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Published in:
International Journal of Cardiology

Publication date:
2006

Document Version
Publisher's PDF, also known as Version of record

ELSEVIER

International Journal of Cardiology 113 (2006) 34 – 38

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Type D personality is associated with increased levels of tumour necrosis factor (TNF)-α and TNF-α receptors in chronic heart failure

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Received 16 June 2005; accepted 15 October 2005
Available online 1 December 2005

Abstract

Background: Pro-inflammatory cytokines and their circulating receptors are powerful predictors of poor outcome in patients with chronic heart failure (CHF). We hypothesized that Type D personality, known to independently predict long-term mortality in patients with coronary heart disease, would relate to immune activation in CHF.
Methods: 91 stable CHF patients (79% males, mean age 57±13 yrs, 58% ischemic heart disease) with left ventricular ejection fraction ≤35% completed a psychological questionnaire to assess Type D personality (i.e., the tendency to experience negative emotions and to inhibit their expression). Plasma levels of tumour necrosis factor (TNF)-α, soluble TNF-α receptor 1 and 2 (sTNFR1 and sTNFR2) and interleukin-6 (IL-6) were measured by ELISA.
Results: Type D patients ($n=30$) had higher levels of TNF-α (5.1±2.9 versus 3.9±2.6 pg/ml, $p=0.066$), sTNFR1 (1656±1057 versus 1098±424 pg/ml, $p=0.009$) and sTNFR2 (2869±1510 versus 2011±794 pg/ml, $p=0.006$) as compared to non-Type D patients ($n=61$), whereas IL-6 was not different. After controlling for sex, age, ischemic etiology and disease severity, multivariate analysis yielded Type D as the strongest predictor of increased TNF-α (OR=2.9, $p=0.048$) and sTNFR2 levels (OR=3.9, $p=0.018$). For sTNFR1, the effect of Type D was no longer significant in this analysis (OR=2.7, $p=0.112$).
Conclusions: Type D personality was independently associated with increased circulating levels of TNF-α and sTNFR2 in patients with CHF. This study provides the strongest evidence to date that chronic emotional distress may be associated with immune activation in heart failure.

Keywords: Chronic heart failure; Inflammation; Cytokines; Type D personality

1. Introduction

There is growing evidence for the role of a disturbed pro-inflammatory cytokine network in the pathogenesis of chronic heart failure (CHF) [1–3]. The determinants and the pathophysiological importance of these elevated concentrations of pro-inflammatory cytokines and their receptors are, however, still a matter of debate [4–8], but strong indications for their prognostic relevance have been obtained [2, 3]. More specifically, circulating levels of soluble tumour necrosis factor (sTNF)-α receptors consistently have emerged as the most important independent predictors of mortality in patients with advanced heart failure [2,3].

Emotional distress (e.g., depression) is not only common in cardiac patients, but is also independently associated with poor outcomes. Evidence is accruing that this complex bi-directional relationship is also relevant in patients with CHF [9,10]. Potential explanations for this link are an unhealthy lifestyle [11] or more direct physiologic mechanisms, such

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doi:10.1016/j.ijcard.2005.10.013

as disturbed autonomic control [12] and impaired platelet function [13].

Psychoneuroimmunology has also unravelled a system of crosstalk between the brain and the immune system [14]. The present study is based on the notion that immunological dysregulation could be another mechanism that may mediate the relation between emotional distress and cardiac prognosis [15,16].

The "distressed" personality or Type D personality (i.e., the tendency to simultaneously experience negative emotions and to inhibit the expression of these emotions) may be a major determinant of chronic emotional stress in cardiac patients [17]. Previous research showed that Type D personality independently predicted long-term mortality in two different cohorts of patients with coronary heart disease [17,18]. Moreover, Type D personality had an unfavourable impact on prognosis in patients with depressed left ventricular function following myocardial infarction [19]. Little is known, however, about the role of psychological factors as a determinant of elevated concentrations of circulating cytokines in cardiac disease.

Preliminary findings in a group of 42 male patients with CHF suggested that Type D personality could be of relevance in the activated immune system characteristic of the heart failure syndrome [20]. We hypothesized that Type D personality was independently related to immune activation in patients with CHF and severely depressed left ventricular function. We therefore analyzed the relation between Type D personality and the plasma levels of interleukin (IL)-6, TNF-α and soluble TNF-α receptors in these patients.

