Increased Sensitivity to Nitric Oxide Synthase Inhibition in Patients With Heart Failure
Potentiation of β-Adrenergic Inotropic Responsiveness

Joshua M. Hare, MD; Michael M. Givertz, MD; Mark A. Creager, MD; Wilson S. Colucci, MD

Background—We previously showed that cardiac nitric oxide (NO) inhibits the positive inotropic response to β-adrenergic stimulation in humans with left ventricular (LV) dysfunction. Whether this effect is specific to heart failure per se or is a generalized feature of normal human myocardium is unknown. We therefore tested the hypothesis that inhibition of cardiac NO potentiates the positive inotropic response to β-adrenergic stimulation in patients with symptomatic LV failure but not in subjects with normal LV function.

Methods and Results—We studied 11 patients with LV failure due to idiopathic dilated cardiomyopathy and 7 control subjects with normal LV function. The β-adrenergic agonist dobutamine was infused via a peripheral vein before and during concurrent intracoronary artery infusion of acetylcholine, which activates the agonist-coupled isoforms of NO synthase, and N°-monomethyl-l-arginine, which inhibits all isoforms of NO synthase. Changes in contractility were assessed by measuring the peak rate of rise of LV pressure (+dP/dt). Dobutamine increased +dP/dt by 40±6% and 73±14% in patients with heart failure and control subjects, respectively. Acetylcholine inhibited the +dP/dt response to dobutamine to a similar degree in patients with heart failure and control subjects (−39±8% and −31±4%, respectively; P=NS). Infusion of N°-monomethyl-l-arginine potentiated the +dP/dt response to dobutamine by 51±15% (P=.01 versus dobutamine) in patients with heart failure but had no effect in control subjects (−6±4%; P=NS versus dobutamine; P=.0002 versus heart failure patients).

Conclusions—Inhibition of cardiac NO augments the positive inotropic response to β-adrenergic receptor stimulation in patients with heart failure due to idiopathic dilated cardiomyopathy but not in control subjects with normal LV function. (Circulation. 1998;97:161-166.)

Key Words: nitric oxide ■ heart failure ■ cardiomyopathy ■ contractility ■ receptors, adrenergic, β

Nitric oxide is a ubiquitous signaling molecule formed by the action of a family of at least three NOSs on l-arginine. At least two isoforms of NOS, termed NOS2 and NOS3, are present in human myocardium. NOS2 is not expressed in normal myocardium, but it is synthesized in response to inflammatory cytokines such as tumor necrosis factor-α, resulting in high levels of myocardial NO production. In contrast to NOS2, NOS3 is expressed constitutively in normal myocardium and cardiac myocytes, in which its activity is increased by a variety of agonists (eg, acetylcholine).

Both the induction of NOS2 by inflammatory cytokines and the activation of constitutively expressed NOS3 by muscarinic cholinergic agonists can inhibit the contractile response to β-adrenergic stimulation in cardiac myocytes and myocardium in vitro (reviewed in Ref. 9). There is evidence that the expression and activity of NOS2 are increased in myocardium obtained from patients with severe heart failure. Consistent with this thesis, we previously found that the intracoronary infusion of the NOS inhibitor L-NMMA potentiated the positive inotropic response to β-adrenergic receptor stimulation in patients with various degrees of LV dysfunction.

However, studies have not consistently shown that NOS2 activity is increased in failing human myocardium. Furthermore, inhibition of NOS potentiated the inotropic response to β-adrenergic stimulation in normal cultured cardiac myocytes, and we found that intracoronary infusion of the NOS inhibitor L-NMMA potentiated the positive inotropic response to the β-adrenergic agonist isoproterenol in normal dogs. Therefore, it is possible that our previous observation was not related to heart failure per se but reflects a general property of normal human myocardium.

To address this important issue, we hypothesized that increased myocardial NOS activity attenuates the positive inotropic response to β-adrenergic receptor stimulation in humans with LV failure but not in those with normal LV function. To test this hypothesis and to examine the relative roles of NOS2 and NOS3 in failing myocardium, we deter-
mined the positive inotropic response to the β-adrenergic agonist dobutamine alone and during concurrent intracoronary infusion of L-NMMA, an inhibitor of all isoforms of NOS in patients with LV failure due to idiopathic dilated cardiomyopathy and control subjects with normal LV function. In addition, because an alternative mechanism for increased NO in failing myocardium is increased expression of NOS3 (rather than NOS2), we examined the positive inotropic response to dobutamine during concurrent intracoronary infusion of acetylcholine, which activates NOS3 but not NOS2.

