L-NMMA (a Nitric Oxide Synthase Inhibitor) is Effective in the Treatment of Cardiogenic Shock

Gad Cotter, MD; Edo Kaluski, MD; Alex Blatt, MD; Olga Milovanov, MD; Yaron Moshkovitz, MD; Ronit Zaidenstein, MD; Ahmed Salah, RN; Daniela Alon, RN; Yoav Michovitz, MD; Michael Metzger; Zvi Vered, MD; Ahuva Golik, MD

Background—The objective was to assess the safety and efficacy of L-NMMA in the treatment of cardiogenic shock.

Methods—We enrolled 11 consecutive patients with cardiogenic shock that persisted after >24 hours from admission, despite coronary catheterization and primary percutaneous transluminal coronary revascularization, when feasible, and treatment with mechanical ventilation, intraaortic balloon pump (IABP), and high doses of catecholamines. L-NMMA was administered as an IV bolus of 1 mg/kg and continuous drip of 1 mg · kg⁻¹ · h⁻¹ for 5 hours. Treatment with catecholamines, mechanical ventilation, and IABP was kept constant throughout the study.

Results—Within 10 minutes of L-NMMA administration, mean arterial blood pressure (MAP) increased from 76±9 to 109±22 mm Hg (+43%). Urine output increased within 5 hours from 63±25 to 156±33 cc/h (+148%). Cardiac index decreased during the steep increase in MAP from 2.0±0.5 to 1.7±0.4 L/(min · m²) (−15%); however, it gradually increased to 1.85±0.4 L/(min · m²) after 5 hours. The heart rate and the wedge pressure remained stable. Twenty-four hours after L-NMMA discontinuation, MAP (+36%) and urine output (+189%) remained increased; however, cardiac index returned to pretreatment level. No adverse events were detected. Ten out of eleven patients could be weaned off mechanical ventilation and IABP. Eight patients were discharged from the coronary intensive care unit, and seven (64%) were alive at 1-month follow-up.

Conclusions—L-NMMA administration in patients with cardiogenic shock is safe and has favorable clinical and hemodynamic effects. (Circulation. 2000;101:1358-1361.)

Key Words: cardiogenic shock ■ hypotension ■ L-NMMA

L-NMMA is a nonspecific NO synthase inhibitor. It is 1 of the most potent vasoconstrictors known; therefore, it has been examined in various types of shock. However, L-NMMA has not been examined in cardiogenic shock due to concerns regarding a possible ischemic effect.

Methods

Patients

Patients with extensive myocardial infarction complicated with cardiogenic shock were considered for this study. All patients were treated with mechanical ventilation and intraaortic balloon pump (IABP). Immediately upon admission, all patients underwent coronary catheterization and primary percutaneous coronary intervention, when feasible. Patients received aspirin, IV heparin, IV fluids, and IV furosemide drip. IV dopamine and dobutamine were administered to doses of at least 10 μg · kg⁻¹ · min⁻¹ for at least 3 hours before enrollment. Cardiogenic shock was defined as persistent unaugmented systolic blood pressure (systolic blood pressure measured without IABP augmentation) below 100 mm Hg, accompanied by pulmonary congestion determined by chest x-ray, cardiac index <2.5 L/(min · m²), and wedge pressure >15 mm Hg despite the above mentioned treatment.

Inclusion and Exclusion Criteria

Patients were enrolled in the study if they experienced refractory cardiogenic shock (cardiogenic shock that persisted or worsened >24 hours after admission and coronary catheterization) and if deemed beyond treatment by the heads of cardiology and coronary intensive care unit (ICU). Subsequent to patients selection, patients and families were required to sign an informed consent form.

Patients with significant tachyarrhythmia or bradyarrhythmia, significant valvular heart disease, or other mechanical complications (secondary heart failure, fever >38°C, or creatinine >200 μmol/mL) were excluded.

Treatment Protocol

An arterial line and Swan-Ganz catheter were inserted at least 3 hours before L-NMMA administration. Throughout treatment, O₂ saturation, pulse, blood pressure, urine output, wedge pressure, and cardiac output were all continuously monitored. L-NMMA (Clinalfa, Cal-Biochem) was administered as 1 mg/kg bolus and then continued as drip of 1 mg · kg⁻¹ · h⁻¹ for 5 hours. During L-NMMA administration, treatment with fluids, catecholamines, mechanical ventilation, and IABP was kept constant. The study was approved by the hospital and Ministry of Health Ethical Review Board.
Outcome Measures

Primary Outcome
Changes in hemodynamic variables during L-NMMA administration.

Secondary Outcome
(1) Clinical outcome during 1-month of follow-up. (2) Adverse events during the treatment period.

