Elevated Serum Levels of Interleukin-10 and Tumor Necrosis Factor Are Both Associated With Vital Exhaustion in Patients With Cardiovascular Risk Factors

Thomas Meyer, M.D., Ph.D., Beate Stanske, M.D.
Michael M. Kochen, M.D., Andreas Cordes, M.D.
Iraz Yüksel, M.D., Rolf Wachter, M.D.
Claus Lüers, M.D., Martin Scherer, M.D.
Lutz Binder, M.D., Burkert Pieske, M.D.
Christoph Herrmann-Lingen, M.D.

Background: Vital exhaustion, a psychological state characterized by unusual fatigue, irritability, and feelings of demoralization, has been identified as a risk factor for cardiovascular diseases and linked to elevated levels of pro-inflammatory cytokines. Objective: The purpose of this study was to investigate the relationship between vital exhaustion and cytokine levels in patients with cardiovascular risk factors. Method: The entire cohort consisted of 356 primary-care patients with cardiovascular risk factors who participated in a study of early recognition of heart failure. All participants completed the Maastricht questionnaire (MQ) for assessing vital exhaustion. Cytokine serum levels were measured in all those subjects (N=178) who were assigned to the highest and lowest quartiles of the MQ, respectively. Results: Elevated serum concentrations of interleukin-6 and tumor necrosis factor, but not other cytokines, were associated with high MQ scores indicative of vital exhaustion. Conclusion: The subjective state of vital exhaustion is linked to a substantial alteration in the pattern of secreted cytokines. Data suggest that a disturbance in the levels of both pro-inflammatory and anti-inflammatory mediators, rather than isolated stimulation by pro-inflammatory cytokines, is associated with the mental and physical changes of vital exhaustion. (Psychosomatics 2010; 51:248–256)

The concept of vital exhaustion encompasses a psychological state of a transient nature, characterized by a combination of increased irritability, loss of mental and physical energy, listlessness, tiredness, and feelings of hopelessness. The concept of vital exhaustion was originally developed in the context of risk factors for cardiac events, to distinguish a state of unusual fatigue from depression. Vital exhaustion appears to be different from depression, in that “vitaly-exhausted” individuals rarely express sadness, guilt, or feelings of worthlessness, which are characteristic symptoms in patients with depression. The negative affects in vitally-exhausted individuals reflect a demoralization, rather than the lowered self-esteem typical of depressed patients. However, there is an apparent overlap between symptoms of vital exhaustion and depression, including sleep alterations, feelings of

Received May 28, 2008; revised July 3, 2008; accepted July 9, 2008.
From the Depts. of Psychosomatic Medicine and Psychotherapy and Cardiology, University of Marburg, Germany; Depts. of Psychosomatic Medicine and Psychotherapy. Dr. Pieske is now Head of the Dept. of Cardiology, at the Medical University of Graz, Austria. Send correspondence and reprint requests to Prof. Dr. Med. Christoph Herrmann-Lingen, Dept. of Psychosomatic Medicine and Psychotherapy, von-Siebold-Str. 5, D-37075 Göttingen, Germany. e-mail: cherrma@gwdg.de
© 2010 The Academy of Psychosomatic Medicine
weakness, and anhedonia. Thus, it is still a matter of debate whether vital exhaustion represents a distinct psychological state clinically distinguishable from depression or just indicates minor or partially-denied depressive feelings.

Although the pathophysiology of vital exhaustion and its exact relationship to depression remain obscure, numerous epidemiological studies have suggested that this condition predicts the manifestation and progression of cardiovascular disease. Vital exhaustion is associated with coronary heart disease (CHD) and appears to precede and follow myocardial infarction (MI).\textsuperscript{1,4} The association between feelings of exhaustion and MI remains stable even after controlling for recognized cardiovascular risk factors, such as elevated blood pressure or serum cholesterol and smoking. Excess fatigue and feelings of general malaise are among the most prevalent precursors not only of MI, but also of sudden cardiac death.\textsuperscript{1,4,5} Also, vital exhaustion was identified as an independent risk factor for first stroke.\textsuperscript{5,7} Vital exhaustion also independently increases the risk of cardiac events after successful percutaneous transluminal coronary angioplasty.\textsuperscript{8}

