Vitamin C Improves Endothelial Function of Conduit Arteries in Patients With Chronic Heart Failure

Burkhard Hornig, MD; Naoshi Arakawa, MD; Christoph Kohler, BS; Helmut Drexler, MD

Background—Chronic heart failure (CHF) is associated with endothelial dysfunction including impaired endothelium-mediated, flow-dependent dilation (FDD). There is evidence for increased radical formation in CHF, raising the possibility that nitric oxide is inactivated by radicals, thereby impairing endothelial function. To test this hypothesis, we determined the effect of the antioxidant vitamin C on FDD in patients with CHF.

Methods and Results—High-resolution ultrasound and Doppler was used to measure radial artery diameter and blood flow in 15 patients with CHF and 8 healthy volunteers. Vascular effects of vitamin C (25 mg/min IA) and placebo were determined at rest and during reactive hyperemia (causing endothelium-mediated dilation) before and after intraradial infusion of L-nitroarginine (L-NAME) to inhibit endothelial synthesis of nitric oxide. Vitamin C restored FDD in patients with heart failure after acute intraradial administration (13.2±1.7% versus 8.2±1.0%; P<.01) and after 4 weeks of oral therapy (11.9±0.9% versus 8.2±1.0%; P<.05). In particular, the portion of FDD mediated by nitric oxide (ie, inhibited by L-NAME) was increased after acute as well as after chronic treatment (CHF baseline: 4.2±0.7%; acute: 9.1±1.3%; chronic: 7.3±1.2%; normal subjects: 8.9±0.8%; P<.01).

Conclusions—Vitamin C improves FDD in patients with CHF as the result of increased availability of nitric oxide. This observation supports the concept that endothelial dysfunction in patients with CHF is, at least in part, due to accelerated degradation of nitric oxide by radicals. (Circulation. 1998;97:363–368.)

Key Words: endothelium • antioxidants • vasoconstriction • vasodilation

Patients with CHF are characterized by systemic vasoconstriction and a reduced peripheral perfusion. While an increased sympathetic tone and an activated renin-angiotensin system have been proposed to be involved in the reduced vasodilator capacity in heart failure,1 the important role of the endothelium in coordinating tissue perfusion has now been recognized.2 Recent clinical studies have documented endothelial dysfunction of peripheral resistance arteries3 and an impaired flow-dependent, endothelium-mediated dilation of conduit arteries (FDD) in patients with CHF.4 An important functional consequence of endothelial dysfunction is the inability of a vessel to dilate in response to endothelium-derived NO after physiological stimuli, such as increases of blood flow,5 reflecting impaired FDD.

The portion of FDD that is mediated by NO is reduced in patients with CHF compared with that of normal subjects.5 Therefore it has been hypothesized that endothelial dysfunction in CHF is caused by a reduced synthesis of NO possibly due to a reduced NO-synthase gene expression.1 However, other mechanisms may be involved as well, such as a reduced availability of L-arginine or enhanced inactivation of NO by radicals. In this respect, there is evidence that radical formation is increased in patients with CHF,6 raising the possibility that endothelial dysfunction in CHF is, at least in part, due to increased inactivation of NO by oxygen free radicals. Antioxidants such as vitamin C7,8 have recently been shown to prevent the inactivation of NO-mediated vasodilation.11 Accordingly, the present study was designed to determine the effect of vitamin C on NO-mediated FDD in patients with CHF, both after acute intraradial administration and chronic oral treatment with vitamin C.

