LINCS: L-NAME (a NO synthase inhibitor) In the treatment of refractory Cardiogenic Shock

A prospective randomized study

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Aims To evaluate the effect of L-NAME (a nitric oxide synthase inhibitor) in the treatment of refractory cardiogenic shock.

Methods and results We enrolled 30 consecutive patients with refractory cardiogenic shock (systolic blood pressure that deteriorated progressively to <100 mmHg during an acute coronary syndrome despite maximal percutaneous coronary revascularization, intra aortic balloon pump, and IV dopamine, furosemide and fluids treatment for at least 1 h, accompanied by signs of peripheral hypoperfusion). Patients were randomized to supportive care alone (n=15, control group) or to supportive care in addition to L-NAME (1 mg/Kg bolus and 1 mg/Kg/h continuous IV drip for 5 h n=15).

Death at one month was 27% in the L-NAME group vs. 67% in the control group (p=0.008). Unaugmented mean arterial blood pressure at 24 h from randomization was 86±20 mmHg in the L-NAME group vs. 66±13 mmHg in the control group (p=0.004). Urine output increased at 24 h by 135±78 cc/h in the L-NAME group vs a decrease of 12±87 cc/h in the control group (p<0.001). Time on IABP and time on mechanical ventilation were significantly shorter in the L-NAME group.

Conclusions The results of the present study further support our previous observation that NO synthase inhibitors are beneficial in the treatment of patients with refractory cardiogenic shock.


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KEYWORDS
Cardiogenic Shock; Nitric-Oxide; NO synthase inhibitors

Background

Despite significant improvement in the treatment of cardiogenic shock, including early revascularization, supportive treatment with intra aortic balloon pump (IABP), mechanical ventilation and diverse pharmacological treatments, the outcome of patients with cardiogenic shock remains dismal.1 In the SHOCK study it was demonstrated that early revascularization improves the outcome of cardiogenic shock patients. However, this effect is delayed (30 days from revascularization and beyond) and the 1-week mortality is not affected.

In previous studies it was demonstrated2,3 that the main haemodynamic findings in patients with cardiogenic shock are a significant decrease in cardiac contractility as reflected by an extremely low cardiac index (CI), mean arterial blood pressure...
(MAP) and cardiac power index (Cpi = MAP × CI). However, in most patients systemic vascular resistance (SVRi) is only mildly increased, sometimes within the normal range. Therefore, low SVRi may have a significant role in the pathophysiology of cardiogenic shock.

Nitric Oxide (NO) is a potent vasorelaxant, counterbalancing sympathetically-mediated vasoconstriction. NO has also been shown to exhibit a bi-phasic effect on the myocardium: low levels result in a positive inotropic effect while high levels cause a negative inotropic effect through suppression of mitochondrial respiration. Recent studies have suggested that increased levels of NO may have a detrimental effect on the outcome of extensive myocardial infarction (MI) in animal models through a direct effect on the myocardium during ischemia-reperfusion. Hence, we hypothesized that excess NO might be a significant contributor to circulatory failure in cardiogenic shock via direct effects on the myocardium and peripheral circulation. Large myocardial infarctions are associated with the release of inflammatory cytokines that trigger NO overproduction in heart and blood vessels. Such NO overproduction by being a potent myocardial depressant and vasorelaxant might induce a vicious cycle of decreased myocardial contractility, vasodilation, decreased end-organ perfusion, ischaemia, shock and death.

In 1988, it was demonstrated that arginine is the biochemical precursor to NO and that N^o^-substituted arginine analogs are competitive inhibitors of NO synthase (NOS) isoforms. Studies in rats and guinea pigs with NOS inhibitors established that arginine-derived NO is a major physiological determinant of resting blood pressure and flow and this result was later confirmed in man. Therefore, it is possible that NO synthase inhibitors (NOSi) by both reducing the direct deleterious effect of NO on the myocardium and by inducing vasoconstriction, hence improving MAP and coronary perfusion pressure, may be efficacious in the treatment of cardiogenic shock.