Methods

Study Population

The study population consisted of 18 adults (8 men and 10 women; mean age, 49±14 years) who were undergoing diagnostic cardiac catheterization. All were in sinus rhythm and were found to be free of significant coronary artery disease during the diagnostic catheterization. Patients in the heart failure group (n = 11) were referred for catheterization for evaluation of heart failure and were diagnosed with idiopathic dilated cardiomyopathy through exclusion of coronary artery disease or other known causes of dilated cardiomyopathy. Patients were in New York Heart Association functional class II (n = 3), III (n = 2), or IV (n = 6). Cardiovascular medications in this group consisted of: diuretics (n = 7), digitalis (n = 9), an ACE inhibitor (n = 11), and other vasodilators (n = 2). The control group consisted of 7 patients who were being evaluated for chest pain (n = 3) or single-lung transplantation (n = 4). All were free of coronary artery disease and had normal LV function and hemodynamics. Cardiovascular medications in this group consisted of: β-blockers (n = 2) and calcium channel antagonists (n = 4). For both groups, medications were withheld at least 12 hours before study. Partial data for 6 of the heart failure patients were reported previously. The study protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women’s Hospital, and written informed consent was obtained before study.

Hemodynamic Measurements

Before the experimental protocol, all subjects underwent routine diagnostic left and right heart catheterization via the femoral approach. Coronary angiography was performed with nonionic contrast media, and the research protocol was begun a minimum of 20 minutes after achieving a steady state response during the fifth or last minute of infusion. Measurements for each intracoronary infusion were made at 5-minute intervals. Once a stable response was established, hemodynamic measurements were obtained and the infusion rate was maintained constant for the remainder of the protocol. (3) Acetylcholine was infused for 5 minutes at a rate calculated to achieve a final coronary artery concentration of 1 μmol/L, assuming a left coronary artery blood flow of 125 mL/min. (4) Acetylcholine infusion was stopped and D,W infusion was resumed for at least 5 minutes and until +dP/dt was stable and had returned to the initial value during dobutamine infusion. (5) L-NMMA was infused for 5 minutes in all subjects. Three normal control subjects and 7 heart failure patients received L-NMMA for 15 minutes. L-NMMA was infused at a rate of 20 μmol/min to achieve a calculated steady state coronary artery concentration of 160 μmol/L (assuming a left main coronary artery blood flow of 125 mL/min). (6) After the fifth minute of L-NMMA infusion, acetylcholine was again infused (at the same rate as before) for 5 minutes. In the patients receiving L-NMMA for 15 minutes, acetylcholine was stopped for the last 10 minutes of the 15-minute infusion. Measurements for each intracoronary infusion were made after achieving a steady state response during the fifth or last minute of the indicated infusion period. At the completion of the drug infusions, radiographic contrast was injected into the coronary artery infusion catheter to confirm the continued position of the catheter in the left main coronary ostium.

Statistical Analysis

All data are presented as mean±SEM. Baseline variables were compared by t test. Corresponding to the prospective study design, the effects of acetylcholine and L-NMMA were analyzed independently. Inhibition of the +dP/dt response to dobutamine by acetylcholine was analyzed by a paired t test. The effect of the 5- and 15-minute infusions of L-NMMA on the +dP/dt response to dobutamine was analyzed by two-way ANOVA using a term for patient identification and posthoc analysis with the Student-Newman-Keuls test. The dose-dependent effects of L-NMMA in control subjects and heart failure patients were compared by ANOVA.

Results

Patient Characteristics

The age, gender, and baseline hemodynamics of study subjects are listed in Table 1. Patients with dilated cardiomyopathy had a lower LV ejection fraction and cardiac index and a higher pulmonary artery wedge pressure than the control subjects, who by definition had normal LV hemodynamics. Baseline +dP/dt was 838±58 and 1366±152 mm Hg/s in the patients with heart failure and control subjects, respectively.

Drug Infusions

Dobutamine (Lilly) was infused via a systemic vein. Five percent dextrose in water (D,W) containing heparin. A 7F micromanometer-tipped pigtail catheter (Millar Instruments) was advanced from the opposite femoral artery to the ostium of the left main coronary artery. The catheter was continuously flushed at a rate of 2 mL/min with 5% dextrose in water (D,W) containing heparin. A 7F micromanometer-tipped pigtail catheter (Millar Instruments) was advanced via the right femoral artery and placed in the LV for measurement of LV pressure. The peak coronary artery concentration of 1 μmol/L, which activates NOS3 but not NOS2.

