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Review

Nitric Oxide Synthase Inhibitors in Post-Myocardial Infarction Cardiogenic Shock—an Update

EDO KALUSKI, M.D., FACC, ALBERTO HENDLER, M.D., ALEX BLATT, M.D., NIR URIEL, M.D.

Department of Cardiology, Assaf Harofeh Medical Center, Zrifin, Israel

Summary: Cardiogenic shock (CS) in acute myocardial infarction, after successful coronary angioplasty, still carries a case fatality rate of 50%. These patients succumb to a systemic metabolic storm, superimposed on extensive myocardial necrosis and stunning. Nitric oxide (NO) overproduction contributes to the pathophysiology of this morbid state. Current data regarding the physiologic effects of NO and nitric oxide synthase (NOS) inhibitors on the cardiovascular system are reviewed. Clinical trials assessing the safety and efficacy of NOS inhibitors in CS are summarized.

Key words: nitric oxide, nitric oxide synthase inhibitors, cardiogenic shock, NG-monomethyl-L arginine acetate, ST-elevation myocardial infarction

Introduction

Cardiogenic shock (CS) is the most common cause of in-hospital mortality after acute ST-elevation myocardial infarction (STEMI), even in the era of primary percutaneous coronary interventions (PCIs). The case fatality rate remains to be 30–50% even in the face of angiographically and clinically successful PCI (as judged by coronary flow or blush criteria and ST-elevation resolution, respectively). Most survivors of CS, however, enjoy a satisfactory quality of life.

Patients who succumb to CS seem to suffer from extreme systemic inflammatory hormonal and metabolic imbalance, along with profound myocardial stunning. It is possible that nitric oxide (NO) overproduction contributes to the pathophysiology of this morbid state. We review the current knowledge regarding the physiologic effects of NO and nitric oxide synthase (NOS) inhibitors on the cardiovascular system and point out their potential role in the pathophysiology of heart failure. We summarize the current data available regarding the safety of NOS inhibitors and the potential role of these agents in CS accompanying STEMI.

Address for reprints:

Edo Kaluski M.D., F.A.C.C.
Director of Coronary Care Unit
Assaf Harofeh Cardiology Institute
Zrifin, DN Beer Yacov
70300, Israel
e-mail: ekaluski@gmail.com

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Nitric Oxide Synthase Physiology (Fig. 1)

Nitric oxide synthase enzymes convert L-arginine to NO and citrulline. Three NOS isoforms play regulatory functions in all tissues and systems. Nitric oxide is a free radical (possesses an unpaired electron) and therefore highly reactive. It is metabolized within seconds to yield nitrite (NO_2-), nitrate (NO_3-), and nitrosothiols. Several pathways reduce NO_2 back to NO, hence NO_2 is considered the major storage pool[1] of NO in mammalian tissue and body fluids. Nitrite,[2] nitrosothiols, or N-nitrosoproteins serve as relatively stable precursors of NO, which allow NO to carry out more sustained and remote paracrine functions. Heiss *et al.*[3] reported that NO-related species can be used as markers of NO levels. Nitrite is also an obligatory intermediate in the formation of NO from nitrates (NO_3-).

Nitric oxide employs two distinct signaling modes: (1) Guanalyl cyclase pathway: low levels of NO (EC 50 of 100 nM) result in activation of the soluble guanalyl cyclase (by binding its haem-moiety and forming an Fe-nitrosyl complex) which augments the production of cyclic guanosine monophosphate (GMP) from guanosine triphosphate (GTP). The latter can activate protein kinase. (2) Protein thiol nitrosylation (S-nitrosylation) modulates the activity of numerous key proteins (such as the L-type Ca+ channel, the ryanodine receptor).

Neuronal NOS (NOS-1) and endothelial NOS (NOS-3) produce NO in low concentration (nM). Their activity depends on the presence of calcium-calmodulin, L-arginine and several co-factors (FAD/ FMN, NADPH and HB4). Inducible (macrophage) NOS (iNOS or NOS –2) is activated under certain states, resulting in extremely high tissue and plasma NO levels (μm). The activity of NOS-2 does not depend on calci-