Since cytokines play important roles both in the pathogenesis of atherosclerosis and the development of chronic psychological stress, it would be important to know whether abnormalities in the cytokine network link vital exhaustion to adverse cardiovascular outcomes.\textsuperscript{9–11} In contrast to depression, for which characteristic changes in the cytokine network are well described, much less is known for patients with fatigue due to vital exhaustion. Only recently, Janszky et al.\textsuperscript{12} showed that inflammatory activity, as assessed by higher levels of circulating C-reactive protein (CRP) and IL-6, was associated with vital exhaustion and self-related health in women hospitalized for acute MI and/or CHD. Elevated inflammatory markers, including IL-6 and IL-10, at baseline, predict cardiac events in patients who are exhausted after percutaneous coronary intervention.\textsuperscript{10} Given the observed association between vital exhaustion and elevated levels of inflammatory markers, we hypothesized that vital exhaustion in patients with cardiovascular risk factors is linked to a shift in the cytokine profile toward pro-inflammatory mediators, with a concomitant reduction in anti-inflammatory cytokines.

METHOD

Patient Selection

The MedViP study was conducted as a cooperative study at the University of Göttingen, Germany, between January 2003 and August 2004. The acronym stands for “Medical care in general practice” (German: “Medizinische Versorgung in der Praxis”) and refers to a clinical project funded by the German Federal Ministry of Education and Research (BMBF) aimed at improving medical treatment by general practitioners.\textsuperscript{13,14}

Consecutive outpatients over age 18 years who saw their general practitioners for medical advice were considered eligible to participate in the study if they showed one or more of the following risk factors for the development of congestive heart failure (CHF): hypertension, diabetes mellitus, hyperlipoproteinemia, smoking, and/or a family history of CHF or CHD. Further details on the recruitment process and study design have been published elsewhere.\textsuperscript{15}

The population of the current substudy consists of 356 patients enrolled in the main study. All potentially eligible patients underwent a medical-history interview and a physical examination with particular emphasis on clinical signs of underlying cardiovascular disorders. Candidates were excluded if they were found to have 1) clinical signs of active congestive heart failure; 2) a known diagnosis of cardiomyopathy; 3) severe cognitive impairment or psychiatric disease, including excessive substance or alcohol abuse; or 4) insufficient knowledge of the German language. After written informed consent was provided, we performed a detailed transthoracic echocardiographical examination for assessment of systolic and diastolic functioning, including left-ventricular ejection fraction (LVEF) and left-ventricular end-diastolic diameter (LVEDD). Physical capacity was routinely assessed by a 6-minute walk test, which measured the distance the patient covers over a period of 6 minutes by strong walking on a level hallway.\textsuperscript{16,17} The Institutional Ethics Review Board of the University of Göttingen approved the study protocol.

Psychometric Tests

As part of the study, the patients were requested to complete the Maastricht Questionnaire (MQ) and the Type D Scale (DS14). The MQ measures levels of vital exhaustion and has been demonstrated to predict adverse outcomes in patients with coronary heart disease.\textsuperscript{12,18} A limitation of the MQ is that it cannot precisely detect the denial or minimization of stigmatized depressive symptoms. The MQ overlaps with the Beck Depression Inventory, a frequently used instrument for the diagnosis of depression, regarding questions relating to tiredness, sleep problems, hopelessness, listless-
ness, irritation, and loss of libido, but it does not cover loss of appetite or weight, indecisiveness, self-dissatisfaction, self-accusation, or suicidal ideation; it concentrates more on fatigue and the lack of vigor.12 The MQ consists of 21 items, with each item rated on a scale from 0 to 2. This instrument has been validated in several studies and was shown to have adequate internal consistency, with a Cronbach α of 0.89.12 On the basis of MQ results, patients were grouped into quartiles, and those in the highest (score ≥21; N=89) and lowest (≤5; N=89) quartiles were selected for participation in the current substudy.

Also, the study patients were asked to complete the DS14. This instrument assesses components of the Type D personality trait, a psychological construct referring to tendencies to simultaneously experience negative emotions and inhibit the expression of these emotions in social interactions.19–23 The concept of the Type D personality considers the inhibited expression of negative affects as a conscious strategy to avoid disapproval by others. The DS14 consists of two subscales, measuring negative affectivity and social inhibition, on two 7-item subscales. The test provides a well-accepted and valid instrument for the assessment of both components of Type D personality and has a high Cronbach α for both subscales. A cutoff of ≥10 on both DS14 subscales was used to classify patients as expressing the Type D personality pattern.