Abbreviations and Acronyms

- IL: interleukin
- L-NMMA: Nω-monomethyl-L-arginine
- LV: left ventricular
- NO: nitric oxide
- NOS: nitric oxide synthase
- TNF-α: tumor necrosis factor-α

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Positive Inotropic Response to Dobutamine

Despite a higher dobutamine infusion rate (10.2±1.5 versus 5.9±0.6 μg·kg⁻¹·min⁻¹, P<.04), the increase in +dP/dt was smaller (40±6% versus 73±14%, P=.02) in heart failure patients versus control subjects (Fig 1).

Inhibitory Effect of Acetylcholine on the Positive Inotropic Response to Dobutamine

Intracoronary infusion of acetylcholine inhibited the +dP/dt response to dobutamine to a similar degree in the control and LV failure groups (Fig 1). Acetylcholine inhibited the dobutamine-stimulated increase in +dP/dt by 31±4% in the control subjects (P<.0001 versus dobutamine alone) and 39±8% in the LV failure patients (P<.001 versus dobutamine alone).

Effect of NOS Inhibition on the Positive Inotropic Response to Dobutamine

In control subjects, the concurrent intracoronary infusion of L-NMMA for 5 or 15 minutes did not affect the +dP/dt response to dobutamine (2282±196 with dobutamine alone versus 2307±184 and 2297±23 mm Hg/s, at 5 and 15 min, respectively) (Fig 1 and 2; Table 2). In contrast, in LV failure patients versus control subjects, respectively. +P<.01 versus Dob-2.

Effect of NOS Inhibition and Activation on Ventricular Loading Conditions

In control subjects, dobutamine did not affect LV end-diastolic or systolic pressure but increased LV developed pressure by 10±2 mm Hg (P<.05 versus baseline) (Table 2). In patients with LV failure, dobutamine decreased LV end-diastolic pressure by 9±2 mm Hg (P<.05 versus baseline) and increased LV developed pressure by 9±3 mm Hg (P<.05 versus baseline) but had no effect on LV systolic pressure. Concurrent infusion of L-NMMA with dobutamine led to an increase in systolic pressure in both control subjects and patients with LV failure. In addition, L-NMMA enhanced the dobutamine-stimulated increase in LV developed pressure in LV failure patients only. Acetylcholine, when added to dobutamine or dobutamine plus L-NMMA, did not affect LV systolic or end-diastolic pressures in normal control subjects but resulted in a small increase in LV end-diastolic pressure when added to dobutamine plus L-NMMA in patients with LV failure (P<.05 versus dobutamine plus L-NMMA).

Discussion

The major new finding of this study is that inhibition of the synthesis of NO in the heart potentiates the positive inotropic response to a β-adrenergic agonist in patients with LV failure but not in control subjects with normal LV function. An important implication of this finding is that NO production in the heart is of functional significance in patients with LV failure.

### Table 1. Baseline Characteristics of Study Population

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Normal LV Function</th>
<th>LV Failure</th>
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<tr>
<td>46±4</td>
<td>50±4</td>
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<tr>
<td>Gender, M/F</td>
<td>2/5</td>
<td>6/5</td>
<td>NS</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>123±6</td>
<td>115±6</td>
<td>NS</td>
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<tr>
<td>LVEDP, mm Hg</td>
<td>9±1</td>
<td>24±2*</td>
<td>.005</td>
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<tr>
<td>LVSP, mm Hg</td>
<td>114±6</td>
<td>91±8</td>
<td>NS</td>
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<tr>
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<td>8±1</td>
<td>10±1</td>
<td>NS</td>
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<tr>
<td>PAWP, mm Hg</td>
<td>14±2</td>
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<td>.03</td>
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<tr>
<td>MAP, mm Hg</td>
<td>74±3</td>
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<td>NS</td>
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<tr>
<td>SVR, dyne · sec⁻¹·cm⁻³</td>
<td>1035±81</td>
<td>1124±112</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>97±5</td>
<td>113±4</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>69±4</td>
<td>23±3*</td>
<td>&lt;.0001</td>
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<tr>
<td>CI, L ·min⁻¹·m⁻²</td>
<td>3.5±0.1</td>
<td>2.3±0.2*</td>
<td>&lt;.01</td>
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<tr>
<td>LV +dP/dt, mm Hg/s</td>
<td>1366±152</td>
<td>838±58</td>
<td>NS</td>
</tr>
</tbody>
</table>

CI indicates cardiac index; EF, ejection fraction; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; MAP, mean arterial pressure; PAWP, mean pulmonary artery wedge pressure; RAP, mean right atrial pressure; and SVR, systemic vascular resistance.

