Vascular Extracellular Superoxide Dismutase Activity in Patients With Coronary Artery Disease
Relation to Endothelium-Dependent Vasodilation

Ulf Landmesser, MD; Roland Merten, MD; Stephan Spiekermann, BS; Karsten Büttner, MD; Helmut Drexler, MD; Burkhard Hornig, MD

Background—Increased inactivation of nitric oxide by oxygen free radicals contributes to endothelial dysfunction in patients with coronary artery disease (CAD). We therefore determined the activity of extracellular superoxide dismutase (EC-SOD), the major antioxidant enzyme system of the vessel wall, and its relation to flow-dependent, endothelium-mediated dilation (FDD) in patients with CAD.

Methods and Results—SOD isoenzyme activity was determined in coronary arteries from 10 patients with CAD and 10 control subjects. In addition, endothelium-bound EC-SOD activity (eEC-SOD), released by heparin bolus injection, and FDD of the radial artery were measured in 35 patients with CAD and 15 control subjects. FDD, determined by high-resolution ultrasound, was assessed at baseline, after intra-arterial infusion of vitamin C, N-monomethyl-L-arginine, and combination of both. EC-SOD activity in coronary arteries (control subjects: 126±14; CAD: 63±11 U/mg protein; \( P<0.01 \)) and eEC-SOD activity in vivo (control subjects: 14.5±1.1; CAD: 3.8±1.1 U · mL\(^{-1}\) · min\(^{-1}\); \( P<0.01 \)) were reduced in patients with CAD. Activity of eEC-SOD was positively correlated with FDD (\( r=0.47; P<0.01 \)) and negatively with the effect of the antioxidant vitamin C on FDD (\( r=-0.59; P<0.01 \)). In young individuals with hypercholesterolemia, however, eEC-SOD activity was increased (21.0±2 U · mL\(^{-1}\) · min\(^{-1}\); \( n=10; P<0.05 \)).

Conclusions—In patients with CAD, vascular EC-SOD activity is substantially reduced. The close relation between endothelium-bound EC-SOD activity and FDD suggests that reduced EC-SOD activity contributes to endothelial dysfunction in patients with CAD. In young hypercholesterolemic individuals, however, endothelium-bound EC-SOD activity is increased and may, in part, counteract impairment of endothelial function as the result of increased formation of oxygen free radicals. (Circulation. 2000;101:2264-2270.)

Key Words: endothelium ■ coronary disease ■ hypercholesterolemia ■ free radicals, antioxidants

Patients with coronary artery disease (CAD) have an abnormal endothelial function.\(^1\) One of the important consequences is the inability of the vessel to dilate in response to physiological stimuli, such as increases in flow, reflecting impaired flow-dependent, endothelium-mediated dilation (FDD; Reference 2). Short-term and long-term administration of the antioxidant vitamin C reversed impairment of endothelium-dependent dilation in patients with CAD, suggesting that increased inactivation of nitric oxide (NO) by superoxide anions contributes to endothelial dysfunction.\(^3\)\(^,\)\(^4\) Recently, extracellular superoxide dismutase (EC-SOD) has been reported to be a major antioxidant enzyme system of the arterial wall, located strategically between endothelium and vascular smooth muscle cells.\(^5\) The EC-SOD concentration within the arterial wall is high enough to suppress pathological effects of superoxide anions such as reaction with NO leading to formation of deleterious peroxynitrite.\(^6\) Inhibition of vascular SOD resulted in impairment of endothelium-dependent dilation in bovine coronary arteries in vitro, suggesting that SOD levels are critical for the ability of NO to modulate vascular tone.\(^6\) This concept finds further support by the in vivo observation that SOD deficiency impaired endothelium-dependent dilation as the result of increased inactivation of NO.\(^7\) EC-SOD activity is decreased in atherosclerotic lesions of human aorta as compared with macroscopically normal segments of the same individual.\(^8\) In contrast, EC-SOD activity is increased in aortas of apolipoprotein (apo)-E–deficient mice\(^9\) and hyperlipidemic rabbits.\(^8\) The present study was therefore designed to evaluate the functional implication of EC-SOD in patients by determination of EC-SOD activity and endothelium-mediated vasodilation and to reconcile the apparently conflicting observations between patients with atherosclerosis\(^8\) and young hypercholesterolemic animals.\(^9\)
Although, vascular EC-SOD activity was measured in coronary artery specimens of patients with and those without CAD. To determine vascular EC-SOD activity in vivo, endothelium-bound EC-SOD (eEC-SOD) activity was measured in patients with established CAD, in age-matched control subjects, and in young individuals with hypercholesterolemia. In addition, eEC-SOD activity was related to endothelium-dependent vasodilation to assess the functional implication of eEC-SOD activity in vivo. Furthermore, the portion of FDD inhibited by oxygen free radicals (ie, recovered by vitamin C) was related to eEC-SOD activity in patients with CAD.

