Effect of NO Donors on LV Diastolic Function in Patients With Severe Pressure-Overload Hypertrophy

Christian M. Matter, MD; Lazar Mandinov, MD, PhD; Philipp A. Kaufmann, MD; Giuseppe Vassalli, MD; Zihua Jiang, PhD; Otto M. Hess, MD

Background—Previous experimental studies have shown that nitric oxide (NO) modulates cardiac function by an abbreviation of systolic contraction and an enhancement of diastolic relaxation. However, the response to NO donors of patients with severe pressure-overload hypertrophy and diastolic dysfunction is unknown.

Methods and Results—Intracoronary NO donors were given to 17 patients with severe aortic stenosis. A dose-response curve was obtained with nitroglycerin (30, 90, and 150 μg) in 11 patients and sodium nitroprusside (1, 2, and 4 μg/min) in 6. Left ventricular (LV) high-fidelity pressure measurements with simultaneous LV angiograms were performed at baseline and after the maximal dose of NO. The dose-response curve for intracoronary NO donors showed a marked fall in LV end-diastolic pressure, from 23 to 14 mm Hg (−39%; \( P<0.0001 \)), whereas LV peak systolic pressure fell only slightly, from 206 to 196 mm Hg (−4%; \( P<0.01 \)). End-diastolic chamber stiffness decreased from 0.12 to 0.07 mm Hg/mL (\( P<0.0001 \)) and end-systolic stiffness from 1.6 to 1.3 mm Hg/mL (\( P<0.01 \)). Heart rate, right atrial pressure, LV ejection fraction, the time constant of isovolumic pressure decay (\( \tau \)), and LV filling rates remained unchanged.

Conclusions—In patients with severe pressure-overload hypertrophy, intracoronary NO donors exert a marked decrease in LV end-diastolic pressure without affecting LV systolic pump function. Thus, the hypertrophied myocardium appears to be particularly susceptible to NO donors, with a marked improvement in diastolic function. (Circulation. 1999;99:2396-2401.)

Key Words: nitric oxide ■ nitroglycerin ■ sodium nitroprusside ■ hypertrophy ■ diastole

Nitric oxide (NO) is known to be an important determinant in the control of vascular tone. However, its influence as a modulator of myocardial function (reviewed in Reference 2) has only recently been appreciated. Smith et al,1 Brutsaert and Andries,4 and Ramaciotti et al5 pioneered the research investigating the role of the endocardial and vascular endothelium to modulate myocardial contraction and relaxation. These and subsequent studies have shown that NO- and/or cGMP-releasing substances increase diastolic cell length, decrease contractility, shorten ejection period, diminish contractile response to β-adrenergic agonists, and slow heart rate.6–8 These findings have been confirmed in the human myocardium, demonstrating a reduction in left ventricular (LV) pressure and an improvement in LV diastolic distensibility after intracoronary administration of NO-releasing compounds in patients with normal LV function9 and in transplant recipients.10 However, the effect of NO donors on LV function in patients with severe pressure-overload hypertrophy and accompanying diastolic dysfunction is still unknown.

Thus, the purpose of the present study was to evaluate the effect of intracoronary NO donors on LV contraction and relaxation in patients with severe aortic stenosis.

Methods

Patient Characteristics

Fifteen men and 2 women (age, 58±10 years) were included in the present analysis. Eleven patients received intracoronary nitroglycerin (NTG) and 6, intracoronary sodium nitroprusside (SNP). All patients underwent diagnostic cardiac catheterization for symptomatic aortic stenosis (NYHA class, 2.2±0.3; mean gradient, 66±17 mm Hg; valve area, 0.7±0.1 cm²; muscle mass index, 175±64 g/m²). There were no significant differences between patients receiving either NTG or SNP with regard to baseline characteristics. Patients with significant coronary artery disease (>50% diameter stenosis), hypertension (systolic blood pressure <100 mm Hg), moderate to severe congestive heart failure (NYHA class III to IV) or age >75 years were excluded from the present analysis. The study protocol was approved by the local ethics committee, and informed consent was obtained from all patients.