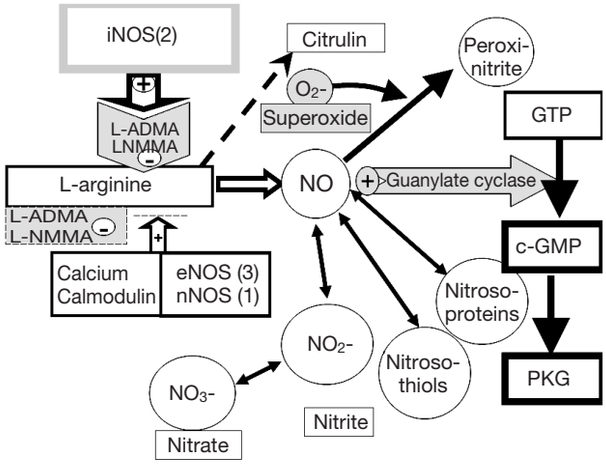

FIG. 1 Nitric oxide (NO) metabolism. Abbreviations defined in text under "Nitric Oxide Synthase Physiology."

um calmodulin. Nitric oxide synthase enzymes have their natural inhibitors: asymmetric dimethyl arginine (L-ADMA) and NG-monomethyl-L-arginine acetate (L-NMMA). High levels of NOS inhibitors are associated with certain pathologic states. Nonspecific inhibitors (such as caveolin) can inhibit NOS –3 in certain pathologic states (such as hypcholesterolemia). The L-ADMA levels soar with oxidative stress and decline with certain medications.

Cyclic GMP in arterial smooth muscle cells (SMC) activates protein kinase G (PKG) that promotes phosphorylation of target molecules, resulting in vascular SMC relaxation. The PKG system counteracts vasoconstrictive effects of the phospholipase C system and its secondary messengers: inositol phosphate and diacylglycerol. The latter, when activated (by endothelins, angiotensin-2, cathecolamines, or vassopressin), results in diacylglycerol-mediated protein kinase C activation and inositol phosphate-mediated releases of calcium from the sarcoplasmic reticulum. These actions result in membrane activation, sodium influx, and contraction of smooth muscle cells. Hence, the major effect of NO on arterial SMC is blocking activation of the phospholipase C system.

The Potential Role of Nitric Oxide in Cardiogenic Shock

Myocardial infarction (MI), heart failure, and cardiogenic shock (CS) are all associated with an inflammatory,[4] neurohormonal,[5,6] and metabolic storm. These systemic effects are clearly associated with unfavorable prognosis.[7] Hochman[8] suggests that ST-elevation myocardial infarction (STEMI) and subsequent CS yield a systemic inflammatory response, activation of iNOS, and excessive NO production. The possible cardiovascular effects of excessive NO are summarized in Table I. Nitric oxide promotes excessive vasodilation at one end and suppression of myocardial contractility, mitochondrial respiration, and response to cathecolamines at the other end. The toxic radical peroxynitrite (produced from superoxide and excessive NO) further suppresses myocardial contractility.

Nitric oxide excess results in a decline of mitochondrial glucose utilization.[9,10] The NOS inhibitors such as N^G-nitro-L-arginine (L-NNA)[11] alleviate inhibition of mitochondrial respiration during high work stress (produced by dopamine and dobutamine) and maximal coronary vasodilatation. This NO-related inhibition results from interference with oxidative phosphorylation. Potential mechanisms are NO competition with oxygen over cytochrome-C oxidase and impaired enzyme activity (NO-related detrimental protein structural alterations of adenine nucleotide translocase, NADH CoQ reductase, succinate CoQ reductase[12]). N^G-nitro-L-arginine[13] reversed impaired oxidative phosphorylation[14] in failing canine hearts. This favorable effect of L-NNA on myocardial metabolism was not observed in the ischemic models.[15]

Another potentially harmful effect of NO is the attenuation of beta-adrenergic inotopic response.[16] Adrenergic agonists

TABLE I Effects of nitric oxide on the cardiovascular system in cardiogenic shock

Effect	Results
Nitrosylation of L-type calcium channels and ryanodine receptor with excess calcium release by the sarcoplasmic reticulum	Contractility↑
Upregulation of caveolin-3 and β_3 resulting in attenuation of β_1-adrenergic response	Contractility↓, chronotropy↓
Deleterious effects on ischemic or infarction and reperfusion models	Contractility↓ mortality ↑
Nitrosylation and suppression of cytochrome-C and other enzymes of the respiratory chain. Inhibition of maximal glucose utilization	Energy depletion, contractility↓
Cyclic GMP-mediated arterial smooth muscle cell relaxation resulting in vasodilatation	Systemic blood pressure↓ Myocardial and organ perfusion↓
Overproduction of peroxynitrite	Contractility↓
Translocation of n-NOS from sarcoplasmic reticulum to plasma membrane cavaeole	Contractility↓
Cyclic GMP mediated protein kinase G phosphorylation of troponin I	Lusitropy↑

Abbreviations: GMP = guanosine monophosphate, NOS = nitric oxide synthase.

stimulate NO release, which in turn results in a negative feedback of reduced adrenergic contractile response (probably via beta-3 adrenergic receptor). This was demonstrated both in rat[17] and human[18] failing hearts.