**Methods**

**Determination of SOD Activity in Coronary Arteries: Ex Vivo Protocol**

Human coronary artery specimens were collected at autopsy from 10 patients with CAD (6 men; age 66±3.3 years; macroscopic coronary atherosclerosis ≥1; stenosis ≥60%) and 10 control subjects (4 men; age 64±4.1 years; no history or pathomorphological evidence of CAD, hypertension, diabetes, hypercholesterolemia, or smoking) within 24 hours after death and stored at −80°C. Control subjects died of diseases not related to atherosclerosis (intracerebral tumor: n=2; pulmonary embolism: n=3; traffic accident: n=2). In coronary arteries serving as controls, foam cell deposition was excluded by histologic evaluation. In patients with CAD, we measured SOD activity in coronary artery segments with (≥60%) and without stenosis. It should be noted that storage of vascular tissue at 5°C for up to 6 days does not change activity of SOD isoenzymes. In addition, EC-SOD activity has been shown to be very resistant to proteolysis, reducing the likelihood of protein degradation in the samples. For extraction of SOD protein from coronary specimens, frozen pieces were pulverized (Microdismembranator II; Brown Biotek Inc), added to 10 vol of 50 mmol/L potassium phosphate (pH 7.4), with 0.3 mol/L KBr and antiproteolytic agents (0.5 mmol/L PMSF, 3 mmol/l DTPA, 90 mg/L aprotinin, 10 mg/L pepstatin, 10 mg/L chymostatin, 10 mg/L leupeptin). Homogenates were sonicated, extracted (30 minutes; 4°C), and centrifuged (15 minutes; 80°C). For protein analysis, a Bio-Rad DC Protein Assay was used after standardization with human serum albumin.

**Assay for SOD-Isoenzyme Measurement**

Activity of SOD was measured at pH 8.2 by a modified nitrite method. Superoxide generated by hypoxanthine and xanthine oxidase was changed to nitrite ion by hydroxylamine. Nitrite ion was measured by color densitometry at 550 nm with the use of a coloring reagent. The amount of SOD required to inhibit the rate of nitrite generation by 50% was defined as 1 U of SOD activity. Reactions were performed with known amounts of purified bovine SOD. To distinguish between cyanide-sensitive isoenzymes (Cu,Zn-SOD and EC-SOD) and the resistant one (Mn-SOD), 2 mmol/L cyanide was used. For specific analysis of EC-SOD activity, chromatography on Con A-Sepharose (Pharmacia Biotech) was performed. Unlike Cu,Zn-SOD and Mn-SOD, the glycoprotein EC-SOD binds to lectin conavalin A. The coefficient of variation for determination of EC-SOD activity in coronary arteries was 7.6%. Cu,Zn-SOD activity was calculated as cyanide-sensitive SOD activity minus EC-SOD activity. Reagents were from Sigma Aldrich.