In a previous feasibility study we had shown that the administration of L-NMMA (NG-monomethyl L-arginine, a NOSi) produced beneficial hemodynamic effects in 11 patients with long lasting (>24 h) refractory cardiogenic shock. We had observed that L-NMMA administration yielded a surprising 64% 1-month survival. No untoward adverse effects of NOSi were observed during the study, and in no patient ischemia was exacerbated or haemodynamic status deteriorated during NOSi administration. Therefore, in the present study we investigated, in a prospective randomized fashion, whether early administration of L-NAME to patients with early, refractory cardiogenic shock would improve their 30-days outcome.

Patients and methods

Patients

All patients admitted to the coronary intensive care unit due to an acute coronary syndrome accompanied by hypotension and peripheral hypoperfusion (cardiogenic shock) were screened to enter the study. Acute coronary syndrome was defined by significant (>2 mm) ST elevations or depressions on 12 lead EKG in at least two consecutive leads representing the same myocardial wall and a significant (>5 times the upper limit of normal) increase in CK-MB. Patients were treated by inotropic amines (dopamine and norepinephrine), intravenous fluids and furosemide, mechanical ventilation. All patients received IABP support and were immediately referred for coronary catheterization and revascularization. Coronary revascularization was performed by percutaneous coronary intervention (PCI) only. Swan-Gantz catheters were placed under fluoroscopy after the coronary catheterization and revascularization.

Inclusion criteria

We included in the present study all consecutive patients that had a deteriorating hypotension as manifested by a progressive decrease in un-augmented systolic blood pressure to <100 mmHg accompanied by signs of peripheral hypoperfusion more than 1 h after PCI, despite intensive support by IABP, mechanical ventilation, intravenous (IV) dopamine (at least 7 µg/kg/min), fluids (at least 100 cc/h) and furosemide. Unaugmented blood pressure was measured after turning off the IABP for 2 min. Fluid administration was guided initially by chest X-ray and O2 saturation by pulse oxymetry. Swan-Gantz catheters were inserted only during coronary angiography.

Since patients were supported by IABP and an aggressive treatment regimen of IV fluids and catecholamines, urine output was not an inclusion criteria. This inclusion criteria was devised based on our previous experience that with the advent of the above mentioned treatment regimen, most cardiogenic shock patients although severely hypotensive and oliguric at admission can be initially...
stabilized and augmented blood pressure and urine output are initially restored in response to the treatment. However, in patients in whom stable blood pressure cannot be maintained despite these aggressive measures and percutaneous revascularization, the prognosis is dismal, they require increasing doses of catecholamines and usually succumb to either multiorgan failure or sepsis. Hence, by the time significant oliguria develops despite such aggressive treatment, the patient has already deteriorated into multiorgan failure and may be beyond treatment. Hence our decision to randomize patients early, based on deteriorating blood pressure despite the aggressive treatment protocol, before patients have developed significant multi-organ failure and oliguria.

Exclusion criteria

Hypotension related mainly to right ventricular infarction or any significant mechanical complication or valvular disease, inability to perform PCI to the infarct related vessel, significant renal impairment as evident by creatinine >2.5 mg/ml and fever >38 °C.

Study protocol

The study protocol was approved by both the hospital and national ethical review board. Informed consent was obtained from patients (when possible) or from next of kin. Patients meeting inclusion criteria and not meeting exclusion criteria were randomized by a blinded investigator according to a pre-determined list to receive L-NAME (N\textsuperscript{G}\textsuperscript{-}Nitro-L-Arginine-Methyl Ester. Hydrochloride by ClinAlfa, CalBiochem).