Laboratory Measurements

From all participants in the main study, venous blood samples were obtained by direct venous puncture on the same day the subjects completed the psychometric questionnaires. After being centrifuged, the serum samples were immediately frozen and stored in aliquots at −70°C until further analyses. All laboratory measurements were performed according to the recommendations of the manufacturer. The sample of 178 patients participating in this substudy (89 from the highest and 89 from the lowest MQ quartile, respectively) was tested for cytokine serum levels. Serum cytokine levels were determined in duplicate by using a commercially available quantitative enzyme-linked immunosorbent assay kit (Fluorokine Kit; R&D Systems Inc., Minneapolis, MN). Plates were read with a Luminex analyzer. For each individual laboratory parameter, the detection limit of the serum concentration was the following: IL–1β: 0.27 pg/ml; IL–6: 0.36 pg/ml; IL–10: 0.13 pg/ml; and TNFα: 0.47 pg/ml. NT-proANP concentrations were determined by microtiter immunoassay (Immunoagnostik; Freiburg, Germany), with values ≥1,320 fmol/ml considered normal. NT-proBNP was determined with the use of a quantitative electrochemiluminescence assay (Elecsys 2010 Analyzer; Roche Diagnostics), with a cutoff value of 1,000 pg/ml. All serum samples were assayed by personnel who were blinded to the diagnostic identity of the study subjects.

Statistical Methods

All data were coded and entered into an anonymized database on a personal computer. The statistical analyses were done with the SPSS Statistical Package, Version 12 for Windows (SPSS, Inc., Chicago, IL). Descriptive values are presented as either mean (standard deviation), medians and interquartile ranges, or percentages. Group comparisons of exhausted and non-exhausted patients were performed by unpaired Student’s t-tests, Mann-Whitney U tests, or χ² tests, as appropriate. Bivariate correlations among cytokine levels were computed with Spearman Brown’s rank correlation. Because the values of most laboratory markers were non-normally distributed and log-transformation also did not result in normal distributions for some of the parameters, we transformed all cytokine levels into quartiles for the multivariate analyses. For multivariate determination of independent predictors of vital exhaustion, logistic-regression models were developed, using an enter approach. Independent predictors were included if their associations with vital exhaustion were at least marginally significant (p <0.1) in the bivariate analyses. After entering clinical predictors, the effects of cytokines were tested by individually adding each cytokine to the regression model in order to avoid multicollinearity. The significance level for all tests was set at p <0.05.

RESULTS

Characterization of Study Population

The mean age of the patients included in the present substudy was 61.9 (11.1) years; 60.7% (N=108) were men. In the lowest exhaustion quartile, the majority of patients were male (74.2%), whereas, conversely, in the subgroup of patients with high exhaustion scores, there were more women (47.2%; p <0.001). Table 1 summarizes
the baseline data of the patient groups with low and high exhaustion scores.

Association Between Vital Exhaustion and Clinical and Personality Variables

First, we assessed the relationship between self-reported vital exhaustion and clinical parameters. We found that there was no significant association between MQ score and either age, systolic or diastolic blood pressure, heart rate, or left-ventricular ejection fraction (see Table 1). However, higher scores for vital exhaustion were significantly associated with a higher body mass index. As expected, study participants presenting high MQ scores had significantly shorter 6-minute walking distances. Between the subgroups of patients with low and high MQ scores, we found no differences in the prevalence of diabetes mellitus, arterial hypertension, hyperlipoproteinemia, or diagnosis of CHD. However, more study patients reporting symptoms of vital exhaustion had a family history of CHD or CHF. Individuals scoring in the lowest quartile for vital exhaustion were more often smokers than were vitally-exhausted patients. Eighteen subjects suffering from chronic autoimmune diseases were on long-term immunosuppressive medication; of these, half (N=9; 10.1%) were in the vitally-exhausted group. Chronic inflammation was diagnosed in 7 high-exhaustion patients (7.9%), versus 3 patients (3.4%) with MQ scores in the lowest quartile (NS). Study participants with higher MQ scores were more often taking psychotropic drugs and beta-blockers. The Type D personality pattern was more often observed in vitally-exhausted patients than in non-exhausted individuals (48.6% versus 7.8%; p <0.001).