**Determination of eEC-SOD Activity In Vivo**

EC-SOD is specifically released from the endothelium into plasma by heparin bolus injection, allowing determination of eEC-SOD activity in humans in vivo without affecting plasma Cu,Zn-SOD or Mn-SOD activity. For measurement of plasma SOD activity at baseline, 2 arterial (brachial artery) and 2 venous (antecebular vein) blood samples were obtained. Then, 1000 U of heparin was injected into the brachial artery, and blood samples were obtained from the antecubital vein of the same arm (1, 3, 5, 7, and 10 minutes after heparin injection). After 60 minutes, when plasma SOD activity had returned to baseline, 5000 U of heparin was injected and blood samples were obtained again. eEC-SOD activity (U·mL⁻¹·min⁻¹) was calculated as the area under the curve of the increase of plasma SOD activity within 10 minutes after heparin injection. A time interval of 10 minutes was used because maximum increase of plasma SOD activity was approached within this time (Figure 1). Coefficient of variation for determination of eEC-SOD activity was 7.6%, as determined by repeated injection of 5000 U of heparin in 8 patients with CAD. For blood sampling, EDTA-containing vacuum tubes were used to avoid cellular leakage of Cu,Zn-SOD from vascular and skeletal muscle cells observed after the use of a tourniquet. Tubes were immediately centrifuged (2000g, 15 minutes, 4°C), with plasma stored at −80°C. To further establish this method, blood samples were obtained in time intervals up to 60 minutes (Figure 1) from 6 control subjects after injection of placebo (10 mL saline) or 1000 and 5000 U of heparin. In 6 additional control subjects, blood samples were drawn simultaneously from both arms to investigate whether eEC-SOD is released locally or systemically in response to intra-arterial heparin bolus injection (5000 U; time intervals up to 10 minutes). To exclude a relevant release of EC-SOD from blood cells or a direct effect of heparin on plasma SOD activity, 5000 U of heparin or an equal volume of saline was added to whole blood (10 mL) of 8 control subjects. After incubation for 20 minutes at room temperature, samples were centrifuged and plasma was collected for SOD analysis.

**Figure 1.** Increase of plasma SOD activity after injection of 1000 and 5000 U of heparin or placebo in control subjects (n=6). Increase of plasma SOD activity was determined as difference between plasma SOD activity before and after heparin injection. At time 0, difference between 2 baseline measurements is shown. Increase of plasma SOD activity was significant from ≥3 minutes after injection of heparin (P<0.01 vs placebo).
TABLE 1. Characteristics of Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Protocol 1</th>
<th>Protocol 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control Subjects (n=15)</td>
<td>CAD (n=35)</td>
</tr>
<tr>
<td></td>
<td>Control Subjects (n=10)</td>
<td>Hypercholes- terolemia (n=10)</td>
</tr>
<tr>
<td>Age, y</td>
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<td>60±2</td>
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<tr>
<td>Male/female</td>
<td>13/2</td>
<td>31/4</td>
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<tr>
<td>Mean blood pressure, mm Hg</td>
<td>87±4</td>
<td>89±5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±4</td>
<td>62±3</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>62±4</td>
<td>60±3</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>120±12</td>
<td>142±11</td>
</tr>
<tr>
<td>Creatine, mg/dL</td>
<td>0.7±0.2</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>73±4</td>
<td>71±3</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±4</td>
<td>173±3</td>
</tr>
</tbody>
</table>

*P<0.01 vs control subjects.

Written informed consent was obtained for all subjects. Each protocol was approved by the local ethics committee.

**Determination of eEC-SOD Activity and FDD in Young Individuals With Hypercholesterolemia: In Vivo Protocol 2**

Ten young untreated individuals with asymptomatic familial hypercholesterolemia (type II A) and 10 age-matched control subjects were studied (Table 1). eEC-SOD activity was determined as described earlier; however, heparin was injected into the antecubital vein because eEC-SOD activity is released systemically by a bolus of 5000 U. FDD of the radial artery was measured as described below; endothelium-independent vasodilation was determined after sublingual nitroglycerin (0.8 mg).

**Measurement of FDD**

Radial artery diameters were measured with the use of high-resolution ultrasound (ASULAB). This method is well established in our laboratory,17,18 has excellent reproducibility and variability, and was used as described in detail recently.6 Blood flow velocity was recorded continuously; radial artery diameter was determined every 30 seconds until stable baseline conditions were obtained. A wrist arterial occlusion (8 minutes) was performed, and FDD in response to reactive hyperemic blood flow was assessed at baseline and after L-NMMA (Calbiochem; 7 μmol/min IA; 5 minutes). When radial artery diameter and blood flow had returned to baseline, FDD was determined after vitamin C (25 mg/min IA; 10 minutes) and after coinfusion of vitamin C and L-NMMA. Sodium nitroprusside was infused (SNP; 10 μg/min IA; 5 minutes) to assess endothelium-independent vasodilation. Six patients with CAD were randomly assigned to receive intra-arterial infusion of placebo instead of vitamin C; Blood flow and diameter data reported for L-NMMA, vitamin C, and SNP represent measurements during last minute of each infusion. All measurements were recorded; subsequently, vessel diameter and blood flow velocity were analyzed by 2 investigators unaware of sequence of interventions.