One milligram per kilogram bolus and 1 mg/kg/h for 5 h or no treatment. The dose used was based on the results of a previous study showing significant haemodynamic benefits in patients with refractory cardiogenic shock.\textsuperscript{13} L-NAME and L-NMMA are equipotent in inhibiting NO production from arginine. After randomization background treatment including IABP rate, mechanical ventilation and intravenous amines, fluids and furosemide were kept constant in both study arms for 24 h unless otherwise required by patients’ condition. Prior to study drug administration and at 2, 6 and 24 h from randomization full haemodynamic assessment was performed including MAP, CI (by thermodilution), right atrial pressure and pulmonary capillary wedge pressure. All CI measurements were performed after IABP was turned off for 2 min.

Primary end-point

All cause mortality at 30 days.

Secondary end-points

(1) All cause mortality at 1-week and 4 months (2) Time on IABP (3) Time on mechanical ventilation (4) MAP at 24 h and MAP change from baseline to 24 h. All MAP measurements were performed with IABP off for 2 min while inotropic amines remained uninterrupted, (5) Urine output at 24 h and change in urine output from baseline to 24 h, (6) Change in CI, Cpi and SVRi at 2, 6 and 24 h from randomization. Cardiac power index (Cpi) is the product of MAP and CI used previously by others and us\textsuperscript{3,14,15} for the evaluation of left ventricular contractile power.\textsuperscript{7}

Echocardiographic ejection fraction and wall motion scores at 4 months follow-up.

Analysis of echocardiographic and coronary catheterization results

The echocardiographic results were analysed immediately by a blinded experienced echocardiographer. All coronary catheterization films were analysed at study end by a blinded invasive cardiologist who was not aware of treatment allocation or patient’s outcome. In all coronary angiographies we determined the TIMI flow grade\textsuperscript{16} and TIMI frame count\textsuperscript{17} according to previously described methods. Blush was determined by previously described methods\textsuperscript{18} as either existing (TIMI myocardial perfusion >1) or non existing (TIMI myocardial perfusion=0).

Statistical analysis

All data were analysed on intention to treat basis. For the analysis of secondary end-points patients who died before 1-week from randomization were assigned 1 week of IABP and mechanical ventilation support. For the analysis of coronary catheterization results patients with TIMI 0 flow were assigned TIMI frame count of 150. We used the Fisher exact chi-square test to compare categorical values and the Student’s t-test to compare continuous values.

Changes in CI, MAP, Cpi and SVRi over the first 24 h were analysed by the one-way analysis of variance with repeated measures. One-month and one-week survival were analysed by the Kaplan–Meier method. \(P\) values <0.05 were considered significant.
### Results

Between November 1999 and June 2002, 30 consecutive patients were enrolled in the study. The baseline characteristics, time-table of cardiogenic shock development, time to randomization and haemodynamic support prior to randomization are presented in **Table 1**. The coronary catheterization and PCI results are described in **Table 2**.

#### Primary end-point

The 1-month survival was 73% in the L-NAME arm vs 33% in the no treatment arm. The Kaplan-Meier survival curves are presented in **Fig. 1**.

#### Secondary end-points

1. One-week survival was 80% in the L-NAME arm vs. 40% in the no treatment arm. The Kaplan–Meier survival curves are presented in **Fig. 2**. Most of the mortality in this study was during the first week due to progressive multi organ failure and shock. In none of the patients death occurred due to withdrawal of life support. Between one week and one month one patient died in the L-NAME arm due to complications of bypass surgery and one patient died suddenly in the no-treatment arm.

2. Changes in MAP and urine output over the first 24 h as well as time on IAPB and mechanical ventilation are presented in **Table 3**. Importantly, L-NAME has induced a statistically significant increase in MAP while at the same time significantly increasing urine output. We observed a significant benefit for L-NAME treatment in all secondary endpoints measured, including time of mechanical ventilation and time of IABP support.

