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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

The Role of Nitroglycerin and Other Nitrogen Oxides in Cardiovascular Therapeutics

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ABSTRACT

The use of nitroglycerin in the treatment of angina pectoris began not long after its original synthesis in 1847. Since then, the discovery of nitric oxide as a biological effector and better understanding of its roles in vasodilation, cell permeability, platelet function, inflammation, and other vascular processes have advanced our knowledge of the hemodynamic (mostly mediated through vasodilation of capacitance and conductance arteries) and nonhemodynamic effects of organic nitrate therapy, via both nitric oxide–dependent and –independent mechanisms. Nitrates are rapidly absorbed from mucous membranes, the gastrointestinal tract, and the skin; thus, nitroglycerin is available in a number of preparations for delivery via several routes: oral tablets, sublingual tablets, buccal tablets, sublingual spray, transdermal ointment, and transdermal patch, as well as intravenous formulations. Organic nitrates are commonly used in the treatment of cardiovascular disease, but clinical data limit their use mostly to the treatment of angina. They are also used in the treatment of subsets of patients with heart failure and pulmonary hypertension. One major limitation of the use of nitrates is the development of tolerance. Although several agents have been studied for use in the prevention of nitrate tolerance, none are currently recommended owing to a paucity of supportive clinical data. Only 1 method of preventing nitrate tolerance remains widely accepted: the use of a dosing strategy that provides an interval of no or low nitrate exposure during each 24-h period. Nitric oxide's important role in several cardiovascular disease mechanisms continues to drive research toward finding novel ways to affect both endogenous and exogenous sources of this key molecular mediator. (J Am Coll Cardiol 2017;70:2393–410) © 2017 by the American College of Cardiology Foundation.

In this review, we detail the discovery of nitroglycerin and its early use in the treatment of angina; the history of the discovery of nitric oxide (NO), its sources, and its roles; the mechanism of action, preparations, and hemodynamic and nonhemodynamic effects of the organic nitrates, as well as their biotransformation; and the clinical uses and adverse effects of nitrate therapy, including tolerance. We conclude by outlining current and future work investigating novel modulators of the NO-soluble guanylyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway that may result in new therapeutic options in the treatment of cardiovascular disease.

EARLY HISTORY OF THE USE OF NITRATES IN CORONARY ARTERY DISEASE

William Heberden is credited with coining the term "angina pectoris" in 1772 (1). Joseph Priestley, an English theologian and chemist, discovered NO 3 years later (2). Not until the next century, however, was NO and its congeners, organic nitrates, linked to the treatment of angina (3). Glyceryl trinitrate, or

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ABBREVIATIONS AND ACRONYMS

ALDH = aldehyde dehydrogenase

BH_4 = tetrahydro-L-biopterin

cAMP = cyclic adenosine monophosphate

CAV1 = caveolin-1

cGMP = cyclic guanosine monophosphate

EDRF = endothelium-derived relaxing factor

eNOS = endothelial nitric oxide synthase

iNOS = cytokine-inducible nitric oxide synthase

nNOS = neuronal nitric oxide synthase

NO = nitric oxide

NOS = nitric oxide synthase

P_{450} = cytochrome P_{450} enzyme(s)

sGC = soluble guanylyl cyclase

VEGF = vascular endothelial growth factor

nitroglycerin, was first synthesized by Ascanio Sombrero in Turin, Italy. In 1847, he noted that "a very minute quantity put on the tongue produced a violent headache for several hours" (4,5). Three year earlier, the French chemist Antoine Balard synthesized amyl nitrite (4). Frederick Guthrie, an English chemist, explored the actions of amyl nitrite and published in 1859 that when it was held near the nostrils, "after a lapse of about 50 seconds, a sudden throbbing of the arteries of the neck is felt, immediately followed by a flushing of neck, temples, and forehead and an acceleration action of the heart" (6).

T. Lauder Brunton, a Scottish physician and medical scientist, first described the clinical effectiveness of amyl nitrite (4,5,7). Brunton began caring for patients with angina pectoris as a house physician at the Edinburgh Royal Infirmary (7). At the time, many treatments, including therapeutic bleeding, were being used to treat angina, largely unsuccessfully. In 1867, Brunton published the first report of the use of amyl nitrite in the treatment of angina pectoris (7,8). He believed "the relief produced by [therapeutic] bleeding to be due to the diminution it occasioned in the arterial tension" and "that a substance which possesses the power of lessening it in such an eminent degree as nitrite of amyl would probably produce the same effect, and might be repeated as often as necessary without detriment to the patient's health" (7,8). In 1903, Charles-Émile François-Franck, a French physiologist, first suggested that amyl nitrite was a coronary vasodilator (7).

In 1879, William Murrell described the symptomatic effects of placing drops of 1% solution of nitroglycerin in alcohol on the tongue (9). In addition to reporting that it relieved angina and prevented subsequent attacks, he also reported the symptoms he felt when he "[tried] its action on [himself]" (9). He described a "violent pulsation in [his] head" and noticed that his pulse was "much fuller than natural" (9). In 1914, Brunton, who originally thought angina was caused by hypertension, acknowledged that the "dilating action of amyl nitrite and nitroglycerine upon the coronary vessels would readily explain the relief they offer in angina pectoris, even in cases where the blood-pressure is normal" (7).

NO IN THE CARDIOVASCULAR SYSTEM

HISTORY OF NO. In 1975, Diamond and Holmes showed that tissue levels of cyclic adenosine monophosphate (cAMP) were increased in rat myometrial strips maintained in a state of sustained contracture. They demonstrated that nitroglycerin could relax the depolarized muscles without significantly increasing cAMP levels and, therefore, concluded that changes in total tissue levels of cAMP were not responsible for the uterine relaxation caused by nitroglycerin (10). These investigators went on to show that nitroglycerin increased cyclic guanosine monophosphate (cGMP) levels in depolarized muscle (10). The following year, Diamond and Blisard showed that 200 μmol/l nitroglycerin increased levels of cGMP by more than 15-fold during relaxation of isolated strips of phenylephrine-contracted canine femoral arteries while having no significant effect on cAMP levels (11). In 1977, pharmacologist Ferid Murad and his colleagues published their seminal work on modulating contractility in bovine tracheal smooth muscle showing that the guanylyl cyclase activators, sodium nitrite, nitroglycerin, and sodium nitroprusside, increased cGMP levels and relaxed tracheal smooth muscle (12). They went on to demonstrate that solutions of NO gas increased cGMP activity in soluble and particulate preparations from various tissues in a dose-dependent fashion, and that NO alone and in combination with sodium azide, sodium nitrite, hydroxylamine, and sodium nitroprusside increased cGMP levels to approximately the same degree; they concluded that the 2 methods activate guanylyl cyclase through a "similar but undefined mechanism" (13). Later, the same group postulated that "while the precise mechanism of guanylate cyclase activation by these agents is not known, activation may be due to the formation of NO or another reactive material since NO also increased guanylate cyclase activity" (14).

Working independently, Robert Furchgott and John Zawadzki published their observations on the importance of the endothelium in blood vessel relaxation in 1980 (4,15). They reported that acetylcholine did not always produce blood vessel relaxation in vitro, even though it was a potent vasodilator in vivo. They found that loss of relaxation in vitro was due to "unintentional rubbing of [the rabbit thoracic aorta's] intimal surface against foreign surfaces during its preparation." When this mechanical injury was avoided during preparation of the tissue, it always relaxed in response to acetylcholine.