**Statistical Analysis**

All data are expressed as mean±SEM. To compare data between different groups, ANOVA was used; to compare repeated measurements within 1 group of patients, a 1-way ANOVA for repeated measures was performed followed by Student-Newman-Keuls test. Linear regression analysis was used to analyze the relation between endothelium-bound EC-SOD activity and FDD. A value of P<0.05 was considered to be statistically significant.

**Results**

**SOD Activity in Coronary Artery Specimens**

EC-SOD activity was reduced in coronary artery segments with and without stenosis of patients with CAD (Table 2). Activity of Mn-SOD and Cu,Zn-SOD were similar in coronary arteries of patients with CAD and in control subjects (Table 2).

**eEC-SOD Activity and FDD in Patients With CAD**

eEC-SOD activity was reduced in patients with CAD (after 1000/5000 U of heparin: control subjects 2.4±0.2/14.5±1.1; CAD 0.5±0.7/3.8±1.1 U·min⁻¹·mm⁻¹, each P<0.01; Figure 2). FDD was impaired in patients with CAD (Figure 3; Table 3). L-NMMA did not change radial artery diameter under resting conditions, but FDD was reduced compared with baseline (Figure 3 and Table 3). Vitamin C did not change radial artery diameter at rest but increased FDD in patients with CAD (Figure 3 and Table 3). Placebo had no effect on FDD (6.1±0.3% vs 6.0±0.4%). The portion of FDD mediated by NO (ie, inhibited by L-NMMA) was reduced in patients with CAD (2.4±0.6% vs control subjects: 8.5±0.7%; P<0.01) and increased after vitamin C (7.4±0.8%; P<0.01 vs before vitamin C). SNP increased radial artery diameter similarly in control subjects and patients with CAD (control subjects: 2.92±0.1 to 3.45±0.1; CAD vitamin C 2.96±0.1 to 3.49±0.1; CAD placebo 2.95±0.1 to 3.49±0.1 mm; each P<0.01 vs before SNP).

**TABLE 2. Activities of SOD Isoenzymes in Human Coronary Arteries**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=10)</th>
<th>CAD Segments Without Stenosis (n=10)</th>
<th>CAD Segments With Stenosis (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC-SOD, U/mg protein</td>
<td>126±14</td>
<td>67±10*</td>
<td>63±11*</td>
</tr>
<tr>
<td>Cu,Zn-SOD, U/mg protein</td>
<td>178±25</td>
<td>169±19</td>
<td>185±25</td>
</tr>
<tr>
<td>Mn-SOD, U/mg protein</td>
<td>39±5</td>
<td>38±9</td>
<td>40±11</td>
</tr>
<tr>
<td>Protein, mg/g wet wt</td>
<td>28.6±3.2</td>
<td>28.2±2.5</td>
<td>25.1±3.1</td>
</tr>
</tbody>
</table>

*P<0.01 vs control subjects.
L-NMMA reduced forearm blood flow at rest; vitamin C had no effect (Table 3). Maximal reactive hyperemia was similar in control subjects and in patients with CAD and not affected by L-NMMA, vitamin C, or combination of both (Table 3). SNP increased forearm blood flow to a similar extent in control subjects and in patients with CAD (control subjects: 25\pm 5 to 41\pm 6; CAD vitamin C 26\pm 4 to 42\pm 5; CAD placebo 27\pm 4 to 43\pm 5 mL/min; P<0.01 vs before SNP). Systemic blood pressure and heart rate did not change during experimental protocol (data not shown).