3. Changes in haemodynamic parameters including MAP, CI, Cpi and SVRi are presented in **Fig. 3**. Overall, the results of the haemodynamic measures of the present study are identical with the results of our previous study. As compared to measures in patients not receiving L-NAME, initially, L-NAME induced a significant vasoconstriction resulting in a steep increase in SVR and blood pressure resulting in a mild decrease in cardiac index. After treatment discontinuation SVR decreased, returning to almost pre-treatment levels at 24 h. On the other hand at 24 h from treatment start (17 h from treatment discontinuation), mean arterial blood pressure and cardiac index remained above baseline measures.
Cardiac power index, a measure of left ventricular power, the product of simultaneously measured CI and MAP, increased throughout the study in patients who received L-NAME. As compared to patients not receiving L-NAME and baseline measures in patients receiving L-NAME cardiac power increase peaked (and became statistically different) at 24 h, 17 h after study drug is continuation, while SVR has already returned to pre-treatment levels. Since most patients in the no-treatment arm died before the 4-months follow up visit, analysis of changes in echocardiographic parameters could not been performed.

Safety
Despite the significant increase in MAP during L-NAME administration we observed no untoward adverse events that could be related to L-NAME treatment. No patient died while on study drug. We observed no cerebrovascular accidents or new focal neurological phenomena in the L-NAME arm. Although no patient developed any mechanical complications including ventricular septal defect or cardiac rupture while on study drug, one patient in the L-NAME arm developed haemoragic pericardial effusion that required percutaneous evacuation. Cardiac rupture was not detected and the patient is alive and well 6 months after the acute event.

Table 2  Coronary catheterization findings and PCI results

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>L-NAME</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of vessels involved.</td>
<td>2.4±0.7</td>
<td>2.6±0.6</td>
<td>0.51</td>
</tr>
<tr>
<td>LAD involvement (%)</td>
<td>100</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Culprit:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Main (%)</td>
<td>7%</td>
<td>7%</td>
<td>1</td>
</tr>
<tr>
<td>Proximal LAD (%)</td>
<td>79%</td>
<td>72%</td>
<td>0.61</td>
</tr>
<tr>
<td>Other LAD (%)</td>
<td>0%</td>
<td>7%</td>
<td>0.31</td>
</tr>
<tr>
<td>Circumflex (%)</td>
<td>7%</td>
<td>7%</td>
<td>1</td>
</tr>
<tr>
<td>RCA (%)</td>
<td>7%</td>
<td>7%</td>
<td>1</td>
</tr>
<tr>
<td>No. of vessels revascularized</td>
<td>1.3±0.5</td>
<td>1.4±0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Stent for Infarct related artery (%)</td>
<td>80%</td>
<td>92%</td>
<td>0.33</td>
</tr>
<tr>
<td>GP IIb/IIIa administration (%)</td>
<td>74%</td>
<td>78%</td>
<td>0.75</td>
</tr>
<tr>
<td>Culprit:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Stenosis pre-PCI</td>
<td>96±5</td>
<td>96±6</td>
<td>0.8</td>
</tr>
<tr>
<td>TIMI flow pre-PCI</td>
<td>0.9±1.1</td>
<td>0.9±1.1</td>
<td>0.98</td>
</tr>
<tr>
<td>TIMI frame count pre-PCI</td>
<td>103±54</td>
<td>104±58</td>
<td>0.94</td>
</tr>
<tr>
<td>% Stenosis post-PCI</td>
<td>12±26</td>
<td>12±26</td>
<td>0.93</td>
</tr>
<tr>
<td>TIMI flow post-PCI</td>
<td>2.2±1</td>
<td>1.9±1</td>
<td>0.41</td>
</tr>
<tr>
<td>TIMI frame count post-PCI</td>
<td>43±44</td>
<td>58±50</td>
<td>0.42</td>
</tr>
<tr>
<td>% with TIMI 3 post-PCI</td>
<td>53%</td>
<td>53%</td>
<td>1</td>
</tr>
<tr>
<td>% with Blush Score 0 post PCI</td>
<td>80%</td>
<td>73%</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Study Discontinuation

After the recruitment of 30 patients the safety committee decided to discontinue recruitment due to the very significant survival benefit in the L-NAME arm.

