = .53
Digoxin	12 (46%)	4 (25%)	<i>p</i> = .32
Aspirin	8 (31%)	2 (13%)	<i>p</i> = .28
Amiodarone	8 (31%)	2 (13%)	<i>p</i> = .28

CHF: chronic heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class.

Table 2. Predictors of Increased Levels of TNF- α and Its Receptors

Variable	Logistic regression model		
	Odds ratio	95%CI	p-value
TNF-α			
Type D personality *	9.5	2.1 to 43.8	.004
Ischemic etiology	2.7	0.6 to 12.4	.20
NYHA class III/ IV	0.9	0.2 to 4.1	NS
Receptors			
Type D personality *	6.1	1.4 to 25.8	.014
Ischemic etiology	1.8	0.4 to 8.2	NS
NYHA class III/ IV	2.3	0.5 to 9.7	NS

* Independent predictor of enhanced immune activation ($p < .05$); increased level of **TNF- α** as indicated by a score above the median; increased level of receptors as indicated by a score above the median on sTNFR1 or sTNFR2. NS: not significant ($p > .20$); NYHA: New York Heart Association class.

FIGURE LEGEND

Figure 1. Plasma Levels of TNF- α and Its Receptors, Stratified by Type D Personality

Mean circulating plasma level of cytokine \pm standard error are presented within each bar.

TNF- α = tumor necrosis factor- α , sTNFR1 = soluble tumor necrosis factor- α receptor 1,

sTNFR2 = soluble tumor necrosis factor- α receptor 2.

Figure 1

