Redox modulation of the inotropic response to dobutamine is impaired in patients with heart failure

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Mak, Susanna, and Gary E. Newton. Redox modulation of the inotropic response to dobutamine is impaired in heart failure. Am J Physiol Heart Circ Physiol 286: H789–H795, 2004. First published October 9, 2003; 10.1152/ajpheart.00633.2003.—It has been suggested that oxidative stress contributes to impaired left ventricular (LV) contractility in the setting of heart failure (HF). To test this hypothesis, we studied the effect of an antioxidant on contractility at rest and in response to dobutamine in 10 HF patients. We hypothesized that vitamin C would augment contractility in HF and that this effect would be of a greater magnitude in HF patients compared with patients with normal LV (NLV) function. Data from 10 patients with NLV function who participated in this study are included in this report and have been published elsewhere. A micro-manometer-tipped catheter was introduced into the LV. In the experimental protocol, an infusion catheter was positioned in the left main coronary artery. The peak positive rate of change of LV pressure (LV dP/dt) was measured in response to the intravenous infusion of dobutamine before and during the intracoronary infusion of vitamin C (96 mg/min). Vitamin C had no effect on basal LV dP/dt in either HF or NLV groups. The infusion of vitamin C augmented the LV dP/dt response to dobutamine by 22 ± 4% in the NLV function group. In contrast, vitamin C had no effect on the inotropic response to dobutamine in the HF group. In the control protocol, without vitamin C, no differences were observed between responses to two sequential dobutamine infusions in either group (HF, n = 11; NLV, n = 9). Therefore, a positive effect of vitamin C on contractility was limited to patients with NLV function. The absence of this effect in HF patients may suggest that normal redox responsiveness is lost in this disease state.

antioxidants; contractility; receptors; β-adrenergic

REACTIVE OXYGEN SPECIES (ROS) are produced ubiquitously during the course of normal cellular oxidative metabolism. It has been suggested that patients with heart failure (HF) may exhibit heightened oxidative stress, as evidence by increased plasma markers of lipid peroxidation (7, 22, 31). Of these, aldehyde products of lipid peroxidation in plasma correlate inversely with left ventricular (LV) contractility (26). It has also been demonstrated that impairment of ventricular function in experimental HF is correlated with evidence for oxidative stress in the myocardium (6, 18, 51) and that gross free radical excess causes overt β-adrenergic receptor dysfunction (35–37). Recently, two separate groups of investigators have demonstrated that allopurinol, a xanthine oxidase (XO) inhibitor, augments the inotropic responses to adrenergic stimulation in a dog model of HF (9, 57). In both experiments, the investigators did not determine whether the positive inotropic effect of allopurinol was due to an antioxidant mechanism (i.e., suppression of XO-mediated superoxide production) or another action of allopurinol.

The purpose of this experiment was to explore redox modulation of basal contractility as well as the inotropic response to adrenergic stimulation in the setting of HF. Vitamin C is a potent aqueous phase antioxidant that is safe for parenteral infusion in humans (28). It has been demonstrated that vitamin C effectively suppresses lipid peroxidation in human plasma (10) and that vitamin C is an effective scavenger of the superoxide anion radical (20), an important ROS in aerobic organisms. To assess whether any effect of vitamin C was specific to HF, the experimental protocol prespecified inclusion of a patient group with normal LV (NLV) function as well as a group with HF. The data from the NLV function group have been published elsewhere (27). We hypothesized that vitamin C would augment basal and/or dobutamine-stimulated contractility in HF and that this effect would be of greater magnitude in HF patients compared with patients with NLV function. Therefore, to appropriately interpret our data from HF patients, previously published data from patients with NLV function are presented in this report.