Discussion

Despite immense improvement in supportive treatment the prognosis of cardiogenic shock remains dismal with 1-month mortality >45% reported in all recent studies. The use of early coronary reperfusion has decreased the 1-month mortality to 47% (1) however; this treatment modality has not reduced the early (1-week) mortality related to cardiogenic shock. Based on haemodynamic calculations we have suggested that cardiogenic shock is related to an acute decrease in cardiac contractility (Cpi) not met by an adequate increase in SVRi.2,3 Moreover, frequently these haemodynamic changes are not reversed immediately by coronary revascularization, probably since revascularization usually does not alleviate stunning during the first few days after reperfusion. This phenomenon is probably even more common in patients with acute coronary syndromes who develop cardiogenic shock in whom TIMI III flow is achieved less frequently by PCI than in patients treated for acute coronary events without cardiogenic shock.19 Indeed, in the present study we found that despite a significant decrease in the stenosis of the culprit coronary artery by PCI (96±6% to 12±26%), TIMI 3 flow was achieved in only 53% of the patients and blush score >1 was achieved in only 13%. Hence, in cardiogenic shock patients early PCI indeed achieves an 'open artery' however it seldom restores flow in the infarct related artery or adequate perfusion of the ischaemic myocardium. Therefore, a new therapeutic approach that will alleviate stunning and improve the significant haemodynamic disturbances is required.

The present report is our second study examining the effect of NOsi in the treatment of refractory cardiogenic shock, i.e. cardiogenic shock that does not respond to supportive treatment and immediate PCI. Similarly to the results of our previous report, the results of the present study show that NOsi induce a favourable haemodynamic response in cardiogenic shock patients. By transiently increasing SVRi and progressively increasing Cpi, NOsi induce a rapid, progressive and long lasting increase in MAP and urine output. This enables early withdrawal of IABP and mechanical ventilation and prevents patient deterioration into multiorgan failure while decreasing significantly complications related to long-term invasive support. Most of the effect of NOsi is achieved during the first few days of treatment and the effect is maintained thereafter throughout 4-months of follow-up.

There are two possible explanations for the positive effect of NOsi in cardiogenic shock:

(1) Direct myocardial effect: During acute ischemic events NO production increases significantly, largely due to induction of NOS.20 Although at low doses NO has beneficial effects on myocardial contractility, at higher doses it has been shown to decrease myocardial contractility.7-9 Furthermore, it was demonstrated in animal models that NO production during ischemia-reperfusion21 is deleterious. Moreover in some recent studies iNOS knockout mice were shown to survive myocardial infarction better than control.11,12

The exact mechanism of this deleterious effect of high levels of NO is not known, however some studies have demonstrated that high levels of NO affect myocardial contractility directly by uncoupling of calcium metabolism.22,23 Hence, it is possible that NOsi by decreasing NO production might counteract this deleterious mechanism, improving rapidly the myocardial stunning induced by toxic levels of NO. Indeed in the present study, we show a gradual increase in Cpi over the first 24 h

Table 3  Secondary Outcome measures in the 2 groups

<table>
<thead>
<tr>
<th></th>
<th>No Treatment</th>
<th>L-NAME</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Patients</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Unaugmented MAP at 24 h (mmHg)</td>
<td>66±13</td>
<td>86±20</td>
<td>0.004*</td>
</tr>
<tr>
<td>Unaugmented MAP Increase (mmHg)</td>
<td>+3.6±9.3</td>
<td>+24.8±18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urine Output at 24 h (cc/h)</td>
<td>110±87</td>
<td>210±86</td>
<td>0.009*</td>
</tr>
<tr>
<td>Urine Output Change (cc/h)</td>
<td>−12±87</td>
<td>+135±78</td>
<td>0.001*</td>
</tr>
<tr>
<td>Time on IABP (h)</td>
<td>103±60</td>
<td>59±58</td>
<td>0.043*</td>
</tr>
<tr>
<td>Time on Mechanical Ventilation (h)</td>
<td>140±55</td>
<td>77±60</td>
<td>0.028*</td>
</tr>
<tr>
<td>4-Month Survival</td>
<td>33%</td>
<td>73%</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

*P<0.05
from L-NAME administration, consistent with such possible effect.