Statistical Methods
The 2-tailed Student’s t test with paired measurements was used to compare continuous variables. Changes within a given parameter over the period of the study were analyzed by ANOVA with repeated measures. Probability values of <0.05 were considered significant.

Results
Eleven patients were recruited for this study. Baseline characteristics of the study population are given in Table 1.

Hemodynamic Changes
Changes in pulse, pulmonary pressure and vascular resistance, and systemic vascular resistance (SVR) are presented in Table 2.

Mean Arterial Blood Pressure and Urine Output
Baseline unaugmented mean arterial pressure (MAP) was 76±9 mm Hg, and urine output was 63±25 cc/h. Both increased steeply in response to L-NMMA administration (Figure 1).

Cardiac Index
Baseline cardiac index (Figure 2) was 2.0±0.5 L/(min · m²). It decreased by 15% during the first hour of treatment,

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**TABLE 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.5±9.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (55%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Background</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Wall</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Posterior</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Peak CK (iu)</td>
<td>3910±883</td>
</tr>
</tbody>
</table>

**Catheterization results**
- 3-vessel disease: 8 (73%)
- 1-vessel disease: 3 (27%)

**Revascularization**
- Stent to left main: 2 (18%)
- Stent to proximal LAD: 5 (45%)
- PTCA to proximal LAD: 1 (9%)
- PTCA to circumflex: 1 (9%)
- Failed PTCA to LAD: 1 (9%)
- None: 1 (9%)
- EF (Echo): 23.3±5.4

CK indicates creatine phosphokinase; LAD, left anterior descending; PTCA, percutaneous transluminal coronary angioplasty; EF, ejection fraction.

**TABLE 2. Haemodynamic Parameters During L-NMMA Administration**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time</th>
<th>Pulse (beats/min)</th>
<th>Systemic Vascular Resistance</th>
<th>Pulmonary BP (mm Hg)</th>
<th>Pulmonary Vascular Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>100±10</td>
<td>1612±764</td>
<td>34±9</td>
<td>309±213</td>
</tr>
<tr>
<td>10 min</td>
<td></td>
<td>95±15</td>
<td>2714±1042</td>
<td>42±9</td>
<td>499±264</td>
</tr>
<tr>
<td>20 min</td>
<td></td>
<td>95±17</td>
<td>2758±1164</td>
<td>42±10</td>
<td>492±270</td>
</tr>
<tr>
<td>30 min</td>
<td></td>
<td>98±21</td>
<td>2878±1171</td>
<td>43±11</td>
<td>549±326</td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td>98±21</td>
<td>2883±1376</td>
<td>42±12</td>
<td>560±411</td>
</tr>
<tr>
<td>2 h</td>
<td></td>
<td>96±22</td>
<td>2872±1375</td>
<td>41±12</td>
<td>546±354</td>
</tr>
<tr>
<td>3 h</td>
<td></td>
<td>97±24</td>
<td>2807±1248</td>
<td>41±12</td>
<td>565±363</td>
</tr>
<tr>
<td>4 h</td>
<td></td>
<td>95±26</td>
<td>2661±1036</td>
<td>40±12</td>
<td>536±349</td>
</tr>
<tr>
<td>5 h</td>
<td></td>
<td>97±25</td>
<td>2506±1105</td>
<td>39±11</td>
<td>480±357</td>
</tr>
<tr>
<td>24 h</td>
<td></td>
<td>94±19</td>
<td>2029±420</td>
<td>37±9</td>
<td>407±267</td>
</tr>
</tbody>
</table>

P value: 0.37, 0.001*, 0.007*, 0.002*

*P<0.05.
whereas MAP and SVR dramatically increased ($P<0.001$); however, despite no further change in MAP after 3 hours of treatment, cardiac index started to recover, increasing to above baseline level at 24 hours of follow-up.

Pulmonary Capillary Wedge Pressure

Similar to cardiac output, the wedge pressure (Figure 2) increased during the first hour of treatment by 13%. However, by the second hour of treatment, wedge pressure decreased to pretreatment baseline and was unchanged at 24 hours.

Clinical Results

Ten out of eleven patients could be weaned off mechanical ventilation and IABP after L-NMMA administration. Eight patients were discharged from the coronary ICU. Seven patients were discharged to home. They were alive at 1 to 3 months of follow-up. Ejection fraction at the 1-month visit was $30.8\pm4.5\%$. The 4 patients that had died succumbed to multiorgan failure, sepsis, sepsis and hemorrhage, and cholesterol emboli at 1, 2, 3, and 6 days after L-NMMA administration, respectively.

Safety

No patient died during L-NMMA administration. We were unable to detect any clinical or laboratory adverse effect of L-NMMA treatment.