Methods

Fifteen patients with congestive heart failure in New York Heart Association functional class III with radiological and echocardiographic signs of cardiomegaly and eight healthy volunteers (8 men; age, 27±0.5 years) were studied. Characteristics of heart failure patients are shown in Table 1. All patients were treated with digitalis, angiotensin-converting enzyme inhibitors, and diuretics but no further vasoactive drugs. Digoxin and captopril were stopped 24 hours, diuretics 12 hours, and enalapril 48 hours before measurements. Alcohol and caffeine were prohibited within 12 hours of the study. Patients with diabetes mellitus, hypercholesterolemia (LDL cholesterol >140 mg/dL), arterial hypertension, or significant hematologic, renal, or hepatic dysfunction were excluded by a careful history, physical examination, ECG, and laboratory analysis. Vitamin C is to a large extent excreted by the kidney. An impaired renal function in patients with heart failure might therefore be associated with elevated plasma levels of ascorbic acid leading to a potentiation of the effect of vitamin C. To rule out an impaired renal function as underlying mechanism for the effect of vitamin C on endothelium-mediated vasodilation in all patients with CHF, plasma creatinine and blood urea nitrogen (BUN) were determined before and after 4 weeks of oral vitamin C administration. All subjects were nonsmokers. Written informed consent was obtained for all subjects, and the protocol was approved by the local ethics committee.
Radial artery diameters were measured by a recently developed high-resolution A-mode ultrasonic echo-tracking device (ASULAB) that allows measurements of arterial diameter with a precision of ±2.5 μm, with the use of a novel oversampling technique. This method is well established in our laboratory, as reported recently. Recordings of arterial diameters (15 cm proximal to the wrist) were obtained with a 10-MHz transducer positioned perpendicular to the vessel without direct skin contact, with ultrasonic gel as the transmitting medium. Stereo Doppler guidance was used to ensure a correct vertical position of the probe over the artery. Each diameter measurement represents data digitized over a 4-second period (three to five beats).

Forearm blood flow was measured continuously by an 8-MHz Doppler probe (Vasoscope III) 5 cm proximal to the 10-MHz probe. Arterial blood flow (mL/min) at the mid-femoral level was calculated as the product of blood flow velocity and cross-sectional area. For each velocity value, at least 15 beats were averaged. Wrist arterial occlusion was performed by inflating an occlusion cuff to 40 mm Hg above systolic blood pressure for 8 minutes. After release of the arterial occlusion, arterial diameter was determined at 20-second intervals for 2 minutes, then every 30 seconds until the diameter returned to baseline. Arterial blood pressure and heart rate were measured on the contralateral arm with a commercially available automatic blood pressure cuff.

In previous experiments, using this technology, we have yielded an excellent reproducibility and variability. To this end, 48 patients with heart failure were studied by the same investigator at two occasions separated by 7 days. The two measurements of radial artery diameter and blood flow were compared by linear regression analysis (Pearson’s formula). Reproducibility and variability of radial artery diameter were as follows: baseline diameter: reproducibility, 3.128 ± 0.06 mm versus 3.129 ± 0.06 mm (r = .99; P < .001); variability, 0.04 ± 0.005 mm (ie, 1.3 ± 0.2%); maximal diameter during flow-dependent dilation: reproducibility, 3.394 ± 0.06 mm versus 3.381 ± 0.06 mm (r = .99; P < .001); variability, 0.06 ± 0.0007 mm (ie, 1.7 ± 0.2%); percent change of radial artery diameter during flow-dependent dilation: reproducibility, 8.5 ± 0.6% versus 8.2 ± 0.6% (r = .85; P < .001); variability, 1.9 ± 0.3%; reproducibility of radial artery blood flow was: baseline, 27.6 ± 2.9 mL/min versus 28.2 ± 3.4 mL/min (r = .93; P < .001); variability, 5.3 ± 0.9 mL/min; maximal blood flow during reactive hyperemia: reproducibility, 87.3 ± 8.3 versus 85.4 ± 7.4 mL/min (r = .9; P < .001); variability, 17.3 ± 2.6 mL/min. Furthermore, we have recently shown that reproducibility of radial artery diameter and blood flow is also very good when measurements are repeated after 4 weeks. These findings compare favorably with previously published data from other groups using high-resolution echo-wall tracking systems to measure radial artery diameter and blood flow.