2. Methods

2.1. Subjects

Between January 2000 and May 2003, 91 consecutive patients with CHF and left ventricular ejection fraction (LVEF) ≤35% who were followed at the outpatient clinic of the University Department of Cardiology were asked to participate in this study. Demographic characteristics of the patients are shown in Table 1. All patients were stable with regard to symptoms and therapy for at least 1 month. Patients were on standard medical treatment (Table 1). Exclusion criteria were active infection, allergy, rheumatoid disease, cancer, and treatment with anti-inflammatory drugs. The study was approved by the Local Ethical Committee. All patients gave written informed consent.

2.2. Laboratory measurements

Fasting blood samples were collected between 8 and 9 AM into ethylenediaminetetraacetic (EDTA) tubes (Vacutainer®, Becton and Dickinson, Meylan, France). Plasma was separated by centrifugation and aliquots were stored at −20 °C. Concentrations of TNF-α, soluble TNF-α receptor 1 (sTNFR1), soluble TNF-α receptor 2 (sTNFR2) and interleukin-6 (IL-6) were measured using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's specifications (Quantikine, R and D Systems, sensitivity: 1.5 pg/ml for sTNFR1, 1 pg/ml for sTNFR2). A high sensitivity kit was used to measure TNF-α and IL-6 (Quantikine HS, R and D Systems, sensitivity 0.18 pg/ml for TNF-α; 0.04 pg/ml for IL-6). All samples were run-in duplicate.

The investigators were blinded with regard to patient demographics and Type D personality status.

Table 1
Demographic characteristics

	Total population (n=91)	Type D patients (n=30)	Non-type D patients (n=61)	p-value
Age	57±13 yrs	61±12 yrs	55±14 yrs	0.051
Male	72 (79%)	24 (80%)	48 (79%)	0.89
LVEF	24.6±7.1%	23.5±6.3%	25.1±7.4%	0.31
NYHA I–II	48 (53%)	11 (37%)	37 (61%)	
				0.021
NYHA III–IV	43 (47%)	19 (63%)	24 (39%)	
Ischemic heart disease	53 (58%)	19 (63%)	34 (56%)	0.49
Treatment				
ACE-inhibitors	80 (88%)	26 (87%)	54 (89%)	0.80
ARB's	8 (9%)	2 (7%)	6 (10%)	0.62
Diuretics	71 (78%)	23 (77%)	48 (79%)	0.83
Spironolactone	59 (65%)	18 (60%)	41 (67%)	0.50
Digoxin	30 (33%)	10 (33%)	20 (33%)	0.96
Beta-blockers	60 (66%)	19 (63%)	41 (67%)	0.71
Aspirin	29 (32%)	9 (30%)	20 (33%)	0.79
Amiodarone	31 (34%)	9 (30%)	22 (36%)	0.57
Warfarin	40 (44%)	14 (47%)	26 (43%)	0.72

LVEF=left ventricular ejection fraction, NYHA=New York Heart Association classification, CMP=cardiomyopathy, ARB=angiotensin receptor blocker.

2.3. Personality

Type D personality predisposes to both chronic emotional stress and cardiac events in patients with coronary heart disease and a decreased left ventricular ejection fraction [19]. Type D patients simultaneously tend to i) experience negative emotions and ii) inhibit the expression of emotions in social interaction. These components were assessed with the Type D Scale-14 (DS14), a modified version of the Type D scale which was used in previous studies [18]. The DS14 comprises a 7-item subscale measuring negative affectivity (the first component of Type D) and a 7-item subscale measuring social inhibition (the second component of Type D). Factor analysis confirmed the two-factor structure of the DS14, and Cronbachs' α indicated a high level of reliability for both 7-items subscales; i.e., α=0.84 and α=0.88, respectively. A cut-off of 10 on both DS14 subscales was used to classify 30

patients as type D (≥10 and ≥10, respectively) and 61 patients as non-Type D.

2.4. Statistical analyses

Data are given as mean±standard deviation (SD). The unpaired Student t and χ^2 tests were used as appropriate. Cytokine levels were also dichotomized (top quartile versus lower 3 quartiles) in order to stratify patients in high- and low-risk groups, respectively. Multiple logistic regression analyses (method=enter) were used to determine the independent effect of Type D personality on cytokine levels, after controlling for older age (>60 yrs), sex, disease etiology and disease severity (i.e., LVEF, NYHA classification). Criteria for entry and removal were based on the likelihood ratio test with limits set at $p \leq 0.05$ and $p > 0.05$. All analyses were conducted using the SPSS software package, release 11.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Patient demographics

Type D ($n=61$) and non-type D patients ($n=30$) were comparable with regard to demographic characteristics, medical treatment (Table 1), and coronary risk factors (i.e.; smoking, hypertension, diabetes mellitus, lipid status, obesity; data not shown, all $p>0.05$). Although patients with Type D were slightly older then non-Type D patients, the difference did not reach statistical significance ($p=0.051$). Patients with Type D personality were more often classified in NYHA functional class III or IV ($p=0.021$). However, maximal oxygen consumption (VO2max), determined in 72 of these patients, was not different as a function of personality (16.8±3.8 ml/kg/min for Type D patients versus 17.7±4.7 ml/kg/min for non-Type D patients, $p=0.47$).