Study Protocol

All vasoactive drugs were withheld for ≥24 hours before the procedure. Right and left heart catheterization was performed according to our protocol (Figure 1). Right-sided pressures were measured by a 6F Cournand catheter introduced from the right femoral vein and left-sided pressure by a 6F pigtail catheter introduced from the right femoral artery. Coronary angiography was carried out with nonionic contrast material (Iopamiro, Iopamidol 300; Sintetica AG). At the end of diagnostic angiography, an interval
of ≥15 minutes was allowed for dissipation of contrast effects. LV pressure was measured with a transseptally introduced 3F Millar catheter (Figure 2). A 6F coronary artery infusion catheter was placed in the left main coronary artery for intracoronary drug administration. Its position was confirmed at the beginning and at the end of the study by contrast injection. A dose-response curve was obtained for both NTG (Perlinganit, Schwarz Pharma AG) injections with increasing doses of 30, 90, and 150 µg and for SNP infusions with doses of 1, 2, and 4 µg/min (Nipride, Roche). Simultaneous biplane LV angiograms in the right and left anterior oblique projections were performed at baseline and after the maximal dose of the intracoronary NO donor with 40 to 50 mL of the nonionic contrast material (injection rate, 12 mL/s). Filming rate was 25 frames per second. The LV angiograms of 3 patients could not be quantitatively analyzed because of premature ventricular contractions (2 patients receiving NTG, 1 SNP). LV volumes were analyzed on a frame-by-frame basis by the area-length method.11 LV muscle mass was calculated according to the method of Rackley et al.12

**Data Analysis**

LV systolic function was determined from LV systolic pressure, peak positive dP/dt, LV systolic volume, and LV ejection fraction. Systolic ejection time was calculated as the time interval from the beginning of the Q wave in the standard ECG to end systole, which was defined as the time of pressure crossover of the LV and aortic pressure curves.

LV diastolic function was estimated from LV diastolic pressure, peak negative dP/dt, LV diastolic volume, the time constant of isovolumic pressure decay (τ), and early and late peak filling rates. Rate of relaxation was calculated from the linear relationship between LV pressure and negative dP/dt by use of a shifting asymptote:13 $P = P_0 - e^{-\tau T} + P_b$, where $P$ = LV pressure (mm Hg), $P_0$ = pressure at the time of peak negative dP/dt, $T$ = time after peak negative dP/dt (ms), $T$ = time constant of isovolumic pressure decay (ms), and $P_b$ = pressure asymptote. LV diastolic filling was measured from instantaneous LV volumes. Early peak filling rate (mL/s) was determined during the first half of diastole and late peak filling rate during the second half. Passive-elastic properties were determined from the diastolic pressure-volume (Figure 3) and stress-strain relationships by use of an elastic model with shifting asymptote: $P = a * e^{S} + c$ and $S = a * e^{P} + b$, where $P$ = LV pressure (mm Hg), $a$ = elastic constant (mm Hg), $b$ = constant of chamber stiffness, $V$ = LV volume (mL), $S$ = pressure asymptote (mm Hg), $S = LV$ midwall circumferential wall stress (kdyne/cm²), $a$ = elastic constant (kdyne/cm²), $S = LV$ midwall circumferential wall stress, and $c$ = stress asymptote (kdyne/cm²). End-diastolic and end-systolic chamber stiffness was calculated from the instantaneous pressure-volume relationship with shifting asymptote: $P = a * e^{S} + c$ and $S = a * e^{P} + b$, where $CS = chamber$ stiffness, $LVEDP = LV$ end-diastolic and $LVESP = LV$ systolic pressure (mm Hg), and $EDV = end-diastolic$ and $ESV = end-systolic volume (mL)$. The chamber stiffness constant $b$ was derived from the exponential curve fit to the diastolic portion of the LV pressure-volume relation.14 The myocardial stiffness constant $\beta$ was calculated from the curve fit to the diastolic portion of the stress-strain relation.14

**Statistics**

Hemodynamic and angiographic data at baseline and after intracoronary NO donors were compared by a paired Student’s $t$ test. Intragroup comparisons of the dose-response curve were carried out by a 2-way ANOVA for repeated measurements. Results are reported as mean±SD.