Laboratory Findings in Vitally-Exhausted and Non-Exhausted Patients

Serum levels for TNFα and IL-6 were significantly elevated in the Exhausted subgroup. The median TNFα concentration in patients without vital exhaustion was 3.23 pg/ml (interquartile range [IQR]: 2.48 pg/ml to 4.46 pg/ml), versus 4.46 pg/ml (IQR: 3.57 pg/ml to 5.17 pg/ml; p <0.001) in the Exhausted subgroup. In the group of Non-Exhausted patients, the median IL-6 concentration was 3.43 pg/ml (IQR: 2.13 pg/ml to 3.95 pg/ml), whereas, in Vitally-Exhausted patients, IL-6 levels were comparably higher, with a median of 3.50 pg/ml (IQR: 3.03 pg/ml to 4.19 pg/ml; p=0.012). Surprisingly, self-reported vital exhaustion was also significantly associated with elevated serum levels of IL-10. As shown in Figure 1, the median IL-10 concentration in patients with vital exhaustion was 1.76 pg/ml (IQR: 1.67 pg/ml to 1.89 pg/ml), versus 1.61 pg/ml (IQR: 1.35 pg/ml to 1.89 pg/ml).

---

**TABLE 1.** Clinical Data and Personality Type of the Two Patient Groups With Low Versus High Exhaustion Scores on the Maastricht Questionnaire (MQ)

<table>
<thead>
<tr>
<th></th>
<th>Not Exhausted</th>
<th>Exhausted</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>74.2</td>
<td>47.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>61.4 (11.9)</td>
<td>62 (10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>67.4</td>
<td>49.4</td>
<td>0.022</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>26.4 (4.6)</td>
<td>30.1 (6.3)</td>
<td>0.045</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>36</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>84.3</td>
<td>89.9</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary heart disease (CHD), %</td>
<td>30.3</td>
<td>27.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipoproteinemia, %</td>
<td>51.7</td>
<td>53.9</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>49.4</td>
<td>65.2</td>
<td>0.034</td>
</tr>
<tr>
<td>Psychotropic drugs, %</td>
<td>4.5</td>
<td>18.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Family history of CHD, %</td>
<td>30.3</td>
<td>49.4</td>
<td>0.014</td>
</tr>
<tr>
<td>Family history of heart failure, %</td>
<td>7.9</td>
<td>23.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean (SD)</td>
<td>148 (27)</td>
<td>149 (27)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean (SD)</td>
<td>84 (14)</td>
<td>85 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, /minute, mean (SD)</td>
<td>72.1 (11.7)</td>
<td>68.2 (13.7)</td>
<td>0.042</td>
</tr>
<tr>
<td>LV ejection fraction %, mean (SD)</td>
<td>61.6 (7.9)</td>
<td>59.4 (7.7)</td>
<td>0.058</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm), mean (SD)</td>
<td>50.7 (5.3)</td>
<td>50.2 (5.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Six-min. walking distance (m), mean (SD)</td>
<td>527 (97)</td>
<td>441 (167)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type D personality, %</td>
<td>7.8</td>
<td>48.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD: standard deviation; LV: left-ventricular.
pg/ml to 1.81 pg/ml) in non-exhausted patients (p < 0.001). In contrast, we found no association between vital exhaustion and the remaining serum markers IL-1β, NT-proANP, and NT-proBNP (all p values >0.05). Significant positive correlations were found among the cytokine levels: TNFα correlated with IL-6 (ρ=0.37; p <0.0005) and IL-10 (ρ=0.42; p <0.0005), and IL-6 also correlated with IL-10 (ρ=0.34; p <0.0005).

**Independent Predictors of Vital Exhaustion**

Finally, we performed multiple logistic-regression analyses to investigate which of the clinical and laboratory parameters we examined independently predicted vital exhaustion. In the first step, we entered the clinical parameters and found that only family history of CHD and shorter 6-minute walking distance were indepen-
In contrast, IL-1 likely over and above clinical variables and personality. Significantly predict the extent of self-reported vital exhaustion, although this effect failed to reach statistical significance once we controlled for clinical variables.