After insertion of a polyethylene catheter into the left brachial artery (nondominant arm), saline was infused. Blood flow velocity was recorded continuously and radial artery diameter was determined every 30 seconds until stable baseline conditions were obtained (approximately 30 minutes). A wrist arterial occlusion was performed and flow-dependent dilation in response to the reactive hyperemic blood flow response was assessed at baseline and after intrarterial infusion of L-NMMA (Calbiochem; 7 μmol/min over 5 minutes). This dose was based on our earlier observations demonstrating that this dose of L-NMMA attenuated FDD by 64 ± 6%. When radial artery diameter and blood flow had returned to baseline values, patients were randomized (ratio 2:1) to receive intraarterial infusion of vitamin C (25 mg/min over 10 minutes) or placebo (saline) followed by determination of FDD with and without confusion of L-NMMA. The dose for intraarterial vitamin C was based on a recent publication demonstrating that this dose of vitamin C improved endothelium-dependent dilation in patients with diabetes mellitus. Finally, all subjects received an intraarterial infusion of SNP (10 μg/min over 5 minutes) to assess endothelium-independent vasodilatory capacity. In 10 patients with heart failure, the protocol was repeated after 4 weeks of oral therapy with vitamin C (n = 5, 1 g twice daily) or placebo (n = 5). These patients were studied 24 hours after the last oral dose of vitamin C or placebo. This interval was chosen, since a recent investigation has shown that 24 hours after 2 g of oral vitamin C ascorbic acid plasma levels had returned to baseline. Since we were interested in evaluating the long-term effect of vitamin C rather than the acute effect of oral dose after long-term therapy, we elected to study these patients 24 hours after the last dose.

Blood flow and diameter data, reported for L-NMMA, vitamin C, placebo, and SNP represent measurements during the last minute of each infusion. All measurements were recorded and subsequently, vessel diameter and blood flow velocity were analyzed by two investigators who were unaware of the sequence of interventions and treatment assignment.

All data are expressed as mean ± SEM. To compare the data at baseline, after L-NMMA, vitamin C or placebo respectively, and SNP within one group of patients, a one-way ANOVA for repeated measures was performed followed by Student-Newman Keuls test. To compare data and in particular NO-mediated FDD between the three groups, we also used a one-way ANOVA followed by Student-Newman-Keuls test. A value of P < .05 was considered to be statistically significant.

Results

Acute Effects of Vitamin C
After wrist occlusion, a significant increase in radial arterial diameter was noted (Table 2), defined as percent increase in vessel diameter. FDD was impaired in patients with CHF compared with normal individuals (Fig 1 and Table 2). Infusion of L-NMMA did not change radial artery diameter under resting conditions (Table 2). However, FDD was significantly reduced by L-NMMA as compared with baseline values (Fig 1 and Table 2). Infusion of vitamin C or placebo did not change radial artery diameter at rest. However, after administration of vitamin C but not after placebo, FDD was significantly increased in patients with CHF (Table 2 and Fig 1).

The portion of FDD that was inhibited by L-NMMA (representing the portion of FDD mediated by NO) was reduced in patients with CHF compared with normal subjects (4.2 ± 0.7% versus 8.9 ± 0.8%; P < .01; Fig 2). After administration of vitamin C, the portion of FDD mediated by NO was

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**TABLE 1. Characteristics of Patients With CHF**

| Age, y | 61 ± 3 | 58 ± 5 |
| Height, cm | 175 ± 3 | 171 ± 8 |
| Weight, kg | 77 ± 4 | 73 ± 7 |
| Left ventricular ejection fraction, % | 22 ± 2 | 20 ± 3 |
| LVEDD, mm | 68 ± 3 | 66 ± 5 |
| LDL cholesterol, mg/dL | 124 ± 18 | 119 ± 21 |
| Cholesterol, mg/dL | 196 ± 10 | 187 ± 14 |
| Creatinine, mg/dL | 0.9 ± 0.2 | 0.8 ± 0.4 |
| Blood urea nitrogen, mg/dL | 56 ± 14 | 60 ± 17 |
| Dilated/ischemic cardiomyopathy, n | 8/2 | 4/1 |

LVEDD indicates left ventricular end-diastolic diameter.

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Selected Abbreviations and Acronyms

CHF = chronic heart failure
FDD = flow-dependent dilation
L-NMMA = N-monomethyl-L-arginine
NO = nitric oxide
SNP = sodium nitroprusside

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**Notes**

1. **Vitamin C Improves Endothelial Function in Heart Failure**

2. **Acute Effects of Vitamin C**

3. **Results**

4. **TABLE 1. Characteristics of Patients With CHF**

5. **Selected Abbreviations and Acronyms**

6. **Notes**

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significantly increased and normalized in patients with CHF (9.1 ± 1.3%; *P < .01 versus baseline; Fig 2).

