Tumor Necrosis Factor Antagonism With Etanercept Improves Systemic Endothelial Vasoreactivity in Patients With Advanced Heart Failure

Stephan Fichtlscherer, MD; Lothar Rössig, MD; Susanne Breuer, MD; Mariuca Vasa, MD; Stefanie Dimmeler, PhD; Andreas M. Zeiher, MD

**Background**—Anti–tumor necrosis factor (TNF)-α therapy with etanercept, a recombinant TNF receptor that binds to and functionally inactivates TNF-α, was shown to improve the functional status of patients with congestive heart failure (CHF). Because administration of TNF-α has been shown experimentally to depress endothelium-dependent relaxation, we hypothesized that TNF-α antagonism with etanercept might improve the depressed systemic endothelial vasodilator function, which importantly contributes to increased peripheral vascular resistance in patients with advanced CHF.

**Methods and Results**—Endothelium-dependent (acetylcholine, ACH; 10 to 50 μg/min) and endothelium-independent (sodium nitroprusside, SNP; 2 to 8 μg/min) forearm blood flow (FBF) responses were measured by venous occlusion plethysmography in 13 patients with documented CHF (New York Heart Association class III) before, 6 hours after, and 7 days after subcutaneous injection of a single dose of 25 mg etanercept. Maximum ACH-induced FBF increased significantly from 6.9±1.0 to 13.0±1.6 mL/min per 100 mL of forearm tissue (P < 0.05) 6 hours after administration of etanercept and returned to 7.0±1.1 mL/min per 100 mL of forearm tissue after 7 days (P=NS), whereas SNP-induced FBF responses were not significantly affected. In contrast, FBF responses were not altered in control CHF patients, who did not receive etanercept (n=5). Etanercept-induced increases in ACH-mediated FBF were closely correlated with baseline TNF-α serum levels (r=0.66; P<0.02).

**Conclusions**—The administration of etanercept profoundly improves systemic endothelial vasodilator capacity in patients with advanced heart failure, suggesting an important role of inflammatory mediators for impaired endothelial vasoreactivity in CHF. Improvement of systemic endothelial function might importantly contribute to the beneficial effects of etanercept on the functional status of patients with CHF. (*Circulation. 2001;104:3023-3025.*)

**Key Words:** inflammation ■ nitric oxide ■ endothelium ■ heart failure

Congestive heart failure (CHF) is associated with elevated circulating levels of the proinflammatory cytokine tumor necrosis factor (TNF)-α.1 Supporting experimental studies that suggested a role for TNF-α in the pathogenesis of heart failure,2,3 two recent clinical studies demonstrated that targeted anti–TNF-α therapy with etanercept, a recombinant TNF receptor that binds to and functionally inactivates TNF-α, improves the functional status of patients with heart failure.4 Increased peripheral vascular resistance is a hallmark of CHF and a major determinant of the degree of exercise intolerance.5 The deficit in peripheral vasodilator capacity at least in part results from attenuated vascular endothelial function and has been attributed to a loss of the ability of the endothelium to release nitric oxide.6 Because administration of TNF-α has experimentally been shown to depress endothelium-dependent relaxation,7 we hypothesized that TNF-α antagonism with etanercept might improve systemic endothelial vasodilator function in patients with advanced heart failure.

**Patients**

Eighteen patients with advanced CHF (New York Heart Association class III) were studied. Thirteen patients received etanercept and 5 patients served as control subjects. In all patients, left ventricular ejection fraction was ≤30% as assessed by echocardiography (see Table). All patients were receiving long-term therapy including ACE inhibitors, diuretics, digitoxin, and β-blockers for at least 3 months before enrollment into the study. Twelve of the patients were treated with coumarin because of the reduced left ventricular function, and 6 of the patients were treated with aspirin because of ischemic origin of CHF. All patients gave written informed consent. The study protocol was approved by the Ethics Committee of the Johann Wolfgang Goethe–University of Frankfurt/Main.