In addition to the clinical predictors, TNFα and IL-10 serum concentrations each independently predicted vital exhaustion. For each quartile increase in TNFα, the odds of vital exhaustion increased by 86% (multivariate odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.30–2.68; p=0.001). In the alternative model, each quartile increase in IL-10 levels increased the odds of vital exhaustion by 62% (OR: 1.62; 95% CI: 1.15–2.28; p=0.006).

When we finally also added Type D personality as independent variable, it turned out to be the strongest predictor of exhaustion, with ORs ranging from 8.9 to 9.6. However, the independent effects of TNFα (OR:1.56; 95% CI: 1.05–2.53; p=0.027) and IL-10 (OR: 1.47; 95% CI: 1.01–2.15; p=0.047), respectively, remained significant. In both final models, correct classifications of vitally-exhausted patients could be obtained in 80% (both R²=0.53).

**DISCUSSION**

In the present study of medical outpatients presenting with cardiovascular risk factors, we provide evidence that circulating TNFα and IL-10 levels both significantly predict the extent of self-reported vital exhaustion over and above clinical variables and personality. In contrast, IL-1β or natriuretic peptides were not associated with vital exhaustion. Since the predictive value of these cytokines was independent from other clinical parameters examined, our results demonstrate that the subjective state of vital exhaustion is linked to increased production of both extracellular mediators. Elevated serum levels of IL-6 were also associated with vital exhaustion, although this effect failed to reach statistical significance once we controlled for clinical variables.

Although the association between TNFα and exhaustion is in line with previous findings, our finding of elevated IL-10 levels in vitally-exhausted patients with risk factors for heart failure was unexpected. It has previously been hypothesized that a shift in the pattern of secreted cytokines toward pro-inflammatory modulators links vital exhaustion to the excess mortality seen in severely exhausted CHD patients. The assumption of increased pro-inflammatory activity in excess fatigue came from epidemiological studies demonstrating elevated CRP levels and a reduced capacity of dexamethasone for inhibiting IL-6 release from monocytes in highly exhausted men. Recently, Janszky and colleagues reported on a significant correlation between IL-6 levels and vital exhaustion in women with CHD. Other prospective studies had shown that serum CRP and IL-6 concentrations are independent risk factors for cardiovascular events.

However, much less is known on the role of IL-10 in the development and progression of atherosclerosis or heart failure as well as on its putative contribution as a mediator in psychological states. Kwajitaal and colleagues reported on increased risk of late cardiac events after successful percutaneous coronary intervention in exhausted patients with elevated serum concentrations of CRP, IL-6, and IL-10 at baseline. It has been shown that IL-10 functions to oppose the immune-stimulatory effects of pro-inflammatory cytokines such as IL-6, and it inhibits the proliferation of both Th1 and Th2 cells. Interleukin-10 negatively regulates inflammation, primarily through inhibiting the transcription of genes crucial to inflammation, such as cytokines, chemokines, cell-surface receptors, and other molecules. It is produced predominantly in macrophages and dendritic cells as well as T-cells, including T-regulatory cells. Macrophages play a pivotal role in the induction and maintenance of arteriosclerotic lesions that are nowadays recognized as immune-mediated tissue injuries caused by chronic vascular inflammation. Analysis of culprit lesions in patients with acute MI has revealed that an inflammatory infiltration of immune-competent cells is a crucial determinant in precipitating plaque rupture. IL-10 was recently termed an anti-atherogenic cytokine that appears to critically restrict inflammatory processes in atherosclerotic lesions. Its expression was detected in a substantial number of human advanced atherosclerotic plaques, mainly, in infiltrating macrophages. Recently, it was suggested that the anti-inflammatory cytokines IL-10 and transforming growth factor–β (TGFβ) produce their anti-atherogenic effects primarily by promoting the proliferation and differentiation of T-regulatory cells that, in turn, negatively influence Th1 and Th2 responses.