Intra-arterial SNP significantly increased radial artery diameter to a similar extent in normal individuals and in patients with CHF; there was a similar response to SNP in patients with CHF treated with vitamin C or with placebo (normal individuals: 2.76 ± 0.1 to 3.24 ± 0.1 mm; CHF placebo: 2.80 ± 0.1 to 3.33 ± 0.1 mm; CHF vitamin C: 2.81 ± 0.09 to 3.31 ± 0.14 mm; *P < .05 versus before SNP).

Forearm blood flow at rest was reduced significantly by infusion of L-NMMA but not affected by vitamin C or placebo (Table 3). Maximal forearm blood flow during reactive hyperemia was similar in normal subjects and patients with CHF and was not affected by L-NMMA, vitamin C, placebo, or combination of both (Table 3).

Infusion of SNP increased forearm blood flow to a similar extent in normal individuals and patients with CHF (normal subjects: 22 ± 5 to 39 ± 6 mL/min; CHF placebo: 27 ± 5 to 44 ± 5 mL/min; CHF vitamin C: 24 ± 4 to 43 ± 5 mL/min; *P < .05 versus before SNP for each). Systemic blood pressure and heart rate did not change during the experimental protocol (data not shown).

Effect of Chronic Treatment With Vitamin C
Five patients with CHF were studied again after 4 weeks of oral therapy with vitamin C. There was no change in the severity of left ventricular dysfunction as assessed by echocardiography (left ventricular ejection fraction: 21 ± 3% versus 22 ± 2% after 4 weeks of vitamin C; left ventricular end-diastolic diameter: 67 ± 4 versus 68 ± 5 mm after 4 weeks of vitamin C; n = 5). Radial artery diameter at rest was similar as compared with baseline (2.87 ± 0.3 versus 2.85 ± 0.2 mm).

However, FDD was significantly increased compared with baseline values (11.9 ± 0.9% versus 8.2 ± 1.0%; *P < .05). The portion of FDD mediated by NO was increased as compared with baseline values (7.3 ± 1.2% versus 2.7 ± 0.6%; *P < .01) and similar to values obtained in normal individuals (8.9 ± 0.8%) (Fig 2). After rechallenge with intra-arterial vitamin C, FDD and the portion of FDD mediated by NO were not significantly affected (Fig 2). Effect of SNP on radial artery diameter was similar before and after 4 weeks of oral vitamin C in patients with CHF (n = 5): before vitamin C: control, 2.79 ± 0.1 mm to 3.28 ± 0.1 mm after SNP; *P < .05 versus baseline.

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Figure 1. Change in radial artery diameter (%) during reactive hyperemia (flow-dependent dilation) after wrist occlusion in normal individuals (n = 8) and patients with CHF (n = 10) before (black bars) and after L-NMMA (open bars); effect of intra-arterial infusion of vitamin C.

Figure 2. Change in radial artery diameter (%) during reactive hyperemia that can be blocked by L-NMMA (representing the part of flow-dependent dilation that is mediated by NO) in normal individuals (Normals; n = 8), patients with congestive heart failure at baseline (CHF; subgroup, n = 5), after intra-arterial infusion of placebo (CHF Placebo; n = 5), vitamin C (CHF acute vitamin C; subgroup, n = 5) and after 4 weeks of oral therapy with vitamin C (CHF chronic vitamin C; subgroup, n = 5). *P < .01 vs CHF; #P < .01 vs CHF placebo.
Normal individuals (n=8)

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Patients with CHF (n=10)

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Patients with CHF after 4 weeks of oral vitamin C (n=5)

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RH indicates reactive hyperemia.

*P<.05 vs control.

Effect of intra-arterial SNP on radial artery blood flow was similar before and after 4 weeks of placebo (patients with CHF; n=5): before placebo, 27.0±1 to 44.5±4 mL/min (P<.05 versus before SNP); after 4 weeks of placebo, 25±6 to 45±5 mL/min (P<.05 versus before SNP).

Renal function tests in patients with CHF were unchanged after 4 weeks of oral vitamin C or placebo (each group n=5): before oral vitamin C: creatinine, 0.9±0.2 mg/dL; BUN, 55±14 mg/dL; after 4 weeks of vitamin C: creatinine, 0.9±0.3 mg/dL; BUN, 51±17 mg/dL; placebo-treated group: before: creatinine, 0.8±0.4 mg/dL; BUN, 60±17 mg/dL; after 4 weeks: creatinine, 0.9±0.3 mg/dL; BUN, 55±16 mg/dL).

