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Comparing Type D personality and older age as correlates of tumor necrosis factor-α dysregulation in chronic heart failure ☆,☆☆

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Abstract

Tumor necrosis factor-α (TNF-α) and its soluble receptors 1 (sTNFR1) and 2 (sTNFR2) have been shown to be implicated in the pathogenesis of chronic heart failure (CHF). Ageing is accompanied by increased plasma levels of pro-inflammatory cytokines. We hypothesized that Type D personality (joint tendency to experience negative emotions and to inhibit self-expression) and age may have similar pro-inflammatory effects in the context of CHF. Participants in this study were 130 consecutive outpatients with CHF (76% men); there were 70 relatively younger (⩽59 years) and 60 relatively older (⩾60 years) patients. They all completed the 14-item Type D Scale (DS14); 43 patients (33%) had a Type D personality. A multivariate model of cytokine levels indicated an independent overall effect of both older age [$F(1,128) = 9.11$, $p = .003$] and Type D personality [$F(1,128) = 8.28$, $p = .005$]. Stratifying patients in age/personality subgroups showed that younger non-Type D patients had the lowest and older Type D patients the highest sTNFR1 and sTNFR2 levels (986 ± 318 *vs* 1661 ± 1128 pg/ml and 1838 ± 777 *vs* 2823 ± 1439 pg/ml, $p < .0001$). Importantly, the mean sTNFR1 level in younger Type D patients (1359 ± 660 pg/ml) was equivalent to that in older non-Type D patients (1360 ± 440 pg/ml, $p = .99$) who were on average 18 years older. Younger Type D and older non-Type D patients also had similar sTNFR2 levels (2406 ± 1329 *vs* 2448 ± 812 pg/ml, $p = .88$). Only older Type D patients had a higher mean TNF-α level as compared to patients who were younger or who were not Type D (5.4 ± 2.9 *vs* 3.9 ± 2.4 pg/ml, $p = .008$). A logistic regression model including sex, severity of CHF, systolic heart failure and ischemic etiology indicated that the combined risk category of older age or Type D was independently associated with substantially increased sTNFR1 and sTNFR2 levels. Hence, Type D personality was associated with increased TNF-α activity. This disease-promoting effect of Type D matched the pro-inflammatory effect of ageing.

Keywords: Heart failure; Inflammation; Cytokines; Ageing; Type D personality

1. Introduction

Chronic heart failure (CHF) is a rapidly growing medical and communal burden and its incidence rises sharply with increasing age (Mosterd and Hoes, 2007). This common cardiac condition carries a grim prognosis and severely impacts quality of life (Schiffer et al., 2005). The pathophysiological determinants of CHF are numerous and involve the activation of several neurohormonal pathways (von Haehling et al., 2004). The concept of CHF as a

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mere cardiologic entity has been modified, and it is now considered to be a multi-facetted systemic disease. It also entails several peripheral maladaptive processes, including skeletal muscle abnormalities and peripheral endothelial dysfunction (Conraads et al., 2002).

Evidence suggests that a pro-inflammatory environment contributes to the development and progression of both central cardiac and peripheral manifestations of the syndrome (Torre-Amione, 2005). Besides their key role in pathophysiological processes, pro-inflammatory cytokines and their receptors are independent prognosticators of mortality in CHF (Deswal et al., 2001; Ferrari et al., 1995; Rauchhaus et al., 2000; Valgimigli et al., 2005). Cytokines are a heterogeneous group of pleiotropic proteins that mediate the inflammatory response, and are key elements of immune activation and modulation. Pro-inflammatory cytokines have also been associated with the development of atherosclerotic diseases (Cesari et al., 2003; Hansson, 2005; Libby et al., 2002; Tedgui and Mallat, 2006).

Although speculative, a presumed causal relation might explain why immune activation in elderly people is frequent and conveys increased mortality risk (Harris et al., 1999; Hasegawa et al., 2000). Ageing is accompanied by a 2- to 4-fold increase in plasma levels of cytokines (Ferrucci et al., 2005; Krabbe et al., 2004). Interestingly, an age-related rise in pro-inflammatory cytokines has also been demonstrated in CHF patients (Deswal et al., 2001; Von Haehling et al., 2003). Apart from aging, psychological stress interferes with immune function, and it has been suggested that chronic stress accelerates the rate of normal age-related immune dysregulation (Graham et al., 2006). The "distressed" or Type D personality is a potential determinant of chronic emotional stress in cardiac patients (Denollet et al., 1996).