Nitric oxide synthase-3 localized with beta-adrenergic receptors and L-type calcium channel in the caveolae allows NO to inhibit beta$_1$-adrenergic-induced inotropy.[19]

The numerous effects of NOS on cardiac physiology and pathophysiology are beyond the scope of this manuscript and are reviewed elsewhere.[20] Hare[21] concludes that NO influences all aspects of excitation-contraction coupling, including receptor signal transduction, L-type calcium channel, sarcoplasmatic reticulum (SR) calcium release through the ryanodine receptor, and mitochondrial respiration. However, controversy regarding the directionality of NO effects remains, even with regard to the impact on myocardial contractility. Other potential effects of NO on the cardiovascular system include inhibition of platelet adhesion, enhancement of angiogenesis, attenuation of smooth muscle proliferation, and augmentation of inflammation.

Cardiogenic Shock in Acute Myocardial Infarction—beyond Revascularization

Cardiogenic shock occurs in 5.5–14% of STEMI and is the most common cause of death in hospitalized patients with STEMI. It is estimated that > 120,000 patients suffer from CS each year in Europe and North America. More than half of these patients do not survive to hospital discharge. Cardiogenic shock varies considerably with regard to time from STEMI onset, ongoing ischemia (chest pain, persistent and ST elevation or depression) and the etiology for pump failure (which is predominantly left heart failure (61–85%),[22] right heart failure (4–15%),[23] and mechanical or valvular complications (10–15%).[24] Of patients with CS, 10–15% present in this state on admission, one-third will develop CS in the first 24 h of admission, and one-half will develop CS > 24 h post admission.[25]

After immediate and brief stabilization efforts in the patient in CS (mechanical ventilation, intra-aortic counterpulsation, inotropes), coronary angiography and revascularization should be executed urgently. This is especially important in the presence of ongoing ischemia (chest pain, persistent and dynamic ST shift, and normal admission or current cardiac isoenzymes), mechanical complication mandating surgery, or when dealing with a deteriorating nonresponsive patient expressing hemodynamic or electrical instability. The role of early percutaneous coronary intervention (PCI) in CS is reflected in the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK) trial: The early invasive arm (PCI performed < 11 h from onset of MI) had a trend of improved survival at 30 days (53 vs. 44% p = 0.109).[26] At 6 months, absolute mortality reduction (13%) reached statistical significance (63 vs. 50%, p = 0.027). Patients aged < 75 years had a 20% absolute risk reduction of 6 months mortality (65 vs. 45%).[27] In the analysis of the SHOCK registry it appears that the 277 older patients (age > 75) benefited from early revascularization at least as much as the 588 younger patients (relative risk of 30 day mortality was 0.46 p = 0.002 for the former and 0.6 p = 0.045 for the latter).[28]

In the early PCI arm, the 30-day mortality was related to successful PCI (obtaining patency and flow in the infarct-related artery): mortality was 39% if PCI was considered successful and 85% if PCI was unsuccessful. Mortality was also related to post-PCI Thrombolysis In Myocardial Infarction (TIMI) flow: 38% for TIMI III, 55% for TIMI II, 100% for TIMI 0–I (p<0.001). Other predictors for mortality were age (p<0.001), lower systolic blood pressure (p = 0.009), increased time from randomization to PCI (p = 0.019), and multivessel PCI (p = 0.04).[29] Additional angiographic parameters that predicted hospital survival were initial TIMI flow (p = 0.032), number of diseased vessels (p = 0.004), culprit artery location, and left ventricular ejection fraction (LVEF).[30]