**Results**

**LV Pressure Response to Intracoronary NO Donors**

A representative pressure recording before and after intracoronary administration of NTG is shown in Figure 2. The dose-response curve (Figure 4) revealed a marked decrease of LV end-diastolic pressure with increasing doses of intracoronary NO donors (maximally ~39% of baseline, $P<0.0001$). LV peak systolic pressure fell slightly but significantly (~4% of baseline, $P<0.01$).
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end-systolic wall stress, and LV chamber and myocardial

NTG 30 decreased slightly (P < 0.01), whereas end-diastolic chamber

of the NO donor (Table 2). LV end-systolic chamber stiffness

LV peak systolic pressure after intracoronary administration

Peak negative dP/dt decreased in parallel to the reduction in

LV Diastolic Parameters

In addition to the fall in LV end-diastolic and peak-systolic

pressure, there was a decrease in LV end-systolic pressure

(P < 0.0001) and in peak ejection rate (P < 0.05) after NO

administration (Table 1).

Heart rate, right atrial pressure, LV ejection time, peak

positive dP/dt, LV developed systolic pressure, LV end-diastolic

volume, LV ejection fraction, and early and late peak

filling rates remained unchanged after the NO donor.

LV Diastolic Function Parameters

Peak negative dP/dt decreased in parallel to the reduction in

LV peak systolic pressure after intracoronary administration

of the NO donor (Table 2). LV end-systolic chamber stiffness

decreased slightly (P < 0.01), whereas end-diastolic chamber

stiffness decreased markedly (P < 0.0001) after the NO donor.

There was also a significant reduction in end-diastolic wall

stress (P < 0.01) and the stress asymptote c (P < 0.05) after the

NO donor. The time constant of LV pressure decay (τ),

end-systolic wall stress, and LV chamber and myocardial

stiffness remained unaffected, whereas the pressure asymptote c* of the diastolic pressure-volume relation decreased slightly. However, there was a downward shift of the LV diastolic pressure-volume curve in 7 of 17 patients (Figure 3).

Furthermore, there was a significant correlation between LV end-diastolic pressure and pressure asymptote c* (r = 0.593; P = 0.026) or stress asymptote c (r = 0.637; P < 0.015).

The nitrovasodilators NTG and SNP are known to differ in their biotransformation of NO and the magnitude of their effects on preload and afterload after systemic administration. The use of intracoronary NTG and intracoronary SNP allowed the exclusion of such differences (Table 3).

Discussion

Diastolic dysfunction is a common finding in patients with severe aortic stenosis. Its pathogenesis is manifold but can be explained by severe LV hypertrophy with a reduced Ca²⁺ reuptake into the sarcoplasmic reticulum, resulting in a defective excitation-contraction coupling; by elevated angiotensin II levels; or by a reduced capillary density and/or an increased collagen content.

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<thead>
<tr>
<th>TABLE 1. Hemodynamic and Angiographic Data</th>
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<td>Heart rate, bpm</td>
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<td>LV peak systolic pressure, mm Hg</td>
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<td>LV end-diastolic pressure, mm Hg</td>
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<td>LV developed systolic pressure, mm Hg</td>
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<td>LV ejection time, ms</td>
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<td>Peak positive dP/dt, mm Hg/s</td>
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<td>LV end-systolic chamber stiffness, mm Hg/mL</td>
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<td>LV end-diastolic pressure, mm Hg</td>
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<td>Peak ejection rate, mL/s</td>
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<td>Early peak filling rate, mL/s</td>
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<td>Late peak filling rate, mL/s</td>
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*P < 0.05, †P < 0.01, ‡P < 0.0001 vs baseline.

<table>
<thead>
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<th>TABLE 2. LV Diastolic Function Parameters</th>
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<tr>
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<td>Chamber stiffness constant b, mL⁻¹</td>
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<td>Pressure asymptote c, mm Hg</td>
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<td>Myocardial stiffness constant β</td>
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<td>Stress asymptote c, kdyne/cm²</td>
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<td>LV end-systolic wall stress, kdyne/cm²</td>
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<td>LV end-diastolic wall stress, kdyne/cm²</td>
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*P < 0.05, †P < 0.01, ‡P < 0.0001 vs baseline.
TABLE 3. Comparison of NTG vs SNP Effects

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>SNP, Δ%</th>
<th>P, NTG vs SNP</th>
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<tr>
<td>LV end-systolic volume index</td>
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<td>+13</td>
<td>NS</td>
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<tr>
<td>LV end-systolic chamber stiffness</td>
<td>−18</td>
<td>−20</td>
<td>NS</td>
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<td><strong>Diastolic parameters</strong></td>
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<tr>
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<td>−32</td>
<td>NS</td>
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<td>LV end-diastolic volume index</td>
<td>−6</td>
<td>+4</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic chamber stiffness</td>
<td>−45</td>
<td>−34</td>
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</tr>
<tr>
<td>τ</td>
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<td>−1</td>
<td>NS</td>
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<tr>
<td>Right atrial pressure</td>
<td>−32</td>
<td>+12</td>
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Δ% indicates % change from baseline.