*Vs normal LV function.
by contributing to hyporesponsiveness of the myocardium to β-adrenergic stimulation. Myocardial β-adrenergic hyporesponsiveness, a characteristic feature of failing myocardium, has generally been attributed to downregulation of β-adrenergic receptors or alterations in G proteins.16,20,21 Our findings suggest that cardiac NO production is an additional mechanism that may contribute to this pathophysiological feature of heart failure. Our findings are consistent with recent studies that have shown that NOS expression and activity are increased in failing human myocardium.2,3 DeBelder et al2 first demonstrated that human myocardium obtained from patients with idiopathic dilated cardiomyopathy contains NOS activity as detected by the conversion of l-arginine to l-citrulline and, furthermore, that the NOS activity is largely calcium independent, suggesting that it is due to NOS2.2,3 More recently, Haywood et al1 demonstrated that NOS2 mRNA and protein are expressed in failing myocardium from patients with idiopathic, ischemic, or valvular cardiomyopathy. However, not all studies have found evidence of increased NOS2 in failing myocardium. Habib et al22 found increased NOS2 immunoreactivity only in myocardium from patients with idiopathic cardiomyopathy and not in patients with ischemic cardiomyopathy, and Theones et al13 found increased myocardial NOS2 immunoreactivity only in patients with sepsis and not in those with idiopathic or ischemic cardiomyopathy.

The effects of NO on myocardial contractility are also controversial. Investigators using isolated adult rat ventricular myocytes,23 perfused rat hearts,24 or intact dogs25,26 have found that NO may have no effect on contractility, a stimulatory effect, or dose-dependent effects (stimulatory at low dose and inhibitory at high dose). Recently, Yamamoto et al27 reported that increased NO induction in myocytes isolated from dogs with pacing-induced heart failure attenuated the positive inotropic response to isoproterenol, an effect that was not seen in control myocytes; and a preliminary report by Drexler et al28 found that increased cardiac production of NO modulates β-adrenergic hyporesponsiveness in explanted myocardium from humans with end-stage heart failure. Our findings are consistent with these in vitro studies and strongly suggest that there is a functionally important increase in NOS activity in patients with LV failure due to idiopathic dilated cardiomyopathy. It should be noted that we studied only patients with idiopathic dilated cardiomyopathy; therefore, our conclusions

| TABLE 2. Changes in Heart Rate, Loading Conditions, and LV +dP/dt With Dobutamine, Acetylcholine, and L-NMMA in 11 Patients With LV Failure and 7 Control Subjects |
|---------------------------------|------------|------------|------------|------------|------------|------------|
|                                | Control    | Dobutamine−1 | Dobutamine+Acetylcholine | Dobutamine−2 | Dobutamine+L-NMMA | Dobutamine+L-NMMA+Acetylcholine | Dobutamine+L-NMMA |
| Heart rate, bpm                 |            |            |            |            |            |            |
| Normal                          | 97±5       | 97±5       | 97±5       | 99±5       | 97±5       | 97±5       | 90±3       |
| LV failure                      | 113±4      | 113±4      | 113±5      | 113±5      | 113±4      | 114±5      | 108±4      |
| LVSP, mm Hg                     | 123±6      | 132±6      | 130±5      | 133±6      | 136±5*     | 140±5*     | 144±10*    |
| LV failure                      | 115±6      | 115±4      | 109±5      | 114±5      | 119±6      | 115±6      | 125±8†     |
| LVEDP, mm Hg                    | 9±1        | 8±1        | 8±1        | 8±1        | 7±1        | 7±1        | 10±2       |
| LV failure                      | 24±2       | 15±3*      | 15±3*      | 13±3*      | 13±3*      | 18±4†      | 15±5*      |
| LVPddev, mm Hg                  | 114±6      | 124±6      | 122±5      | 125±6      | 129±5*     | 133±5*     | 134±11*    |
| LV failure                      | 91±8       | 100±6*     | 94±7       | 101±7*     | 105±7*     | 97±9       | 111±11†    |
| LV +dP/dt, mm Hg/s              | 1366±152   | 2282±196*  | 2013±170†  | 2381±184*  | 2307±184*  | 2000±146†  | 2297±23*   |
| LV failure                      | 838±58     | 1171±88*   | 1084±91*   | 1191±94*   | 1235±94*   | 1198±123*  | 1330±72†   |

See Table 1 for abbreviations.