METHODS

Study Population

HF patients. Twenty-one HF patients referred for elective diagnostic heart catheterization participated in this study. All patients were being evaluated for stable New York Hospital Association II-III HF and none had significant vascular disease. The experimental protocol (n = 10, 8 men and 2 women, mean age 54 ± 3 yr) included two patients with stable coronary artery disease and eight patients with normal coronary arteries. The left anterior descending coronary artery was unobstructed in all patients. Their mean LV ejection fraction measured by radionuclide ventriculography was 26 ± 3%. Two patients had treated hypertension, one patient had hypercholesterolemia controlled by medical therapy, and three patients had non-insulin-dependent diabetes. Medical therapy for HF included angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (n = 10), diuretics (n = 6), digoxin (n = 7), and β-blockers (n = 6). The control protocol (n = 11, 8 men and 3 women, mean age 56 ± 4 yr) included four patients with stable coronary artery disease and seven patients with normal coronary arteries. Their mean LV ejection fraction measured by radionuclide ventriculography was 23 ± 2%. Six patients had treated hypertension, two patients had hypercholesterolemia controlled by medical therapy, and three patients had non-insulin-dependent diabetes. Medical therapy for HF included ACE inhibitors or angiotensin II receptor blockers (n = 11), diuretics (n = 9), digoxin (n = 8), and β-blockers (n = 2). All patients...
in this study were nonsmokers. Vitamin and/or antioxidant supplements were withheld for at least 7 days before the study.

**NLV function patients.** We have previously reported on these 19 patients (n = 10, mean age 55 ± 4 yr, experimental protocol; n = 9, mean age 52 ± 4 yr, control protocol) with NLV function (27). All patients were being evaluated for a chest pain syndrome, and no patient had significant valvular disease or ventricular dysfunction detected by two-dimensional echocardiography. There were no significant differences between patients with NLV function and patients with HF with respect to age and comorbid conditions.

This study was approved by the University of Toronto Ethical Review Committee for Experimentation Involving Human Subjects, and all patients gave written informed consent.

**Cardiac Catheterization Procedure and Hemodynamic Measurements**

Patients were awake, nonsedated, and studied after a diagnostic left and right heart catheterization via the femoral approach. All medications were withheld on the morning of the investigation. In all patients, a 7-Fr micromanometer-tipped catheter (Millar; Houston, TX) was advanced via the right femoral artery into the LV for measurement of LV pressure. Femoral artery pressure was monitored via a 7-Fr sidearm sheath (Terumo Medical; Elkton, MD). In the experimental protocol, a 6-Fr L4 Judkins catheter (Cordis Laboratories; Miami, FL) was advanced from the opposite femoral artery to the ostium of the left main coronary artery. When vitamin C was not being infused, the catheter was continuously flushed with the vehicle for drug infusion (0.9% saline) at a rate of 1.6 ml/min with the use of a Harvard infusion pump.

The ECG, femoral artery pressure, LV pressure, and peak positive rate of change of LV pressure (LV \(dP/dt\)) were acquired using methods previously described (26, 27).

**Study Protocol**

All patients received heparin (5,000 units iv) and a rest period after placement of the catheters. In the experimental protocol, hemodynamic and inotropic measurements were made sequentially under several conditions. First, the intracoronary infusion of the vehicle solution (0.9% saline) was maintained at 1.6 ml/min (baseline). Second, dobutamine (Lilly; Indianapolis, IN) diluted in 5% dextrose-solution (0.9% saline) was maintained at 1.6 ml/min (baseline). Similarly, in the experimental protocol, the intracoronary infusion of vitamin C was selected to approximate an intracoronary concentration of between 1 and 10 mmol, assuming coronary blood flow of 100 ml/min. This concentration is sufficient to achieve a 25% rise in LV \(dP/dt\) and until LV \(dP/dt\) remained stable (±5%) for three consecutive measurements each separated by 1 min (Dob-1). Third, the dobutamine infusion was stopped for at least 10 min and peak LV \(dP/dt\) was similar to baseline (within 10%) (Recontrol). Fourth, vitamin C (ascorbic acid injection, 500 mg/2 ml, pH adjusted with sodium hydroxide, Sabex; Boucherville, QC, Canada) diluted in the vehicle solution (60 mg/ml) was infused into the left main coronary artery for 10 min at a rate of 1.6 ml/min (96 mg/min) (Vit C). The infusion rate of vitamin C was selected to approximate an intracoronary concentration of between 1 and 10 mmol, assuming coronary blood flow of 100 ml/min. This concentration is sufficient to inhibit free radical activity in vitro and in vivo (10, 20, 49). Finally, during the continued intracoronary infusion of vitamin C, dobutamine was reinfused intravenously at the same rate as Dob-1 until peak LV \(dP/dt\) remained stable (±5%) for three consecutive measurements each separated by 1 min (Dob-2 + Vit C).