Pump Failure—Old Problem New Concepts

The modern patient with CS (who benefits from intra-aortic counterpulsation and mechanical ventilation along with inotropes) is not the "historical CS patient" described in the medical literature. Most of these fully supported patients with CS are not "cold and clammy" and maintain adequate arterial oxygen saturation (on mechanical ventilation) and adequate urine output. The contemporary patient with CS usually suffers from low cardiac output, low unaugmented mean arterial blood pressure, and elevated pulmonary capillary wedge pressure; however, multisystem failure due to tissue hypoperfusion does not occur in the majority of these maximally supported patients. Recently, new descriptors of pump performance, namely cardiac power (CPO = mean systemic arterial blood pressure multiplied by cardiac output) and Cardiac Power Index (CPI = mean arterial blood pressure multiplied by cardiac index) were introduced. Our work[31] as well as the work of others clearly shows that CS is characterized by the extreme reduction of CPI (usually < 120) that, if not reversed, is inconsistent with life. Finke *et al.*[32] reported that CPO and CPI were found to be the strongest independent hemodynamic correlates of in-hospital survival in 541 patients with CS enrolled to the SHOCK registry and SHOCK study. Despite early revascularization only 47% of the 152 patients in the early invasive arm of SHOCK survived at 30 days; the rest died mostly from intractable cardiogenic shock due to left pump failure. Zeymer *et al.*[33] reported similar results from the German ALKK registry: Between 1995 and 2000, 1,333 of 9,422 primary PCIs were performed on patients with CS. The in-hospital mortality was 46.1% and was related to post-PCI TIMI flow of the infarct-related artery. Other predictors were older age, multivessel disease, and PCI time delay.

Picard *et al.*[34] noted that severity of mitral regurgitation and LVEF were the major echocardiographic predictors of mortality. Surprisingly, mean LVEF reported was 31%,[34] which is frequently encountered in patients who are asymptomatic or minimally symptomatic.

Destunning or Reversal of Cardiac Dysfunction by Medical Therapy

The post-PCI CS following STEMI results from extreme pump failure related to late and suboptimal tissue reperfusion (impaired flow and reduced tissue perfusion) and profound myocardial stunning due to inflammatory, neurohormonal, and metabolic distemper;[4] some of this myocardial dysfunction is probably reversible.

The evidence supporting this notion is that among the 1-year survivors in the SHOCK trial (51.6% of the early revascularization arm and 33.3% in the medical stabilization arm), 58 and 57%, respectively, were in New York Heart Association (NYHA) functional class I and 27 and 23% were NYHA class II.[35]

Pump failure may be superimposed on suboptimal vasomotor regulation (insufficient vasoconstriction). Data from the SHOCK registry and trial reveal that systemic vascular resistance varied considerably among patients with CS averaging 1350–1400 dyne·s·cm^{-5} despite vasopressor therapy. Actually, the first line of therapy includes inotropic support, including dopamine, dobutamine, noradrenaline, and adrenaline. Although the literature suggests that noradrenaline is an inappropriate drug (from the hemodynamic standpoint) for STEMI-CS, our experience is quite different. Moreover, since most patients are relatively tachycardic, sometimes noradrenaline is the only inotrope that can be employed without subjecting the patient to extreme tachycardia, resulting in further hemodynamic embarrassment. The role of calcium enhancers such as levosimandan is yet to be defined. Although the literature has a few reports regarding the favorable role of amrinone and milrinone in CS, we were not impressed with these drugs in the post-STEMI CS cohort.

Nitric Oxide Synthase Inhibitors in Percutaneous Coronary Intervention Refractory Cardiogenic Shock

Seeking a relatively safe agent that would counteract profound hypotension on one hand while enhancing contractility without resulting in tachycardia or arrhythmias, we encountered NOS inhibitors. We conducted two separate studies that assessed the value of NOS inhibitors in patients with CS not responsive to optimal percutaneous coronary intervention (PCI) reperfusion and maximal medical therapy.

The first study employed L-NMMA (Clinalfa™, Calbiochem™, EMD Biosciences, Inc., an Affiliate of Merck KGaA, Darmstadt, Germany). This is a naturally occurring competitive NOS inhibitor with a theoretic half life of 60 min and was a natural choice for our first study, especially in view of its excellent safety records in previous trials employing a very high dose of this agent. We subjected 11 consecutive patients post STEMI and with CS who remained in refractory CS and hypotension after PCI, despite intra-aortic counterpulsation and high doses of dopamine. The dosage was 1 mg/kg intravenous bolus and 1 mg/kg/h intravenous drip for 5 h.[36] The study assessed the safety as well as the hemodynamic and clinical effects of the drug. We noted a 75% increase in systemic vascular resistance, along with mean arterial blood pressure rise exceeding 25 mmHg, accompanied by improved pump performance; CPI increased by 37.5% when compared with baseline (Fig. 2). Urine output was nearly tripled in the initial 24 h of therapy. Of the 11 patients treated, 8 (73%) were discharged from the coronary care unit and 7 (63%) remained alive at 3 months. Therapy was well tolerated and did not result in any notable adverse drug reactions. This was consistent with 320 studies that administered this drug to 7,000 men and women without notable clinical significant side effects.[37] The drug lacks clinical toxicity and carries a terrific safety profile. N^{G}-monomethyl-L-arginine acetate is safe for intravenous administration in humans up to a dose of 9 mg/kg/day for 24 h.