**Study Protocol**

Forearm blood flow (FBF) measurements were performed by venous occlusion plethysmography essentially as previously described8 before, 6 hours after, and 7 days after the subcutaneous injection of 25 mg etanercept (Wyeth Pharma). In the control group, FBF measurements were performed at baseline and 6 hours after baseline

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Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (n=13)</th>
<th>Control Group (n=5)</th>
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<td>Age, y</td>
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<td>Idiopathic dilated cardiomyopathy</td>
<td>7</td>
<td>2</td>
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<tr>
<td>Ischemic heart disease</td>
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<td>Left ventricular ejection fraction by echocardiography, %</td>
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<td>TNF-α serum levels, pg/mL</td>
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<td>3.4±1.8</td>
<td>NS</td>
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</table>

Statistical Analysis

Data are expressed as mean±SEM values. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and compared by 1-way ANOVA. Categorical variables were compared using the χ² test and compared by Fisher exact test. In the case of nonnormal distribution, nonparametric methods were used (Mann-Whitney U test or Kruskal-Wallis ANOVA on ranks). Differences in forearm vascular reactivity were examined by repeated-measures ANOVA. Linear regression analysis and nonparametric bivariate correlation (Spearman rank correlation coefficient [r]) were used to compare FBF with TNF-α values. Statistical significance was assumed at a level of P<0.05. All statistical analyses were performed with SPSS for Windows 7.0 (SPSS Inc).

Results

The clinical characteristics of the study population are summarized in the Table. All patients had sinus rhythm. Arterial blood pressure did not differ among the 3 measurements.

Baseline FBF was not affected by the administration of etanercept (2.01±0.2 versus 2.1±0.1 versus 2.1±0.2 mL/min per 100 mL of forearm tissue; P=NS). However, as illustrated in Figure 1A, FBF responses to acetylcholine significantly increased 6 hours after the administration of etanercept (ACHmax, 6.8±1.0 versus 12.9±1.6 mL/min per 100 mL of forearm tissue; P<0.05). Seven days after a single injection of etanercept, FBF responses to acetylcholine had returned to pretreatment levels (ACHmax, 7.0±1.1 mL/min per 100 mL of forearm tissue; Figure 1A). Etanercept-induced increases in FBF responses to ACH did not differ between patients with ischemic compared with nonischemic causes of CHF. Moreover, female patients (n=3) exhibited a similar increase in ACH-induced FBF responses 6 hours after etanercept treatment (area under the curve change, 33.6±19.2%) compared with male patients (area under the curve change, 30.5±5.7%; n=10; P=NS). In contrast, in the control patients (n=5), ACH-induced FBF responses remained essentially unchanged (6.9±1.5 versus 7.2±1.6; P=NS) (Figure 1B).

The FBF responses to endothelium-independent sodium nitroprusside (SNP) were also slightly but not significantly improved by the administration of etanercept (SNPmax, 8.7±1.1 versus 11.1±1.5 mL/min per 100 mL of forearm tissue; P=0.07) and returned to pretreatment levels after 7 days (SNPmax, 8.9±1.2 mL/min per 100 mL of forearm tissue; Figure 1C). In the control patients, no change in SNP-stimulated FBF was detectable (Figure 1D). Importantly, there was a close correlation between the increase in ACH-induced FBF responses and baseline TNF-α serum levels (r=0.66, P<0.02) (Figure 2).

Discussion

The results of the present study demonstrate that the administration of a single dose of etanercept transiently but pro-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Effect of etanercept on ACH- and SNP-induced FBF responses. A and B, FBF dose-response curves to ACH pretreatment, 6 hours after injection of etanercept, and 7 days after injection of etanercept (A) or in control subjects at baseline and after 6 hours (B). C and D, FBF dose-response curves to SNP at pretreatment, 6 hours after injection of etanercept (C) or in control subjects at baseline and after 6 hours (D). Values represent mean±SEM.
foundly improves the impaired systemic endothelial vasodilator capacity in patients with advanced heart failure. Importantly, the extent of improvement in endothelium-dependent FBF responses was directly correlated with baseline TNF-α effects and baseline TNF-α-dependent FBF responses was consistently observed. Thus, in addition to its effects on left ventricular function and remodeling, TNF-α antagonism with etanercept might interfere with multiple pathways known to impair endothelial cell function. Although the present study—designed as a pilot trial to investigate potential effects of etanercept on endothelial vasoreactivity—lacks a double-blind, placebo-controlled study design, the salutary effects observed support the concept that TNF-α is a potentially important therapeutic target to improve systemic vascular reactivity in patients with heart failure.

Acknowledgments

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References

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