Type D personality refers to the combination of negative affectivity (tendency to experience negative emotions) and social inhibition (tendency to inhibit self-expression in social interaction) and has been associated with poor prognosis in coronary patients (Denollet et al., 2000; Pedersen et al., 2004), in myocardial infarction patients at risk for CHF (Denollet and Brutsaert, 1998), and following heart transplantation (Denollet et al., 2007). Preliminary findings in a group of 42 male patients with CHF suggested that Type D personality could also be of relevance in the activated immune system characteristic of the heart failure syndrome (Denollet et al., 2003). In this study, circulating levels of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and its soluble receptors—soluble TNF receptor 1 (sTNFR1) and 2 (sTNFR2)—were significantly higher in Type D patients as compared to non-Type D patients (Denollet et al., 2003). Type D personality was also independently associated with increased circulating levels of TNF-α and sTNFR2 in a subsequent study of CHF patients (Conraads et al., 2006).

The purpose of the present study was to compare Type D personality and older age as correlates of tumor necrosis factor-α dysregulation in the context of CHF. We hypothesized that Type D personality and older age may have similar effects in terms of an increased pro-inflammatory cytokine activity in CHF patients.

2. Methods

2.1. Participants

Participants in this study were 130 consecutive patients with CHF from the outpatient heart failure clinic of the University Hospital of Antwerp. This sample included 99 men (76%) and the mean age was 59.1 ± 13.6 years. While being diagnosed with CHF later in life is a highly undesirable but not completely unexpected major life event, it definitely is an unexpected major event in midlife. The latter subgroup has a far more aggressive development of heart failure, and has a whole lot of other psychosocial issues to deal with, as compared to the older subgroup. Therefore, we used a cutoff of 60 years (which was about the mean of the age distribution in this study) to classify patients in age subgroups. There were 70 relatively younger ($\leqslant$59 years) and 60 relatively older ($\geqslant$60 years) patients.

All patients were stable with regard to symptoms and therapy for at least 1 month, and were on standard medical treatment consisting of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers, beta-blockers, diuretics, or spironolactone as indicated (Swedberg et al., 2005). Patients with active infection, patients on anti-inflammatory drugs and patients with allergy, rheumatoid disease or cancer were excluded from the study. This study was approved by the Local Ethical Committee. All patients gave written informed consent.

2.2. Type D personality

All participants completed the DS14 scale to assess Type D personality (Denollet, 2005). Type D refers to the tendency to simultaneously (a) experience negative emotions and (b) inhibit self-expression in social interaction, and may predispose to chronic emotional distress. Accordingly, the DS14 comprises a 7-item subscale measuring negative affectivity (tendency to experience negative emotions as the first component of Type D) and a 7-item subscale measuring social inhibition (tendency to inhibit self-expression as the second component of Type D). These DS14 subscales have good psychometric qualities (Cronbach's $\alpha = .88/.86$ and 3 month test–retest reliability $r = .72/.82$ for negative affectivity and social inhibition, respectively). According to previously published findings (Denollet, 2005; Emons et al., 2007), a standardized cutoff $\geqslant$10 on both DS14 subscales was used to classify 43 patients as Type D ($\geqslant$10 on negative affectivity *and* $\geqslant$10 on social inhibition).

2.3. Cytokine levels

Between 8 and 9 AM, fasting blood samples were collected into ethylenediaminetetraacetic (EDTA) tubes (Vacutainer®, Becton and Dickinson, Meylan, France); plasma was separated by centrifugation and aliquots were stored at −20 °C. Enzyme-linked immunosorbent assay (ELISA) was used to measure circulating plasma levels of TNF-α, sTNFR1) and sTNFR2 because elevated concentrations of these pro-inflammatory cytokines have been shown to be implicated in the pathogenesis and progression of CHF (Deswal et al., 2001; Rauchhaus et al., 2000; Torre-Amione, 2005; Von Haehling et al., 2004). In addition, we measured interleukin-6 (IL-6) because some studies suggest that this pro-inflammatory cytokine is also related to poor prognosis in CHF (Deswal et al., 2001). 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). Concentrations of sTNFR1 and sTNFR2 were measured according to the manufacturer's specifications (Quantikine, R and D Systems, sensitivity: 1.5 pg/ml for sTNFR1, 1 pg/ml for sTNFR2). All samples were run-in duplicate, and the investigators were blinded with regard to patient demographics and Type D status.