LA419, a Novel Nitric Oxide Donor, Prevents Cardiac Remodeling Via the Endothelial Nitric Oxide Synthase Pathway

NO Donors as a Means of Antiremodeling

Ludovit Paulis, Fedor Simko

The discovery of NO as the endothelium-derived relaxing factor unleashed new horizons. NO is a ubiquitous radical exerting both hemodynamic and tissue growth-modifying effects. The vasodilative and antiproliferative properties of NO produced by endothelial NO synthase are considered to act beneficially within the cardiovascular system. However, under certain circumstances, the inducible NO synthase may produce large quantities of NO that may be harmful. Most NO effects can be attributed to the activation of soluble guanylate cyclase and the subsequent cascade of events including enhanced cGMP concentration, activation of cGMP-dependent kinase-1, and reduced intracellular calcium levels in target cells. NO acts as a principal regulator of vascular function. Venodilation and arterial relaxation result in a decrease of left ventricular pressure and chamber size, leading to attenuation of oxygen consumption. NO dilates epicardial coronary arteries, enhances collateral flow, and inhibits platelet aggregation. Moreover, NO was shown to inhibit collagen synthesis and to reduce cardiomyocyte growth. NO, thus, represents an opposing force to vasoconstrictors and growth-promoting substances, such as angiotensin II and endothelin.

The depression of NO signaling, including downregulated expression and attenuated enzymatic activity of NO synthase and scavenging of NO by oxygen-derived free radicals, seems to be a principal disorder in endothelial dysfunction. NO deficiency is, therefore, related to many cardiovascular pathologies, such as coronary atherosclerosis with myocardial ischemia, arterial hypertension with left ventricular hypertrophy, or heart failure. It is obvious that NO plays an important role in the circulatory physiology.

Nevertheless, the impact of therapeutically increased NO bioactivity on cardiovascular morbidity and mortality is unclear. In the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico 3 and International Study of Infarct Survival 4 trials, nitrates failed to reduce mortality when given after myocardial infarction. Although the effect of the combination of isosorbide dinitrate and hydralazine in the Vasodilator-Heart Failure Trial I and African American Heart Failure Trial compared with placebo was encouraging for heart failure treatment, the vasodilators were still inferior in comparison with enalapril. Moreover, no trial has been performed to show the effect of the sole use of NO donors on the reduction of cardiovascular events in hypertension or in chronic heart failure. At present, NO donors do not belong to first-line therapy in ischemic heart disease, heart failure, or hypertension, and NO delivery is recommended only when a well-established treatment is contraindicated or has an insufficient effect. The explanation for the failure of NO donors to become established in the evidence-based medicine is hard to address. The most prominent problems of NO donors are drug tolerance and NO resistance. An effort has been made to overcome these complications either by direct targeting of the soluble guanylate cyclase, the downstream messenger of NO pathway, or by developing novel NO donors with decreased susceptibility to free radicals or with enhanced cardioselectivity.

Recently, LA419, a new organic nitrate containing a thiol group, has been designed to treat clinical conditions associated with NO deficits. The thiol group in the molecule of LA419 was expected to protect the formed NO from being degraded by free radicals and, thus, to avoid nitrate tolerance and NO resistance. Experiments have shown that LA419 has anti-ischemic, antithrombotic, and antiatherosclerotic effects at doses that do not influence blood pressure. In this issue of Hypertension, Ruiz-Hurtado et al report the effect of LA419 on left ventricular hypertrophy and fibrosis induced by aortic stenosis. The use of LA419 in this study yields novel information for hypertension research on 2 major points. First, it directs attention from therapeutic approaches aimed at restoring the neurohumoral balance by attenuating adrenergic and renin-angiotensin-aldosterone system activation back to efforts to restore the balance by the enhancement of the NO vasodilator and antiproliferative activity. Second, the use of NO donors without hypotensive effects could enable the differentiation between effects mediated by hemodynamic load and effects of NO, per se. Ruiz-Hurtado et al found that LA419 reversed left ventricular remodeling and restored endothelial NO synthase:heat-shock protein 90 interaction, restored endothelial NO synthase and caveolin-3 expression, and restored cGMP content in the left ventricle but without reducing blood pressure. The
authors suggested that LA419 ameliorates cardiac remodeling via the restoration of NO signaling. Thus, NO is again placed in the role of a mighty molecule in the process of heart remodeling.