**Discussion**

The salient finding of the present study is that the impaired FDD in patients with CHF is improved by the antioxidant vitamin C both after intra-arterial administration and 4 weeks of oral therapy, whereas FDD was not affected by vitamin C in healthy volunteers. Furthermore, this study indicates that the beneficial effect of vitamin C on FDD in humans is mediated by an increased availability of NO, since the portion of FDD mediated by NO was increased by vitamin C.

### TABLE 4. Effect of 4 Weeks of Oral Vitamin C and Placebo on Radial Artery Blood Flow at Baseline and During Reactive Hyperemia: Effect of Intra-arterial L-NMMA, Vitamin C, and Placebo

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RH indicates reactive hyperemia.

*P<.05 vs control.
We and others have demonstrated endothelial dysfunction of peripheral conduit and resistance arteries in patients with CHF.34,16 The blunted endothelium-mediated vasodilation in this setting could be attributed to impaired intracellular availability of L-arginine (the precursor of NO), decreased expression of NO synthase (the enzyme that generates NO from L-arginine), impaired receptor-mediated release of NO in response to pharmacological or mechanical stimuli (such as shear stress), or an increased degradation of NO as result of increased endothelial and/or vascular smooth muscle production of oxygen free radicals.

The latter possibility is supported by previous studies indicating increased radical formation in heart failure both in the circulation9 and the heart.17 Belch and coworkers8 measured plasma lipid peroxides as a marker of free radical production in the circulation and demonstrated that in patients with CHF, plasma lipid peroxides are increased compared with normal control subjects. Furthermore, they have shown that there is an inverse correlation between left ventricular ejection fraction and plasma lipid peroxide levels.8 One possible source of increased radical formation in heart failure might be the cardiac myocyte. In this respect, Mohazzab and coworkers17 have recently shown that the basal release of superoxide anion (O₂⁻) is increased in failing human cardiac myocytes, apparently due to increased O₂⁻-production by mitochondria and NADH-oxidoreductases. In addition, myocardial antioxidant reserve may be reduced in heart failure, as suggested by increased protein oxidation in cardiac myocytes in heart failure and its prevention by concomitant therapy with the antioxidant vitamin E.18 Leukocytes may represent another potential source of increased radical formation in heart failure.19 The results of these previous studies support the notion that free radical formation is increased in CHF. Since enhanced generation of free radicals inactivate NO, the availability of NO and its release during FDD would be impaired in CHF. Thus it is conceivable that increased radical formation is involved in the pathogenesis of endothelial dysfunction in patients with CHF. In the present study, intra-arterial infusion of vitamin C completely restored FDD in patients with CHF. In particular, the portion of FDD mediated by NO (ie, the part of FDD that was blocked by L-NMMA) was normalized immediately after intra-arterial infusion of vitamin C. Vitamin C has been shown to act as a strong water-soluble antioxidant in vitro and in vivo,9,10 and its intra-arterial application has been shown to improve endothelial dysfunction in patients with diabetes,14 another clinical entity in which enhanced radical formation has been reported. Therefore our observation would support the notion that an increased inactivation of NO was involved in the impaired NO-mediated FDD in our patients with heart failure. Interestingly, the beneficial effect of vitamin C was maintained after a 4-week treatment with 2 g per day given orally. These first preliminary observations during long-term supplementation need to be confirmed in a larger group of patients; however, if confirmed, they may have important clinical implications.

We cannot exclude the possibility that vitamin C might directly improve heart failure (thereby secondarily improving vascular function) and not specifically endothelium-mediated vasodilation. However, the acute effect of vitamin C on endothelium-mediated vasodilation cannot be explained by changes in the severity of heart failure. It is highly unlikely that vitamin C given acutely into the brachial artery results in a major improvement in central hemodynamics in patients with NYHA class III heart failure. Notably, neither the acute intra-arterial infusion of vitamin C nor the chronic oral treatment with vitamin C had any effect on systemic blood pressure, heart rate, radial artery blood flow, or radial artery resting diameter. In addition, there was no change of echocardiographic characteristics of left ventricular function after 4 weeks of vitamin C in any of these patients. Taken together, we think that the hypothesis that vitamin C improves heart failure per se is unlikely and cannot explain our results. However, a final answer to this question awaits further studies involving a large patient population.