3.2. Type D personality and cytokine levels

Table 2 depicts plasma levels of TNF-α, sTNFR1, sTNFR2 and IL-6 for the total population and for subgroups determined by Type D status. Type D patients had

Table 2
Cytokine plasma levels in type D and non-type heart failure patients

	Total population ($n=91$)	Type D patients ($n=30$)	Non-type D patients ($n=61$)	p-value
TNF-α	4.3±2.8	5.1±2.9	3.9±2.6	0.066
sTNFR1	1282±741	1656±1057	1098±424	0.009
sTNFR2	2294±1149	2869±1510	2011±794	0.006
IL-6	5.4±7.2	6.6±8.4	4.8±6.6	0.28

IL-6=interleukin-6, TNF-α=tumour necrosis factor-α, sTNFR1=soluble tumour necrosis factor-α receptor 1, sTNFR2=soluble tumour necrosis factor-α receptor 2.

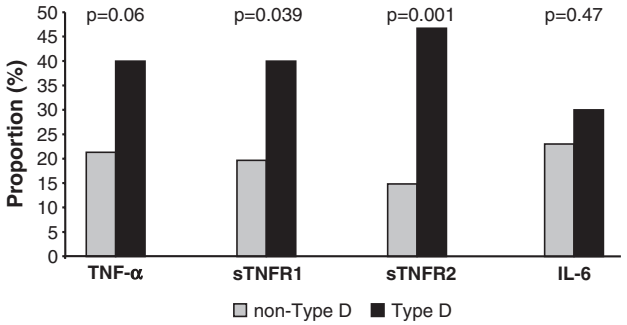

Fig. 1. Percentage of patients with increased cytokine levels according to type D personality. Patients were classified as having increased cytokine levels on the basis of quartile analyses (i.e., TNF-α>5.2 pg/ml for top quartile, sTNFR1>1390 pg/ml for top quartile, sTNFR2>2819 pg/ml for top quartile, IL-6>5.5 pg/ml for top quartile), and were stratified according to their personality type. TNF-α=tumour necrosis factor-α, sTNFR1=soluble tumour necrosis factor-α receptor 1, sTNFR2=soluble tumour necrosis factor-α receptor 2.

significantly elevated levels of sTNFR1 and sTNFR2 and showed a strong trend for increased TNF-α concentrations. IL-6 was not different in Type D versus non-Type D patients. Patients were then divided in to the highest quartile (>5.24 pg/ml for TNF-α; >1390 pg/ml for sTNFR1, >2819 pg/ml for sTNFR2, >5.5 pg/ml for IL-6) versus the 3 lower quartiles according to cytokine and cytokine receptor levels.

Patients with a Type D personality were significantly more likely to display increased levels in the top quartile for both sTNFR1 ($p=0.039$) and sTNFR2 ($p=0.001$) as

Table 3
Independent predictors of increased TNF-α and TNF-α receptor levels

Variable	Logistic regression model		
	Odds ratio	95% CI	p-value
TNF-α			
Male sex	1.3	0.3 to 4.8	0.72
Age>60 yrs	1.5	0.5 to 4.4	0.44
LVEF	1.0	1.0 to 1.1	0.51
Ischemic heart failure	1.0	0.3 to 2.9	0.96
NYHA class III/IV	1.2	0.4 to 3.4	0.78
Type D personality	2.9	1.01 to 8.5	0.048
sTNFR1			
Male sex	1.6	0.3 to 7.7	0.56
Age>60 yrs	3.9	1.2 to 13.2	0.029
LVEF	1.0	0.9 to 1.1	0.94
Ischemic heart failure	3.4	0.8 to 14.6	0.10
NYHA class III/IV	3.1	0.9 to 10.9	0.08
Type D personality	2.7	0.8 to 8.8	0.11
sTNFR2			
Male sex	1.4	0.3 to 5.6	0.66
Age>60 yrs	2.3	0.7 to 7.1	0.16
LVEF	1.1	1.0 to 1.1	0.23
Ischemic heart failure	1.5	0.4 to 4.9	0.54
NYHA class III/IV	2.4	0.8 to 7.8	0.13
Type D personality	3.9	1.3 to 12.1	0.018

TNF-α=tumour necrosis factor-α, sTNFR1=soluble tumour necrosis factor-α receptor 1, sTNFR2=soluble tumour necrosis factor-α receptor 2, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.

compared to non-Type D patients (Fig. 1). There was also a strong trend for Type D patients to display elevated levels of TNF-α ($p=0.06$) but there was no significant association between Type D and increased levels of IL-6 ($p=0.47$).