*P<.05 vs control; †P<.05 vs Dobutamine−1; ‡P<.05 vs Dobutamine+L-NMMA.
must be limited to such patients and may not be relevant to patients with other etiologies of LV failure. It should also be noted that the greater effect of L-NMMA in LV failure patients could be due to increased sensitivity to NO rather than increased NO activity per se.

A potential mechanism for increased NOS activity in failing myocardium is provided by the observation that plasma levels of TNF-α and IL-6 are increased in patients with heart failure. Recently, Torre-Amione et al and Habib et al have further demonstrated that the expression of TNF-α is increased in the myocardium of patients with severe heart failure. TNF-α and IL-6 are potent stimuli for the induction of NOS2 in myocardium, cardiac myocytes, and cardiac microvascular endothelial cells.

Gulick et al demonstrated that exposure of cardiac myocytes to inflammatory cytokines results in attenuation of the responsiveness to β-adrenergic stimulation. Subsequently, Balligand et al demonstrated the role of myocardial NOS activity in mediating this effect by showing that NOS inhibitors enhance the contractile response to β-adrenergic stimulation in isolated beating myocytes induced to express NOS2 by exposure to immunological stimuli. There are several mechanisms by which NO might inhibit the positive inotropic response to β-adrenergic stimulation. NO activates soluble guanylyl cyclase to produce cGMP, which inhibits cAMP-dependent protein kinase G and increases the degradation of cAMP by protein kinase G catalytic subunit. NO also inhibits β-adrenergic stimulation in patients with idiopathic dilated cardiomyopathy but not in control subjects with normal LV function. This finding suggests that increased myocardial NO activity in the failing human heart is of functional significance by attenuating β-adrenergic responsiveness. Given the potential for excessive NO activity to cause cardiac myocyte death, and inhibition of mitochondrial function, it is possible that these observations have additional, broader implications for the role of myocardial NO in the pathophysiology of heart failure.

In summary, this study demonstrates that inhibition of NO synthesis potentiates the positive inotropic response to β-adrenergic stimulation in patients with idiopathic dilated cardiomyopathy but not in control subjects with normal LV function. By using the direct intracoronary artery infusion of L-NMMA, we were able to avoid changes in loading conditions that might otherwise confound the interpretation of +dP/dt, and thus we were able to observe the effect of a selective inhibition of NOS in the myocardium. To avoid an indirect effect of L-NMMA on the coronary artery concentration of dobutamine due to changes in coronary blood flow, dobutamine was infused via a systemic vein. On the other hand, because acetylcholine was infused via the intracoronary route, it is possible that differential effects of L-NMMA on coronary blood flow could have had quantitative effects on the interpretation of our data.

Studies in cardiac myocytes and dogs indicate that muscarinic receptor stimulation, which activates NOS3 in cardiac myocytes, inhibits the positive inotropic response to β-adrenergic agonists by a mechanism that involves an increase in NO activity. We therefore examined the possibility that increased agonist-stimulated NO activity in the myocardium attenuates the contractile response to β-adrenergic stimulation in failing myocardium. We previously used the intracoronary infusion technique to show that the muscarinic agonist acetylcholine inhibits the positive inotropic response to dobutamine in humans with normal LV function. Using this approach in the present study, we found that acetylcholine inhibits the positive inotropic response to dobutamine to a similar degree in patients with LV failure and control subjects with normal LV function. To the extent that this action of acetylcholine reflects agonist-stimulated NOS activity, this finding suggests that NOS3 is not increased in failing myocardium and is unlikely to account for the increased effect of L-NMMA in patients with heart failure. Interestingly, Drexler et al reported a reduction in NOS3 mRNA in failing human myocardium. Our data provide agreement that NOS3 activity is not increased in heart failure, although we cannot exclude a decrease as reported by Drexler and coworkers. In this and other studies, inhibition of NOS does not fully inhibit the effect of acetylcholine; therefore, it is likely that cholinergic receptor activation increases cGMP by non-NOS pathways as well.

Elucidation of the functional role of NO in humans is complicated by the systemic pressor effect of NOS inhibitors.

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Acknowledgments

This work was supported by National Institutes of Health grants HL-52320 (W.S.C., M.A.C.) and HL-03238 (J.M.H.). Dr Hare was a Physician-Scientist of the American Heart Association, Massachusetts Affiliate. We wish to acknowledge Dr Thomas W. Smith for his intellectual guidance, support, and encouragement. We would also like to acknowledge the excellent technical support and patience of Diane Gauthier, RN, and the Staff of the Cardiac Catheterization Laboratory at the Brigham and Women’s Hospital.

References


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Circulation. 1998;97:161-166
doi: 10.1161/01.CIR.97.2.161
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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