To confirm that any augmentation of the LV \(dP/dt\) response to the second dobutamine infusion was not an aftereffect of the previous dobutamine infusion, a similar control protocol was designed with the following exceptions: 1) the vitamin C infusion was replaced by a second recontrol (Recontrol-2) of similar duration and 2) the second intravenous dobutamine infusion (Dob-2) therefore occurred without coinfusion of vitamin C.

**Statistical Analysis**

All data are presented as means ± SE. A statistical software package was used for all analyses (SigmaStat version 1.0, Jandel). Raw hemodynamic data were analyzed using a two-way ANOVA with protocol (experimental or control) as one factor and protocol condition (baseline, Dob-1, Recontrol, Vit C/Recontrol-2, or Dob-2 + Vit C/Dob-2) as the second factor. Absolute and percent changes of LV \(dP/dt\) in response to serial dobutamine infusions were compared between patients participating in the experimental protocol and those participating in the control protocol by use of a paired two-way ANOVA. For patients who participated in the vitamin C experimental protocol, serial dobutamine responses were also compared between HF patients and NLV function patients with the use of a paired two-way ANOVA. Post hoc testing was performed using the Student-Newman-Keuls test. *p* < 0.05 was required for statistical significance.

**RESULTS**

**Baseline Characteristics**

No significant differences in baseline hemodynamics were observed between patients participating in the experimental or control protocol in either HF or NLV function groups (Table 1).

**Effect of Vitamin C on Basal and Dobutamine-Stimulated LV Contractility**

In HF patients participating in the control protocol, dobutamine (mean infusion rate 5.0 ± 0.6 \(\mu g\cdot kg^{-1}\cdot min^{-1}\)) increased LV \(dP/dt\) by 30 ± 3%. The second infusion of dobutamine resulted in a 31 ± 4% increase in LV \(dP/dt\) that was not significantly different from that elicited by the first infusion. Similarly, in NLV function patients (27) participating in the control protocol, there were no differences between the inotropic responses to the first (39 ± 4% increase in LV \(dP/dt\)) and second (35 ± 4% increase in LV \(dP/dt\)) infusion of dobutamine (mean infusion rate 2.8 ± 0.3 \(\mu g\cdot kg^{-1}\cdot min^{-1}\)) (see Table 2 and Fig. 1).

In HF patients and NLV function patients (27) participating in the experimental protocol, the intracoronary infusion

<table>
<thead>
<tr>
<th>HF Patients</th>
<th>NLV Function Patients</th>
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<td>Control protocol (n = 11)</td>
<td>Experimental protocol (n = 10)</td>
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<tr>
<td>Control protocol (n = 9)</td>
<td>Experimental protocol (n = 10)</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>80 ± 5</td>
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<td>FA systolic pressure, mmHg</td>
<td>132 ± 7</td>
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<td>FA diastolic pressure, mmHg</td>
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<tr>
<td>RAP, mmHg</td>
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<td>PAP mean, mmHg</td>
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<td>Cardiac output, l/min</td>
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<tr>
<td>LVEDP, mmHg</td>
<td>16 ± 3</td>
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<tr>
<td>LV systolic pressure, mmHg</td>
<td>121 ± 6</td>
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<td>LV + dP/dt, mmHg/s</td>
<td>921 ± 88</td>
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Values are means ± SE; n, no. of patients. FA, femoral artery; RAP, right atrial pressure; PAP, pulmonary artery pressure; LVEDP, left ventricular (LV) end-diastolic pressure; LVSP, LV systolic pressure; LV + dP/dt, peak positive rate of change of LV pressure. Data from normal LV (NLV) function patients taken from Mak and Newton (27).
of vitamin C alone had no effect on basal contractility (see Table 2).

