Organic Nitrates in Heart Failure Revisited: Pentaerythritol Tetrinitrate Induces Heme Oxygenase 1 to Protect the Myocardium

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See related article, pp 978–987

Organic nitrates are efficacious drugs for treatment of angina pectoris attacks, acute coronary syndromes, pulmonary edema, and hypertensive crisis. They work by releasing nitric oxide (NO•) or a NO•-related compound (eg, nitrosothiols). Thereby, they activate soluble guanylyl cyclase/cyclic GMP–dependent pathways and lead to antiaggregation. Thereby, they activate soluble guanylyl cyclase/nitrosothiols). Thereby, they activate soluble guanylyl cyclase/cyclic GMP–dependent pathways and lead to antiaggregation and vasodilation (preferentially venodilation) resulting in venous pooling, preload and afterload reduction, reduced left ventricular filling pressures, and reduced myocardial oxygen demand. This pharmacodynamic profile promises benefits also for chronic treatment of cardiovascular disease like stable coronary heart disease or chronic heart failure. However, the use of organic nitrates is limited by the rapid development of nitrate tolerance. It is driven mainly by a loss of NO bioavailability caused by increase in reactive oxygen species (ROS) like superoxide (O2•−) originating from activated nicotinamide adenine dinucleotide phosphate oxidases, a dysfunctional mitochondrial respiratory chain, or uncoupled NO synthases. Especially O2•− undergoes an avid reaction with NO• to yield peroxynitrite (ONOO•−), one of the most deleterious ROS. In addition to cutting down the vasoprotective effects of NO•, ROS as such are harmful to the vasculature. Just to name a few culprits, oxidized LDL, advanced glycation end products, deprivation of reducing thiols, as well as mitochondrial damage and associated cell death pathways are all facilitated by ROS or by the loss of antioxidant protective systems.

Heme oxygenase 1 (HO-1, encoded by Hmox1) exerts beneficial antioxidant and anti-inflammatory effects resulting from clearance of toxic free heme and from the heme-breakdown products carbon monoxide and biliverdin/bilirubin. HO-1 deficiency leads to tissue damage by systemic iron deposition and promotes apoptosis. HO-1–deficient mice reveal increased ROS formation in macrophages, whereas HO-1 induction reduced ROS levels and inflammatory cell chemotaxis. Interestingly, the organic nitrategentaerythritol tetrinitrate (PETN), which is well tolerated and effective in patients with stable coronary artery disease, is devoid of the development of nitrate tolerance at least in part by inducing HO-1 expression. In this issue of Hypertension, Fracarollo et al7 provide novel evidence that PETN can improve left ventricular remodeling and function in rats with ischemic heart failure. In this model of extensive myocardial infarction, heart failure is associated with severe mitochondrial dysfunction and mitochondrial-derived ROS formation. The authors were able to show by gene set enrichment analysis that PETN prevented heart failure–related downregulation of important mitochondrial antioxidant systems like thioredoxin-2 and superoxide dismutase-2. In isolated cardiac fibroblasts, PETN induced HO-1 upregulation, and inhibition of HO-1 by Sn-protoporphyrin IX completely abolished the protective effect of PETN on transforming growth factor β–mediated oxidative stress.

Heart failure caused by arterial hypertension, ischemic heart disease, or other causes will be one of the leading healthcare challenges in the coming decades. Although the mortality and morbidity of acute myocardial infarction will stagnate or decline, the burden of chronic heart failure and heart failure–related hospitalizations is predicted to continuously rise. The study of Fracarollo et al therefore provides a therapeutic outlook with a fine mechanistic angle on a timely issue. Cardiomyocyte-specific overexpression of HO-1 protected mice from ischemia–reperfusion injury by reducing inflammatory cell infiltration and oxidative stress. Recently, Hinkel et al showed in a preclinical model that transgenic pigs overexpressing hHO-1 are protected from cardiac ischemia–reperfusion injury, partially by dampening the influx of inflammatory myeloid cells; vice versa, Hmox1−/− mice had an augmented influx of inflammatory cells into ischemia–reperfusion injury hearts. Therapeutically, Hmox1 gene transfer using the recombinant adeno-associated virus vector system (raaV. hHO1) was able to recapitulate the protective effects seen in hHO1 pigs. A similar approach was successful in rats with chronic ischemic heart failure earlier. While gene therapy is far from being used in clinical routine, PETN is a frequently used and well established drug, at least in many European countries. In a human study, application of PETN reduced endothelial dysfunction caused by ischemia and reperfusion injury. It remains to be shown whether PETN can improve heart function in humans with congestive heart failure. The
prospects, that this concept might indeed hold true, are not too bad: In the African-American Heart Failure (AHeFT) trial, the combination of isosorbide dinitrate with the antioxidant hydralazine has been shown to improve survival in patients with congestive heart failure.\(^\text{13}\) The currently recruiting Goal-Directed Afterload Reduction in Acute Congestive Cardiac Decompensation Study (GALACTIC; ClinicalTrials.gov Identifier: NCT00512759, www.clinicaltrials.gov) tests the hypothesis that nitroglycerin patches added to optimal medical care improve survival and rehospitalization of acute heart failure compared with optimal medical care alone. This concept is intriguing, because nitroglycerin is viewed to be one of the most efficacious organic nitrates but also the one that most rapidly induces nitrate tolerance. A nitrate with the intrinsic capacity to induce antioxidant systems like PETN has the potential to elegantly improve treatment of heart failure without inducing nitrate tolerance not only in acutely decompensated but also in chronic disease.

Disclosures

None.

References


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_Hypertension_. 2015;66:933-934; originally published online September 8, 2015;
doi: 10.1161/HYPERTENSIONAHA.115.06035

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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