It is important to note that the maximal reactive hyperemic blood flow response after wrist occlusion was not different at control, vitamin C, placebo, or L-NMMA. Therefore the stimulus that caused endothelium-mediated dilation was similar during the different interventions. Furthermore, an unspecific attenuation of vasodilator capacity during heart failure appears to be unlikely because the vasodilator response to SNP was preserved in our patients compared with the normal volunteers. In addition, an effect of vitamin C on vascular smooth muscle function rather than the endothelium appears to be unlikely, because vitamin C per se did not affect radial artery diameter and blood flow and the vasodilator response to SNP was similar in patients treated with vitamin C and placebo. These results are consistent with the notion that in patients with CHF, inactivation of NO by oxygen free radicals occurs within the vascular wall, that is, between the endothelium, where NO is synthesized, and the vascular smooth muscle, the target organ. The enhanced inactivation of NO leads to a reduced availability of NO for the vascular smooth muscle, which per se has a preserved vasodilatory capacity as indicated by a preserved vasodilation in response to excessive doses of exogenously administered NO. Our observations are consistent with recent reports using SNP and vitamin C in patients with coronary artery disease or diabetes.14,15 Our observations as well as reports by others therefore suggest that using excessive doses of exogenous NO donors appears to overcome an increased vascular stress. We therefore think that during physiological conditions in humans, endothelium-mediated vasodilation is a question of balance between NO availability and NO inactivation by oxygen free radicals within the vascular wall as discussed recently.20 This balance, however, may be lost in pathophysiological conditions; that is, our results indicate a pathophysiological role of increased oxidative stress in CHF.

It is also unlikely that a correction of an absolute vitamin C deficiency may explain our findings, because it has recently been shown that there is no correlation between baseline vitamin C plasma levels, endothelial dysfunction, or improvement with treatment.15 Therefore, our results support the concept that the impaired NO-mediated FDD in CHF is, at least in part, due to increased inactivation of endothelium-derived NO by radicals and that vitamin C exerts its antioxidant properties within the vasculature by directly scavenging
oxygen derived free radicals\(^{20}\) such as superoxide anion or hydroxyl radicals.

The present study was not designed to elucidate the underlying mechanism(s) leading to increased oxidative stress in CHF. However, there is evidence that angiotensin II, whose plasma and tissue levels are typically elevated in CHF, activates NADH/NADPH-driven oxidases located within the vascular wall\(^{21}\) that appear to be the main enzymes responsible for vascular synthesis of radicals within the vessel wall. However, other factors may be involved as well, such as increased levels of cytokines such as tumor necrosis factor-\(\alpha\), which in turn may enhance oxidative stress.

The functional significance of the beneficial effect of vitamin C on large-artery function in patients with CHF remains to be fully determined. It is important to note, however, that large arteries are more than passive conduits\(^{22}\) and that NO appears to be involved in the regulation of the passive elastic properties of the arterial wall, thereby controlling the mechanical properties of the arterial wall and contributing to the dynamic control of cardiac performance. Previous studies have shown that the compliance of peripheral conduit arteries is reduced in patients with CHF.\(^{23}\) Furthermore, there is evidence that endothelial control of conduit artery distensibility is impaired in patients with CHF.\(^{24}\) Despite the fact that our observations are limited to the radial artery, it is conceivable that if similar changes were found to be present throughout the large arterial tree, they would increase the impedance to the failing left ventricle. Moreover, there is evidence that an intact endothelium appears to protect large vessels against constrictor effects of catecholamines during exercise.\(^{25}\)

In conclusion, the present study demonstrates that endothelial dysfunction in patients with congestive heart failure can be improved and normalized by acute intra-arterial as well as by chronic oral treatment with the antioxidant vitamin C. Our observations support the notion that CHF is associated with increased radical formation which, in turn, affects endothelium-mediated vasomotor tone. Our results extend previous findings reporting beneficial effects of acute administration of vitamin C on endothelium-mediated vascular relaxation in patients with coronary artery disease, diabetes, or chronic smoking. Importantly, the present study indicates that the beneficial effect is related to increased availability of NO. While our initial observations suggest that this beneficial effect may be sustained during long-term supplementation, this finding needs to be confirmed in large-scale clinical trials.

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References

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