Therapeutic approaches have been used to reduce LV diastolic filling pressure (dyspnea on exertion) and to improve subendocardial perfusion (angina pectoris) to ameliorate clinical symptoms and ultimately diastolic dysfunction. In severe aortic stenosis, valve replacement is the therapy of choice. Nevertheless, aortic valve obstruction with moderate to severe LV hypertrophy may profit from therapy that is able to improve LV diastolic function.

The major findings of the present study were (1) that intracoronary NO donors improve diastolic function in patients with severe pressure-overload hypertrophy, with a decrease in LVEDP and a reduction in LV end-diastolic chamber stiffness and (2) that the hypertrophied myocardium seems to be particularly susceptible to NO donors, with a marked improvement in diastolic function.

Pathophysiological Mechanisms

Recent reports have underlined the role of NO as a modulator of cardiac function. In isolated cardiomyocytes and papillary muscles, NO- and cGMP-releasing substances are associated with a decrease in systolic cell length and an improvement in diastolic relaxation. This has been attributed to either a desensitization of myofilaments to Ca\(^{2+}\), reaction of NO with oxygen radicals to form toxic peroxynitrites, or binding of NO to the iron-containing proteins, such as those in the respiratory chain of the mitochondria.

Similar data have been obtained in Langendorf preparations and animal models after administration of NO-releasing compounds, revealing a decrease in systolic contraction and an improvement in diastolic relaxation. Complementary results were reported by Paulus and coworkers after bicoronal administration of SNP in healthy patients or infusion of substance P in transplant recipients, with a decrease in LV filling pressure and an increase in LV distensibility.

Impact of NO Donors on LV Hypertrophy

In contrast to the previous findings of Paulus et al., NO donors led to a pronounced decrease in LV end-diastolic pressure but had no effect on LV systolic pump function.

Similar observations have been reported with the use of intracoronary ACE inhibitors in patients with pressure-overload LV hypertrophy. A decrease in LV filling pressure with an improvement in regional LV relaxation was found after intracoronary enalapril. These effects may be in part NO-mediated by the reduced degradation of bradykinin. Other studies have shown a link between ACE inhibition and NO effects under in vitro and in vivo conditions. Thus, NO may contribute to the beneficial effects of ACE inhibitors with regard to LV diastolic function. However, the physiological relevance of NO in this setting remains speculative.

It must be pointed out that in our patients with pressure-overload hypertrophy, administration of intracoronary NO decreased LV filling pressures without affecting LV volumes. This combination suggests a parallel downward shift of the LV pressure-volume relation (Figure 3), which was seen in nearly half of our patients and which implies a change in LV distensibility. This trend was supported by a decrease in LV end-diastolic chamber stiffness, \(ΔP/ΔV\). However, the chamber and myocardial stiffness constant \(b\) or \(β\) did not show a significant change after NO donors. This apparent contradiction can be explained by the fact that there was a parallel downward shift of the pressure-volume relation without a change in slope (resulting in an unchanged \(b\) or \(β\)), whereas the pressure asymptote \(c^*\) decreased slightly and the stress asymptote \(c\) significantly (Table 3). Furthermore, there was a significant correlation between LV end-diastolic pressure and the pressure asymptote \(c^*\) or stress asymptote \(c\). Taken together, these findings support the concept of a downward shift of the diastolic pressure-volume curve in response to intracoronary NO donors, which was also observed by Paulus et al.

LV end-diastolic pressure is known to be influenced by external forces, such as the pericardium and right ventricular filling pressure. Thus, biventricular interaction may account for the parallel decrease of both right ventricular and LV filling pressures in the context of pure preload reduction. However, to avoid systemic effects, NO donors were administered by the intracoronary route, and the fall in LV end-diastolic pressure was not achieved by a change in right atrial pressure, suggesting a direct effect of NO on the myocardium.