(2) Increased vascular resistance, blood pressure and coronary perfusion: As previously stated the main haemodynamic changes observed in patients with cardiogenic shock are severely decreased Cpi and inadequate increase in SVRI leading to low CI and MAP resulting in decreased coronary perfusion. Since in most cardiogenic shock patients other coronary vessels (beside the culprit artery) have significant atherosclerotic lesions, the decreased blood pressure and hence coronary perfusion might lead to further ischemia in remote regions leading to a spiral decrease in myocardial contractility and increased severity of shock. Furthermore, in an elegant study Karunanithi et al.24 have shown that a direct correlation exists between cardiac contractility and afterload. Hence, the decreased MAP observed in cardiogenic shock patients might lead to a vicious cycle by which hypotension begets more ischemia, less myocardial contractility and shock. Therefore, by inducing a short period of increased MAP via the strong vasoconstrictive properties of NOSi, this vicious cycle may be terminated. Indeed, in the present study we were able to demonstrate that L-NAME induces significant rapid vasoconstriction leading to a brisk increase in MAP that is later maintained despite the decrease in SVRI.

In the present study we could not determine the exact mechanism of L-NAME’s effect. However, in the future we are planning further studies in which NOSi will be administered in lower doses over a longer period of time. Since lower doses of NOSi are not expected to induce significant vasoconstriction and hence an increase in MAP, this will enable us to differentiate between those two possible mechanisms of action of NOSi. Although we have not observed any significant side effects in the L-NAME arm, one must remember that all our patients were treated by primary PCI and no thrombolytics. Theoretically, the haemodynamic “turmoil” induced by NOSi at the doses used in the present study, especially the significant acute increase in MAP, might be disadvantageous in patients treated by lytics. Hence, if a lower dose NOSi retains the efficacy observed by higher doses it will enable its safe use in a larger cohort of patients treated by thrombolytics.

Fig. 3 Haemodynamic changes during 24 h of treatment in the two treatment arms: (a) Mean arterial blood pressure (mmHg), (b) Cardiac Index (Liter/min./M²) (c) Cardiac power index (Cpi=MAP*CI), (mmHg*Liter/min./M²) (d) SVRI (SVRI=[MAP-RAP]/CI), (mmHg/Liter/min./M²).
In the present study the effect of NOSi was examined in a small cohort of selected patients with refractory cardiogenic shock. A larger multi-centre, placebo controlled randomized study is required in order to confirm the results of the present study. Furthermore, NOSi administration should be examined in other patient groups (prior to PCI or in patients who are not candidates for PCI) and also different doses.

In recent years, L-NMMA was examined in patients with septic shock. Although initial phase II studies have suggested that L-NMMA was beneficial in such patients, a later phase III study (which was never published) has shown negative results. However, the doses used in the septic shock trials, and especially in the negative phase III study were extremely high (up to 20 mg/h for up to 14 days). Also, in this study dobutamine was administered at relatively high doses in order to maintain the CI >3 litter/min/M², despite the significant vasconstriction induced by the high-dose L-NMMA. Hence, we believe that interpretation of these results, especially in the doses used is difficult and the applicability of this data to patients with cardiogenic shock administered low-doses of L-NAME for a relatively short period is limited.

Conclusions

This study further supports our previous results indicating that NOSi may be a new, safe, efficacious treatment modality for patients with cardiogenic shock. Further studies examining different doses of NOSi in larger patients cohorts will be required to confirm the results of the present study.

References

24. Karunanithi MK, Young JA, Kalnins W et al. Response of the intact canine left ventricle to increased afterload and