3.3. Independent predictors of increased TNF-α, sTNFR1 and sTNFR2 levels

Multiple logistic regression analyses (enter procedure) including the Type D effect, age, sex, ischemic aetiology, LVEF, and NYHA class were used to determine the independent predictors of increased levels of circulating cytokines. The final regression models provided comparable results for TNF-α and sTNFR2, with Type D personality independently predicting increased circulating concentrations of these pro-inflammatory markers (Table 3). With reference to increased levels of sTNFR1, Type D was no longer retained in the final model as a significant predictor.

4. Discussion

The present findings indicate that Type D personality is associated with increased plasma concentrations of TNF-α and TNF-receptors in patients with moderate to severe left ventricular systolic dysfunction. For TNF-α and sTNFR2 this association was independent of age, sex, disease aetiology and severity. The results of this study suggest that personality-related stress may act as a modulator of the dysregulated cytokine network of CHF patients.

The associations between Type D personality, TNF-α and TNF-receptors in the present study, together with the prognostic significance of these receptors [2,3], are in line with previous work. In a group of 87 patients with decreased LVEF following myocardial infarction, Type D independently predicted cardiac death and non-fatal myocardial infarction [19]. A 5-year prospective follow-up study in 319 patients with coronary artery disease confirmed that Type D represents a high-risk category [18].

The present findings support the notion that chronic emotional stress may also elicit inflammatory changes that could mediate the relation between stress and prognosis in cardiac patients [15,16,20].

In animal models and human investigations of both somatic and psychological stress, cytokine secretion was altered, depending on the nature of the stressor, the intensity and the duration, and the organ or cells being investigated [21].

Inflammation induces activation of the two major outflow pathways of the brain, namely the HPA axis [22] and the autonomous nervous system [15], leading to hypercortisolemia and disruption of the sympathetic–vagal balance. Vagal withdrawal and sympathetic activation seem equally important in situations of acute mental stress. Kop and colleagues have shown that mental stress promotes coronary vasoconstriction, in association with activation of the sympathetic nervous system leading to higher blood pressure and heart rate [23]. These same investigators pointed at vagal withdrawal, preceding ischemic events, particularly during high mental activities [24].

In patients with CHF, an increase in TNF-α levels is associated with raised cortisol/dehydroepiandrosterone ratios [25], while high circulating levels of catecholamines predict poor prognosis [26].

At present, we cannot exclude the role of an activated immune system promoting the development of both Type D personality and severe CHF. Alternatively, Type D personality could be an epiphenomenon, reflecting disease severity in patients with severe CHF. In the present study, Type D patients were more likely to be classified as NYHA functional class III or IV, whereas more objective measures of disease severity such as left ventricular ejection fraction and maximal oxygen consumption (VO2max) were not different. Therefore, the very fact that NYHA class was higher in the Type D patient group, as opposed to VO2max, which is considered one of the strongest independent prognostic markers in CHF, could reflect its subjective nature and the reliance of physicians to score NYHA functional class according to patients' perception. In this respect, it is not unlikely that one of the key traits of Type D personality, i.e.; negative affectivity, could have skewed NYHA classification [27]. In addition, Type D personality predicted TNF-α and TNF-receptor levels in the present study after adjustment for disease severity (i.e., NYHA classification and LVEF).

The findings of the present study need to be interpreted with some caution. A causal relation between Type D personality and a pro-inflammatory cytokine profile in patients with CHF remains to be proven. The co-occurrence of increased levels of these cytokines and Type D personality in our investigation at least suggests that the latter personality construct could serve as an easily assessable marker of immune activation. We did not include a control group of healthy individuals. Therefore, it still is unknown whether the association between Type D personality and pro-inflammatory cytokines observed in the present study is specific for patients with a chronic cardiac condition.

In summary, we observed a distinct relationship between Type D personality and TNF-α/TNF-receptor plasma levels in patients with CHF. Whether personality traits have prognostic impact on a broader population of heart failure patients via immunoregulatory pathways is unknown. Given the prognostic power of increased TNF-α and TNF-receptor levels in patients with CHF on the one hand, and the prognostic power of Type D personality in patients with coronary disease on the other hand, further research in this domain is warranted.

Acknowledgements

We are indebted to Nadine Possemiers and Lieve Scheurweghs for their dedicated efforts.

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