In HF patients participating in the experimental protocol, the first infusion of dobutamine (mean infusion rate 4.0 ± 0.5 μg·kg⁻¹·min⁻¹) yielded a 28 ± 2% increase in LV +dP/dt, whereas the coinfusion of dobutamine and intracoronary vitamin C yielded a 32 ± 3% increase in LV +dP/dt (P = not significant). The inotropic responses to sequential dobutamine infusions were similar between HF patients participating in either the experimental or control protocols. Thus vitamin C had no significant effect on the inotropic response to dobutamine in HF patients (see Table 2 and Fig. 1).

In NLV function patients (27) participating in the experimental protocol, the first infusion of dobutamine (3.4 ± 0.4 μg·kg⁻¹·min⁻¹) yielded a 39 ± 5% increase in LV +dP/dt, whereas the coinfusion of dobutamine and intracoronary vitamin C yielded a 47 ± 7% increase in LV +dP/dt (P < 0.05). This represented a 22 ± 4% augmentation in the inotropic response to dobutamine associated with the coinfusion of vitamin C in this patient population (see Table 2 and Fig. 1).

Effect of Vitamin C and Dobutamine on Other Hemodynamic Variables

In the HF patients participating in the experimental protocol, as expected, intravenous dobutamine caused systolic blood pressure and LV systolic pressure to increase. Vitamin C had no effect on the response to dobutamine with respect to heart rate, systolic or diastolic blood pressure, LV end-diastolic pressure, or LV systolic pressure (see Table 3). Similarly, in the NLV function patients (27), intravenous dobutamine caused systolic blood pressure and LV systolic pressure to increase. Again, vitamin C had no effect on the response to dobutamine with respect to heart rate, systolic or diastolic blood pressure, LV end-diastolic pressure, or LV systolic pressure (see Table 4). Therefore, the positive impact of vitamin C on the inotropic response to dobutamine in patients with NLV function occurred without any change in loading conditions or chronotropic state.

Effect of Vitamin C on Dobutamine-Stimulated LV Contractility: NLV Function Versus HF

We compared the effect of vitamin C on dobutamine-mediated inotropic responses found in HF patients with the responses documented in patients with NLV function. The addition of vitamin C augmented the LV +dP/dt response to dobutamine by 22 ± 4% in patients with NLV function compared with only 3 ± 1% in patients with HF (Fig. 2). Similar differences in the effect of vitamin C on inotropic responses to dobutamine were observed when absolute changes in LV +dP/dt were compared.
ergic receptor density and function to postreceptor events (21), or direct perfusion by hydrogen peroxide (21, 36) lead to overt adrenergic dysfunction, although these models may not be generalizable to chronic HF. In multiple animal models of chronic HF, free radical excess and/or impaired antioxidant defenses have been implicated as a mechanism by which ventricular dysfunction progresses (6, 18, 51, 52). Relevant to this discussion, Liang et al. (24) have demonstrated in healthy ferrets that chronic catecholamine excess mimics the myocardial adrenergic abnormalities of HF, and these adrenergic derangements can be prevented by treatment with antioxidant vitamins. Taken together, the demonstration that free radical excess acutely impairs adrenergic pathways and the evidence that oxidant injury occurs in the failing myocardium suggested that antioxidant administration would have a positive effect on stimulated contractility in the failing heart.

Therefore, several explanations for the lack of effect of vitamin C on inotropic responses to dobutamine in HF patients observed in this experiment merit consideration. It is possible that free radical activity in the failing ventricle is sufficiently increased as to be resistant to the antioxidant intervention. However, vitamin C was administered in supraphysiological concentration by high-affinity protein binding (25). Experimentally, a prooxidant effect of vitamin C could not be demonstrated even under conditions of transition metal supplementation (1, 42, 43, 54), and at present the hypothesis that vitamin C augments contractility is associated with increased endogenous free radical activity. An intriguing hypothesis suggests that endogenous ROS, as a product of myocardial O2 consumption, may function as a physiological messenger, as well as mediators of cellular damage.