In patients with CAD, we found a positive correlation between eEC-SOD activity and FDD (r=0.47; P<0.01 vs before L-NMMA). A negative correlation was seen between eEC-SOD activity and effect of vitamin C on FDD, representing the portion of FDD inhibited by oxygen free radicals (r=-0.59; P<0.01 vs before L-NMMA).
**Characterization of eEC-SOD Measurement In Vivo**

Heparin bolus increased plasma SOD activity in 6 control subjects; placebo injection had no effect (Figure 1). Increase of plasma SOD activity was related to a cyanide-sensitive SOD isoenzyme, since it was inhibited in the presence of cyanide (Cn; 2 mmol/L), which inhibits EC-SOD and Cu,Zn-SOD (increase of plasma SOD activity after 5000 U of heparin without Cn: 25.7±2.3 with Cn: 0.1±2.1 U/mL; *P*<0.01). Increase of plasma SOD activity after heparin bolus was mediated by increase of EC-SOD and not Cu,Zn-SOD activity because EC-SOD was specifically identified in plasma by the use of Con A Sepharose chromatography (increase of plasma EC-SOD activity after 5000 U of heparin 25.1±3.5 U/mL; total plasma SOD activity: 25.7±2.3 U/mL). Heparin increased plasma SOD activity to a similar extent in the ipsilateral (i) and contralateral (c) arms (heparin 5000 U: i: 25.2±2.5; c: 24.9±2.4 U/mL). Relevant release of EC-SOD from blood cells or direct activation of plasma SOD by heparin is unlikely because the addition of heparin to whole blood had no effect on plasma SOD.

**Discussion**

The major findings of the present study are: (1) The activity of vascular EC-SOD is substantially reduced in coronary arteries of patients with CAD as compared with age-matched control subjects. (2) In vivo, endothelium-bound EC-SOD activity is severely reduced in patients with CAD and closely related to NO-mediated vasodilation, suggesting that reduced SOD activity contributes to reduced bioavailability of NO in CAD. (3) In addition, in patients with CAD, endothelium-bound EC-SOD activity is inversely related to the beneficial effect of vitamin C on NO-mediated vasodilation, supporting the concept that SOD activity is crucial to prevent inactivation of NO by oxygen free radicals. (4) In young individuals with familial hypercholesterolemia, however, endothelium-bound EC-SOD activity is increased as compared with age-matched control subjects, suggesting that other mechanisms are responsible for impaired NO-mediated vasodilation. Thus, the present study supports the concept that reduced vascular EC-SOD activity contributes to impaired NO-mediated vasodilation in patients with CAD, whereas increased activity of EC-SOD may counteract, in part, excess radical formation in young individuals with hypercholesterolemia.

Increased inactivation of NO by oxygen free radicals is involved in endothelial dysfunction in patients with CAD.3,4 EC-SOD represents a major antioxidant enzyme system located strategically between endothelium and vascular smooth muscle cells, that is, in the compartment of the arterial wall where NO is expected to be inactivated by superoxide anions.5 Human arteries contain extraordinarily large amounts of EC-SOD that are ~100 times higher as compared with skeletal muscle or fat tissue.5,13 pointing out the special function of this protein within the vessel wall. There is evidence that vascular SOD activity is critical for the ability of NO to modulate vascular tone, since inhibition of SOD resulted in impaired endothelium-mediated vasodilation in different animal models.6,7,19 To elucidate the apparently conflicting observations between humans with chronic ath erosclerosis8 and animals with hypercholesterolemia,8,9 we measured vascular EC-SOD activity in patients with chronic CAD and in young asymptomatic individuals with hypercholesterolemia. In coronary arteries of patients with CAD, we found a specific reduction of EC-SOD isoenzyme activity because activity of Cu, Zn-SOD and Mn-SOD isoenzymes was similar in normal and atherosclerotic coronary arteries. Furthermore, EC-SOD activity was reduced in coronary artery segments with and without stenoses, supporting the concept that reduction of EC-SOD activity is a systemic defect in arteries of patients with CAD. To further evaluate this concept, we determined vascular EC-SOD activity in vivo by release of endothelium-bound EC-SOD into plasma after heparin bolus injection. Heparin releases EC-SOD from heparan sulfate, which is located on endothelial cell surfaces.20 Heparin specifically binds the subtype of EC-SOD (type C) that is bound to the endothelium.14,15,21