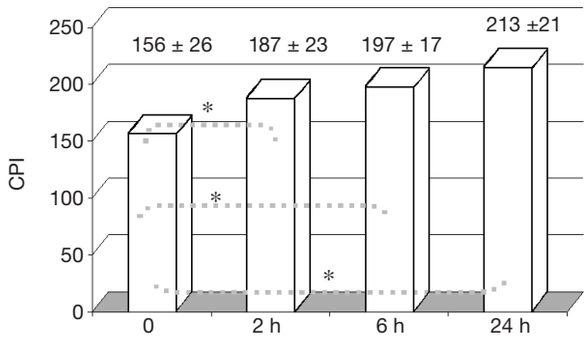

FIG. 2 L-NMMA effects on cardiac power index (CPI) (*p < 0.001).

Encouraged by these initial results, we randomized 30 consecutive patients in postinfarction PCI refractory cardiogenic shock to the double-blind, placebo-controlled study (L-NAME in Cardiogenic Shock, the LINCS study), which assessed the efficacy of L-NAME (NG-nitro-L-arginine-methyl ester hydrochloride) (ClinAlfa, CalBiochem), 1 mg/kg bolus and 1 mg/kg/h drip for 5 h in PCI-refractory cardiogenic shock.[38]

Death at 1 month (Fig. 3) was 27% in the L-NAME-treated patients and 67% in the control group (p = 0.008). At 24 h post

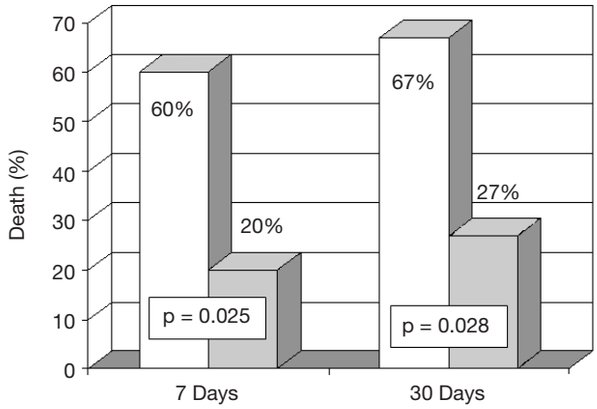

FIG. 3 L-NAME IN Cardiogenic Shock (LINCS) study: 7- and 30-day mortality. □ Control (n = 15), ▩ L-NAME (n = 15).

TABLE II LINCS—secondary study endpoints

	Control	L-NAME	p Value
Unaugmented SBP (mmHg) [a]	66 ± 13	86 ± 20	0.004
Change in mean SBP (mmHg) [a]	3.6 ± 9.3	24.8 ± 18	< 0.001
Change in urine volume (ml)/h [a]	−12 ± 87	135 ± 78	0.009
Intra-aortic counterpulsation duration (h) [a]	103 ± 60	59 ± 58	0.043
Mechanical ventilation time (h) [a]	140 ± 55	77 ± 60	0.028

[a] Mean ± standard deviation.
Abbreviations: SBP = systemic blood pressure, LINCS = L-Name IN Cardiogenic Shock.

TABLE III SHOCK-II primary endpoint (unpublished data[25])

	Placebo	0.15 mg/kg/h	0.5 mg/kg/h	1 mg/kg/h	1.5 mg/kg/h
2-h SVR change (dyne·sec·cm^{-5})	−58	+126	+50	+95	+206
2-h change in MAP (mmHg)	−1	+3	+1.3	−7	+4.5
15 m change in MAP (mmHg)	−2	+3	+4	+4.3	6.3
Inotrope downtitration (%)	15	20	6.7	26.7	35.7

Abbreviations: SHOCK = SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK?, MAP = mean arterial blood pressure, SVR = systemic vascular resistance.

randomization, mean arterial blood pressure was 86 ± 20 in the former and 66±13 in the latter (Table II). Urine output at 24 h was significantly increased in the former (135 ± 78 cc/h) and was reduced in the control arm (12 ± 87) with $p < 0.001$. There was a significant reduction in intra-aortic counterpulsation and mechanical ventilation duration. With the exception of the measurements obtained after 24 h, L-NAME did not affect CI favorably, but resulted in a significant rise (80% at 24 h) of CPI (Fig. 4).