However, in relation to the antihypertrophic effect of LA419, several questions emerge. The first issue is that LA419 did not reduce blood pressure, either in clipped or in sham-operated rats. The NO release by LA419 may be expected to lead to peripheral vasodilation and blood pressure decrease. Nevertheless, we still do not have unequivocal evidence of the participation of endothelial products, including NO, in the pathogenesis of hypertension. Moreover, despite the fact that LA419 seemed to enhance the NO-soluble guanylate cyclase pathway in the left ventricle, NO formation was investigated neither in conduit or in smaller arteries nor in the brain or kidney, major organs participating in blood pressure regulation. We have shown previously that, although l-arginine improved NO synthase activity in the left ventricle, it failed to restore NO synthase activity in the kidney and brain of NGS-nitro-l-arginine methyl ester–induced hypertensive rats. Subsequently, l-arginine failed to prevent NGS-nitro-l-arginine methyl ester hypertension. Similarly, a potential cardioselectivity expected from the new generation of NO donors could be associated with predominant NO delivery in the heart, which may be insufficient to induce systemic effects on blood pressure.

Another major concern is the discrepancy between the success in left ventricular hypertrophy reduction and the failure of blood pressure attenuation. This interesting and almost revolutionary finding questions the role of hemodynamic load as the principal issue in the development of left ventricular hypertrophy and supports the idea that local stimulators of cardiac growth may be decisive in pathologic heart remodeling. The weakness of the experimental design, however, is that blood pressure was not assessed continuously, but rather was assessed from a single measurement under acute conditions. Therefore, this study cannot completely discount the possibility that hemodynamic effects may have contributed to the attenuated left ventricular hypertrophy. Nevertheless, there are several lines of indirect evidence that suggest that NO may be involved in the process of myocardial hypertrophy. However, LA419 may not only increase the release of NO but may be expected to interfere with local oxidative status. Because LA419 contains a thiol group, it may improve NO stability by converting NO to nitrosothiols. This cannot only stabilize the NO molecule from degradation by free radicals. Enhancement of NO bioactivity and subsequent activation of cGMP signaling decreases the intracellular Ca2+ concentration in cardiomyocytes. Additionally, the potential diminution of myocardial levels of angiotensin converting enzyme (ACE), angiotensin (Ang) II, endothelin (ET), and/or particular growth factors and cytokines could result in a reduction of growth gene expression and attenuation of left ventricular hypertrophic growth.

Figure. The possible pathways through which NO donors containing a thiol group could attenuate left ventricular hypertrophy development independently on blood pressure reduction. First, the thiol group is responsible for NO binding and formation of nitrosothiols. As a result, NO reaction with molecular oxygen, superoxide anion, or with heme and non-heme iron can be attenuated, thus stabilizing the NO molecule and preserving its biological activity. Second, the thiol group may protect the NO molecule from degradation by free radicals. Enhancement of NO bioactivity and subsequent activation of cGMP signaling decreases the intracellular Ca2+ concentration in cardiomyocytes. Additionally, the potential diminution of myocardial levels of angiotensin converting enzyme (ACE), angiotensin (Ang) II, endothelin (ET), and/or particular growth factors and cytokines could result in a reduction of growth gene expression and attenuation of left ventricular hypertrophic growth.

with local renin-angiotensin-aldosterone, sympathetic, or endothelin systems. Furthermore, studies on the potential interaction of LA419 with inflammatory cytokines and local growth factors participating in the process of heart remodeling need to be performed (Figure).

Despite these concerns, the results of Ruiz-Hurtado et al10 are encouraging, and new fields for the experimental hypertension research emerge. Future studies should be designed to disclose how the effect of LA419 is associated with NO bioactivity. If LA419 really attenuates hypertrophy through NO restoration, it would be an encouraging fact for the development and investigation of novel NO donors, which could prove beneficial in the clinical setting. However, irrespective of the outcome of clinical trials designed to find out the therapeutic potential of LA419 and derived agents, these substances are likely to become useful experimental research tools, enabling researchers to design experiments disclosing the different roles of hemodynamic load, NO, and other endothelial factors in cardiovascular pathologies.

Disclosures
None.

References


LA419, a Novel Nitric Oxide Donor, Prevents Cardiac Remodeling Via the Endothelial Nitric Oxide Synthase Pathway: NO Donors as a Means of Antiremodeling
Ludovit Paulis and Fedor Simko

Hypertension. 2007;50:1009-1011; originally published online November 5, 2007; doi: 10.1161/HYPERTENSIONAHA.107.100032

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/50/6/1009

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/