Discussion

The ideal pharmacological treatment of cardiogenic shock is elusive. Treatments designed to improve myocardial contractility of patients with cardiogenic shock have repeatedly failed in clinical studies. This might be explained by the finding that cardiac function parameters (cardiac index, ejection fraction) in the range found in most patients with cardiogenic shock are commonly found in patients without shock. However, as demonstrated in the present study, SVR measurements in most patients with cardiogenic shock are only slightly above normal. Therefore, it is possible that maladaptive mechanisms, rather than the decreased cardiac function per se, may contribute to the high morbidity and mortality in cardiogenic shock.

In the present study, we have found that L-NMMA administration to patients with cardiogenic shock induces a selective and significant vasoconstriction leading to a steep increase in MAP without clinical signs of further cardiac or other ischemia. This increase in SVR (afterload) was accompanied by a small and transient decrease of cardiac index and virtually no change in pulse rate and pulmonary capillary wedge pressure (preload), implying that myocardial contractility increases during L-NMMA administration. Accordingly, L-NMMA induced a brisk diuresis and allowed for rapid weaning of mechanical ventilation and IABP. Seven out of eleven patients deemed by 2 senior cardiologists to be beyond treatment are alive and well at 1 month of follow-up. The results of the present study could be explained by the following mechanisms:

Improved Myocardial Perfusion

Review of the literature shows conflicting data regarding the effect of L-NMMA on coronary blood flow. In some studies, it was demonstrated that L-NMMA actually increases coronary blood flow after ischemia, thus improving contractility.\(^1\) In a further study, myocardial perfusion was not restored despite successful revascularization of the infarct related artery in patients with acute ischemia.\(^2\) Therefore, it is possible that a viscous cycle exists, starting with a decrease in cardiac contractility not compensated by sufficient peripheral vasoconstriction, which leads to decreased MAP. In the presence of ischemia, the autoregulation of coronary flow in the infarct related myocardium is lost; therefore, the decreased MAP leads to impaired myocardial perfusion, inducing more ischemia, stunning, and further decrease in cardiac performance. Accordingly, the significant increase in MAP achieved by L-NMMA might improve myocardial perfusion, thus relieving ischemia and stunning and improving myocardial performance.

Direct Effect on Myocardial Contractility

Recent experimental data have shown that NO has a biphasic effect on the myocardium\(^3\): at low levels NO induces a beneficial effect in coupling of local myocardial contractility to coronary supply and on myocardial relaxation, hence maintaining the Frank-Starling mechanism.\(^4\) Therefore, too little NO release may lead to self-perpetuating ischemia and pulmonary edema. Indeed, we have demonstrated that in patients with severe pulmonary edema not complicated by
hypotension, administration of high-dose nitrates improves control of pulmonary edema and prevents myocardial infarction.\textsuperscript{5} However, at higher concentrations, NO decreases myocardial contractility, an effect that can be reversed with L-NMMA administration.\textsuperscript{6,7} This effect is especially important in the context of the present study because it has been demonstrated that NO levels increase substantially during acute cardiac decompensation.\textsuperscript{8}

Two further mechanisms may explain the beneficial effect of L-NMMA. First, NO inhibits the positive inotropic response to $\beta$-adrenergic stimulation in humans. Therefore, L-NMMA may augment the effect of catecholamines. Second, NO might have some negative effects on the ischemic myocardium glucose metabolism, which can be blocked by L-NMMA.

In the present preliminary study, we were unable to determine which mechanism is responsible for the observed beneficial effect of L-NMMA. However, one important conclusion emerges from our data, as well as recent studies of cardiogenic shock. It seems that drugs that increase cardiac performance have a negative effect in such patients; IABP has only a transient effect on hemodynamic variables without improving outcome and even immediate coronary revascularization was shown lately to produce only a modest effect on immediate survival.\textsuperscript{9} Therefore, increasing cardiac contractility per se should no longer be regarded as the only target in the treatment of cardiogenic shock. It is possible that in acute heart failure, similar to chronic heart failure, the effect of neurohormonal vascular mediators may be an equally important determinant of clinical outcome, and specific targeting of these deleterious mediators should take precedence to nonspecific and possibly harmful attempts to increase cardiac output and blood pressure. Manipulation of the NO pathway could be one of these new treatment strategies.

**Limitations of the Present Study**

The results of the present study are only a preliminary report of L-NMMA in a small number of patients with the most extreme form of cardiogenic shock. Larger, prospective, placebo-controlled studies are required to examine the effect of different doses of L-NMMA in patients with cardiogenic shock of various etiologies and different degree of severity.

**References**

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