These encouraging results prompted a multicenter, randomized phase II study called SHOCK-2. The study was planned to assess efficacy and safety of L-NMMA in PCI-refractory cardiogenic shock following STEMI. The primary endpoint of the study was systemic blood pressure response 2 h after drug initiation. The secondary endpoints were mortality at 1 and 6 months and change of hourly urine output. Additional objectives included cardiac power at 2, 6, and 24 h, the duration of vasopressor administration, and intra-aortic counterpulsation and ventilation support, as well as mortality as based on the presence of high-risk characteristics (age ≥ 75, creatinine > 1.5). The dosing of the L-NMMA arm ranged from a 0.15 mg/kg bolus (followed by 0.15 mg/kg/h drip for 5 h) to 1.5 mg/kg (followed by 1.5 mg/kg/h drip for 5 h).

This study suffered from many shortcomings:[39] uneven distribution of high-risk predictors (anterior STEMI) between the groups; relatively low dose of L-NMMA in two of the treatment arms; and chaotic downtitration of inotropes mostly in the two higher-dose LNMMA arms (which jeopardized any interpretation of the effect of L-NMMA on systemic blood pressure [Table III]). It was noted, however, that blood pressure rise at 15 min and systemic vascular resistance at 2 h were significantly higher in the medication group.

The Phase III International, Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled [parallel assignment] Study to Assess the Safety and Efficacy of Nitric Oxide Synthase Inhibition with Tilarginine Acetate Injection in Patients with Cardiogenic Shock Complicating Acute Myocardial Infarction (TRIUMPH)[40] study is an ongoing study to assess the safety and efficacy of NOS inhibitor tilarginine acetate versus placebo in patients with post-STEMI cardiogenic shock, following optimal PCI; the primary outcome is 30-day mortality; the secondary endpoint is resolution of cardiogenic shock. The study is expected to enroll 650 patients and to conclude data collection by January 2007.

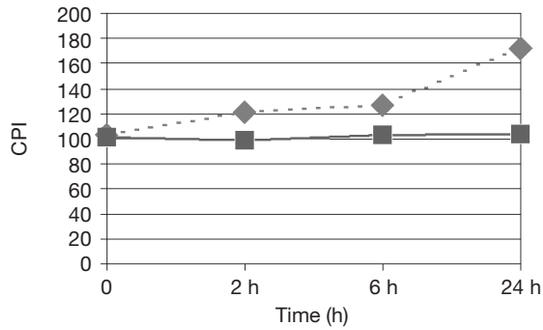

FIG. 4 Mean cardiac power index (CPI) over 24 h ($p = 0.03$). ◆ = L-NAME, ■ = control.

Conclusion

Cardiogenic shock due to ischemic left heart failure results from profound pump failure (as assessed by CPI < 120 or CPO < 180). Treatment involves stabilization and support of the patient, followed by urgent reperfusion and revascularization. However, post-PCI cathecolamine-refractory CS continues to claim the lives of nearly half of these patients. Pump failure appears to be partially reversible. Myocardial infarction and CS are associated with an inflammatory and neurohormonal activation, which is associated with unfavorable prognosis. It is possible that excessive NO production, along with other inflammatory mediators, is a contributing mediator to the pathophysiology of CS. The mechanisms by which NOS inhibitors exert their favorable hemodynamic effects (elevation of CPO, systemic vascular resistance, excessive diuresis, and improved mitochondrial respiration) are not completely understood. Initial single center studies assessing the role of two nonselective NOS inhibitors (L-NMMA and L-NAME) appear promising. The SHOCK II study demonstrated that L-NMMA possesses an excellent safety profile; however, efficacy data were difficult to ascertain. The role of tilarginine acetate (a nonselective NOS inhibitor) in STEMI-related CS should be elucidated by the ongoing TRIUMPH study.

Addendum

Results of the 50% interim analysis of TRIUMPH failed to show significant efficacy of tilarginine in the treatment of cardiogenic shock. The Data Safety and Monitoring Board stated that there was no safety issue; however, both groups of patients had the same number of adverse events. When efficacy was examined, there was no difference between the groups. The trial was therefore discontinued in August 2006.

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