**REFERENCES**

1. Meyer et al. Psychosomatics 51:3, May-June 2010

http://psy.psychiatryonline.org
Factors in Vital Exhaustion

The role of IL-10 in limiting immune responses is most evident in IL-10-deficient mice, which develop chronic enterocolitis after colonization of the gut by normal bacterial flora. Although these mice exhibited an exaggerated and often lethal immunopathology, they may clear certain intracellular pathogens more efficiently than wild-type animals. In two independent studies, blockade of IL-10 signaling has been shown to result in the rapid resolution of chronic viral infection. Interleukin-10 increases host susceptibility to numerous pathogenic microorganisms, such as Mycobacterium bovis, Listeria monocytogenes, Pseudomonas aeruginosa, Klebsiella pneumonia, and others, as determined in either IL-10 knockout mice or by administration of monoclonal antibodies to IL-10. Thus, elevated IL-10 serum levels may be associated with a less successful eradication of a broad spectrum of microbial pathogens, which favor viral persistence or chronic bacterial infection. Therefore, it would be worthwhile to test the hypothesis that the elevated serum levels of IL-10 seen in our vitally-exhausted patients may directly reflect ongoing viral replication or persistence of subclinical bacterial infection.

Our finding that elevated TNFα and IL-10 levels are both associated with vital exhaustion indicates that, in these patients, pro-inflammatory, as well as anti-inflammatory, mediators are both increased. The combined and exaggerated production of counteracting cytokines such as the immune-stimulating TNFα and IL-6, on one hand, and the suppressive cytokine IL-10, on the other, may result in a clinical condition of vital exhaustion that closely resembles the known cytokine-induced “sickness behavior,” a well-described and highly efficient adaptive strategy in challenge of infectious pathogens. Elevation of pro-inflammatory cytokines have been reported in the acute-phase response to infectious diseases. In those conditions, they may act on the brain to induce the common symptoms of illness, such as fever, fatigue, aching joints, sleepiness, loss of appetite, and withdrawal from normal social activities. The elevated serum concentrations of IL-6, TNFα, and IL-10 detected in our vitally-exhausted patients may elicit direct effects on the central nervous system, which may, in turn, result in a stereotypic pattern of endocrine, autonomic, and behavioral changes. As we show here, complex abnormalities in the cytokine network, rather than an isolated shift toward pro-inflammatory mediators, seem to contribute to the fatigue associated with cardiovascular risk factors. Our data confirm a previous report by Pedersen and Middel, showing that CHD patients with Type D personality are at a substantially increased risk of suffering from vital exhaustion, which seems also true for medically ill outpatients presenting with cardiovascular risk factors. Recently, it has been reported that Type D personality was independently associated with increased circulating levels of TNFα and soluble TNFα receptors in patients with chronic heart failure.

Our study was performed with a relatively large sample of well-characterized patients recruited from a representative primary-care setting, using established diagnostic procedures. A limitation of our study is that the exact course of atherosclerotic heart disease in our study participants is unknown. However, neither the percentage of patients with diagnosed CHD nor the ejection fractions or natriuretic peptide levels differed between exhausted and non-exhausted patients. Thus, it appears that, in our sample, at least, these commonly-used indicators of heart disease severity had no major impact on self-reported vital exhaustion. Because of the cross-sectional study design, we do not know whether the observed difference between vitally-exhausted and non-exhausted individuals is of prognostic relevance. We can only speculate as to whether the elevated IL-10 levels observed in vitally-exhausted patients function to counteract the rise in pro-inflammatory cytokines, thus reflecting an adaptive process. Alternatively, IL-10 itself may be more directly involved, as it may increase the susceptibility to primary infections, which then leads to the development of vital exhaustion.

Taken together, we demonstrate that circulating TNFα and IL-10 levels are significantly elevated in vitally-exhausted patients with cardiovascular risk factors and that, moreover, they function as independent predictors for excess fatigue. Our data link raised levels of the anti-inflammatory cytokine IL-10 to the psychological state of vital exhaustion. Moreover, we demonstrate that vital exhaustion is associated with a profound disturbance in the levels of both pro-inflammatory and anti-inflammatory mediators, rather than an isolated stimulation by pro-inflammatory cytokines. Further studies are required to elucidate the pathophysiological mechanisms behind the striking association of elevated IL-10 with vital exhaustion and to identify the prognostic relevance of this association.
References


22. Conraads VM, Denollet J, De Clerck LS, et al: Type D personality is associated with increased levels of tumour necrosis factor (TNF)-α and TNF-α receptors in chronic heart failure. Int J Cardiol 2006; 113:34–38


Factors in Vital Exhaustion

37. Pedersen SS, Middel B: Increased vital exhaustion among Type D patients with ischemic heart disease. J Psychosom Res 2001; 51:443–449