Although patients with HF may be expected to exhibit responses to antioxidant administration that are different from patients with NLV function, the lack of impact of vitamin C on basal or stimulated contractility was surprising. It has been shown that HF patients have increased serum markers of oxidative stress (7, 22, 31) and we have demonstrated that these indexes are inversely correlated with LV contractility (26). Most in vitro and animal in vivo experiments indicate that adrenergic-stimulated contractility in the failing heart is redox sensitive. The evidence suggests that free radical species impair several components of adrenergic pathways from β-adrenergic receptor density and function to postreceptor events (21, 36–38, 58). Relatively toxic concentrations of radical species produced by ischemia-reperfusion (37, 38, 58), xanthine/XO (21), or direct perfusion by hydrogen peroxide (21, 36) lead to overt adrenergic dysfunction, although these models may not be generalizable to chronic HF. In multiple animal models of chronic HF, free radical excess and/or impaired antioxidant defenses have been implicated as a mechanism by which ventricular dysfunction progresses (6, 18, 51, 52). Relevant to this discussion, Liang et al. (24) have demonstrated in healthy ferrets that chronic catecholamine excess mimics the myocardial adrenergic abnormalities of HF, and these adrenergic derangements can be prevented by treatment with antioxidant vitamins. Taken together, the demonstration that free radical excess acutely impairs adrenergic pathways and the evidence that oxidant injury occurs in the failing myocardium suggested that antioxidant administration would have a positive effect on stimulated contractility in the failing heart.

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<th>Table 3. Effect of vitamin C on hemodynamic responses to dobutamine in HF patients</th>
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<tr>
<td>Heart rate, beats/min</td>
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<td>FA systolic pressure, mmHg</td>
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Values are means ± SE. *P < 0.05 vs. baseline.

DISCUSSION

The observation that the inotropic response to β-adrenergic stimulation with dobutamine was augmented by the intracoronary infusion of vitamin C in patients with NLV function (27) provides compelling support for the hypothesis that ventricular function in humans can be modulated by redox environment. Somewhat unexpectedly, a similar impact of vitamin C on the inotropic response to dobutamine was not observed in HF patients.

In patients with NLV function (27), the observation that intracoronary vitamin C augmented the inotropic response to dobutamine but did not affect basal LV +dP/dt suggested that augmented contractility is associated with increased endogenous free radical activity. An intriguing hypothesis suggests that endogenous ROS, as a product of myocardial O2 consumption, may function as a physiological repressor on stimulated ventricular contractility (34). This concept has been investigated in striated muscle where it has been demonstrated that increased force development is a stimulus to the generation of ROS, likely because of increased O2 consumption (30, 46, 55). Furthermore, it has been demonstrated that the generation of ROS modulates contractile function of the diaphragm and is an important mediator of muscle fatigue (45, 53). These reports are consistent with the concept that ubiquitously produced free radicals can function as physiological messengers, as well as mediators of cellular damage.

Although patients with HF may be expected to exhibit responses to antioxidant administration that are different from patients with NLV function, the lack of impact of vitamin C on basal or stimulated contractility was surprising. It has been shown that HF patients have increased serum markers of oxidative stress (7, 22, 31) and we have demonstrated that these indexes are inversely correlated with LV contractility (26). Most in vitro and animal in vivo experiments indicate that adrenergic-stimulated contractility in the failing heart is redox sensitive. The evidence suggests that free radical species impair several components of adrenergic pathways from β-adrenergic receptor density and function to postreceptor events (21, 36–38, 58). Relatively toxic concentrations of radical species produced by ischemia-reperfusion (37, 38, 58), xanthine/XO (21), or direct perfusion by hydrogen peroxide (21, 36) lead to overt adrenergic dysfunction, although these models may not be generalizable to chronic HF. In multiple animal models of chronic HF, free radical excess and/or impaired antioxidant defenses have been implicated as a mechanism by which ventricular dysfunction progresses (6, 18, 51, 52). Relevant to this discussion, Liang et al. (24) have demonstrated in healthy ferrets that chronic catecholamine excess mimics the myocardial adrenergic abnormalities of HF, and these adrenergic derangements can be prevented by treatment with antioxidant vitamins. Taken together, the demonstration that free radical excess acutely impairs adrenergic pathways and the evidence that oxidant injury occurs in the failing myocardium suggested that antioxidant administration would have a positive effect on stimulated contractility in the failing heart.