We found a close inverse relation between eEC-SOD activity and the beneficial effect of vitamin C on FDD, that is, vitamin C improved NO-mediated vasodilation, particularly in patients with low eEC-SOD. The improvement of endothelium-mediated dilation after vitamin C was mediated by increased bioavailability of NO. Therefore, the present study suggests that reduced vascular EC-SOD activity contributes to increased radical load in patients with CAD, leading to reduced bioavailability of NO. The concept that reduced EC-SOD is pathophysiologically relevant finds further support by recent data demonstrating that low EC-SOD plasma levels are associated with a history of myocardial infarction.22 In young asymptomatic individuals with hypercholesterolemia, however, eEC-SOD activity is increased consistent with observations in apo E–deficient mice24 and hypercholesterolemic rabbits.8 In this situation, increased EC-SOD activity may represent a compensatory mechanism that counteracts, in part, inactivation of NO by excess radical formation.23,24 Obviously, other pathophysiological mechanisms may explain endothelial dysfunction in young hypercholesterolemic individuals, since SOD activity is increased. They can be summarized in mechanisms that increase inactivation of NO as the result of increased radical formation and mechanisms that reduce NO formation. Mechanisms that increase radical formation may include increased vascular activity of NAD(P)H-oxidase25 and xanthine oxidase.25 In addition, increased LDL cholesterol levels26 or intracellular l-arginine depletion27 may cause uncoupling of NO synthase, which then generates superoxide anions in addition to NO, leading subsequently to increased peroxynitrite formation. Mechanisms that lead to reduced NO formation in hypercholesterolemia include increased plasma concentrations of the endogenous NO synthase inhibitor asymmetric dimethylarginine (ADMA; Reference 28). The concept of a competitive antagonism between l-arginine and ADMA as the underlying mechanism for reduced NO formation finds further support by the observation that supplementation of l-arginine improves endothelium-dependent vasodilation in patients with hypercholesterolemia,29 particularly in young adults.30 In addition, a tetrahydrobiopterin deficiency,31 increased endothelin-1 concentrations,32 and increased inhibitory
caveolin-eNOS complex formation may contribute to reduced NO formation in hypercholesterolemia.

Impairment of endothelial-dependent vasodilation was more pronounced in patients with established CAD than in young individuals with hypercholesterolemia. These results are in line with the finding that endothelial dysfunction may progress to symptomatic CAD. It should be noted, however, that NO synthase expression and NO production decreases from hypercholesterolemia to chronic atherosclerosis. Therefore, progressive loss of EC-SOD activity and NO production over time may both contribute to progression of endothelial dysfunction. The present study was not designed to elucidate the mechanism responsible for changes in vascular EC-SOD activity over time. However, our data correspond in many ways to findings of a recent experimental study. Fukai et al found 2 transcripts of EC-SOD in apo-E–deficient mouse aortas. One transcript corresponded to usual EC-SOD made by normal vessels (probably by vascular smooth muscle cells). The other was found to be made by lipid-laden foam cells. In keeping with our results, the transcript corresponding to normal EC-SOD went down as apo-E–deficient mice aged and their atherosclerosis worsened. Furthermore, preliminary data suggest that EC-SOD expression is dependent on NO bioavailability, since EC-SOD expression was reduced by 50% in eNOS-deficient mice. Therefore, reduced NO availability in CAD may contribute to reduced EC-SOD activity. In patients with CAD, secretion of tumor necrosis factor-α is increased and may contribute to depression of EC-SOD activity because it has been shown that tumor necrosis factor-α inhibits EC-SOD expression.

Study Limitations

A heparin bolus releases only a limited part of vascular EC-SOD that has been estimated to be ~3% of total vascular EC-SOD. For ethical reasons, we did not use doses of heparin >5000 U to avoid long-lasting anticoagulatory effects possibly leading to vascular complications after catheterization of the brachial artery. This limited release of eEC-SOD in response to heparin, however, cannot explain the difference of EC-SOD activity between healthy control subjects and patients with CAD. Furthermore, EC-SOD activity was also severely reduced in coronary artery specimens from patients with CAD as compared with coronary arteries from patients without CAD or cardiovascular risk factors, supporting our concept that reduced EC-SOD activity in response to heparin injection represents reduced total EC-SOD activity of the arterial wall.

In conclusion, the present study demonstrates that vascular EC-SOD activity is reduced in patients with CAD and contributes to impaired NO-mediated vasodilation. Importantly, the present study indicates that reduced EC-SOD activity is associated with increased oxidative stress in vivo, since the effect of the antioxidant vitamin C on NO-mediated vasodilation was negatively correlated to EC-SOD activity. In addition, the present study suggests that EC-SOD activity is increased in young asymptomatic individuals with hypercholesterolemia and may thereby counteract, in part, inactivation of NO by excess radical formation.

References

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