There were minor changes in LV systolic function after NO donors. A decrease in peak systolic pressure and peak ejection rate would ordinarily suggest a decline in contractility. However, developed pressure and LV ejection fraction remained stable, indicating no change in LV contractile state. Accordingly, a decline in peak ejection rate associated with a decrease in end-diastolic wall stress and stable end-diastolic volume may be caused by an effect via the Frank-Starling mechanism.

Role of NO in LV Hypertrophy

Why does the hypertrophied myocardium differ from the normal myocardium in its response to NO donors? Is constitutive NO synthase (NOS) activity impaired in the hypertrophied myocardium compared with the normal heart, or are some of the downstream signals of NO altered in LV hypertrophy?

Two recent reports from animal models of pressure-overload hypertrophy may provide some explanations. The
authors administered SNP to isolated rat cardiomyocytes and demonstrated a decrease in systolic contraction and an increase in diastolic cell length in normal but not in hypertrophied myocytes. These findings were explained by a blunting of the downstream signaling effect of cGMP on the sodium proton exchange. In normal cardiomyocytes, this leads to an increase in contraction, whereas this response is impaired in hypertrophied cardiomyocytes.

In a canine model of pressure-overload hypertrophy, basal and stimulated myocardial cGMP levels after the NO donor morpholinosynonimine were higher in LV hypertrophy than in controls. However, the NOS inhibitor N-nitro-L-arginine methyl ester had no effect on cGMP levels in either group. It is of interest that LV mechanics remained unaffected after the NO donor in the group with hypertrophy, whereas it changed in the control group. These findings suggest that animals with hypertrophy have increased myocardial cGMP levels that are independent of NOS activity.

No data on myocardial NOS activity in pressure-overload hypertrophy in humans are available. The levels of constitutive NOS levels could not be determined because no myocardial biopsies were performed in the present study.

Taken together, the data derived from the animal experiments support our findings, which showed no effect of NO donors on contraction or relaxation in patients with severe pressure-overload hypertrophy. They suggest that the downstream targets of NO in the hypertrophic myocardium may be less responsive to NO than the normal one.

Clinical Implications

Our data show that NO donors improve diastolic function in patients with severe LV hypertrophy. LVEDP dropped by 39% after small intracoronary doses of NO donors, whereas systolic pump function remained unchanged. In contrast, Paulus and coworkers reported a 21% decrease in baseline peak LVEDP after 4 μg/min SNP in patients without cardiac disease. Because the hypertrophied myocardium is associated with a high incidence of LV diastolic dysfunction, NO donors may be particularly suitable for decreasing elevated diastolic filling pressures. Thus, nitrovasodilators may be able to reduce lung congestion and dyspnea on exertion on a short-term basis. Their long-term effect remains to be determined.

Study Limitations

1. SNP and NTG were used as NO donors for the purpose of the present study. These substances differ in their biotransformation of NO. NTG requires the presence of S-thiol enzymes, whereas SNP liberates NO spontaneously. It is known that nitrovasodilators do not accurately mimic endothelial or myocardial NO release. However, these compounds are widely used in clinical application for acute and chronic treatment of coronary and valvular heart disease.

2. Single coronary administration of the NO donors was used instead of bicoronary infusions. This may have led to an underestimation of the NO donor effect, but systemic side effects may have been minimized.

3. A control group of patients with administration of vehicle was not included. A previous collaborative study from our laboratory showed no effect on diastolic function with the intracoronary infusion of vehicle (normal saline) and repeated angiography in patients with severe aortic stenosis.

Conclusions

The present study shows that administration of small intracoronary doses of NO donors leads to a marked decrease in LV filling pressure, suggesting that the hypertrophied myocardium appears to be particularly susceptible for exogenously administered NO donors. This may be explained by either a reduced production or release of NO by the endothelium in the hypertrophied myocardium.

In contrast to previous studies in healthy volunteers, the hypertrophied ventricle shows no effect of intracoronary NO donors on LV contraction and relaxation. This effect may be explained by a blunting of the downstream signaling effects of cGMP in the hypertrophied cardiomyocytes due to an increased constitutive NOS activity and/or increased guanylate cyclase activity.

References


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Circulation. 1999;99:2396-2401
doi: 10.1161/01.CIR.99.18.2396

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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