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Table 4. Effect of vitamin C on hemodynamic responses to dobutamine in NLV function patients

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<td>Heart rate, beats/min</td>
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Values are means ± SE. Data are taken from Mak and Newton (27). *P < 0.05 vs. baseline.
HF patients with a muscarinic agonist (32). Similarly, Hare et al. (14) have demonstrated augmentation of the inotropic response to dobutamine by the acute administration of L-arginine, an inhibitor of nitric oxide (NO) synthase.

Another interpretation of the differing responses observed between patients with and without HF to antioxidant administration is that sensitivity to redox environment is a physiological characteristic of the myocardium that is somehow lost or impaired in the failing heart. There is accumulating evidence that redox environment may be integrated with the activity of the L-arginine/NO synthase (NOS) pathway has been demonstrated in HF (8). Moreover, it has been demonstrated that endogenous NOS activity limits the contractile response to adrenergic stimulation. This modulatory effect of NO was observed in HF patients but was not evident in humans with preserved LV function (13). Thus the negatively inotropic influence of NO on the failing ventricle is of great relevance to the control of striated muscle function (44).

The potential interaction between antioxidants and the L-arginine/NOS pathway in our studies of contractility requires further scrutiny in light of recent information showing that both antioxidants and NO may have important favorable consequences for mechanoenergetic coupling in HF. Inotropic agents such as dobutamine worsen the imbalance between increased myocardial O2 consumption and impaired LV work in the failing heart, further worsening myocardial efficiency (16, 50). It has been demonstrated that the negative effect of NO on the inotropic response to dobutamine in HF results in preservation of myocardial efficiency in the face of inotropic stimulation (50). More recently, XO inhibition with allopurinol has been demonstrated to enhance basal myocardial efficiency in humans with HF (4). In companion experiments of a dog model of HF, a similar benefit of allopurinol (9, 47) and vitamin C (47) on myocardial efficiency suggested the relevant effect of XO inhibition was meaningful suppression of superoxide production. Moreover, these investigators demonstrated that improved myocardial efficiency was related to potentiation of NO activity by antioxidant administration (47). Of major importance to our experiments, improved myocardial efficiency by allopurinol was achieved in humans with HF by decreased O2 consumption rather than any change in LV performance, including contractility (4). Therefore, a beneficial effect of vitamin C in preserving myocardial efficiency with dobutamine stimulation would not be detected in our experiments because myocardial O2 consumption was not measured.

Some methodological issues merit discussion. Vitamin C may augment endothelium-dependent vasodilation of the coronary vasculature in response to the potential increase in shear stress associated with dobutamine (33). However, such an effect would have been expected to augment inotropic responses by Gregg’s phenomenon. Importantly, dobutamine was infused by the intravenous route to maintain consistent intracoronary concentration, regardless of changes in coronary flow. The experimental group exhibited a greater pressor response to dobutamine than did the control group. However, vitamin C did not measurably alter loading conditions, nor were there any differences in hemodynamic responses between the first and second dobutamine infusion in either the experimental or the control group. Medical therapy for HF was withheld only on the morning of the study to ensure clinical stability and included β-blockers and/or ACE inhibitors for the majority of the patients studied. These medications may have antioxidant properties and may have therefore blunted any effect of vitamin C. However, we observed an effect of vitamin C in preserving myocardial efficiency with dobutamine stimulation despite treatment with β-blockers and/or ACE inhibitors in the majority of this group (27).

The results of the present study refute the hypothesis that an antioxidant intervention alone acutely modifies basal or dobutamine-stimulated contractility in humans with HF. Importantly, the finding that vitamin C augments inotropic responses in patients with NLV function suggests that absence of this effect is abnormal in HF. The demonstration that responses to adrenergic agonists are inhibited by NOS activity in humans with HF (14) raises the intriguing hypothesis that an inotropic effect of an antioxidant may be counterbalanced by the potentiation of NO (17, 19), possibly as a means of preserving NO, and their interaction also play an important role in the control of striated muscle function (44).
myocardial efficiency. The interaction between ROS and NO as regulators of LV performance and mechanoenergetics in the setting of HF requires further exploration.

GRANTS

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