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Role of isosorbide in the treatment of angina pectoris

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Abstract
Angina pectoris is characterized as chest pain which results from an imbalance in the coronary vessels where the oxygen demand in the heart is greater than the oxygen supplied to the heart. Nitrate's action involves the formation of free radical nitric oxide (NO), which interacts with & activates guanylate cyclase. These compounds also decrease peripheral arterial resistance & reduce venous tone, thereby increasing venous capacitance & decreasing venous return to the heart.

Keywords: angina pectoris, isosorbide, guanylate cyclase

Introduction
Rapidly growing cardiovascular diseases are the most common causes of death in the United States. It included following disease are hypertension, congestive heart failure, ischemic heart disease, stroke and peripheral arterial disease. A sedentary lifestyle, unhealthy diet, too much of tobacco use and alcohol abuse are some of the risk factors for developing a cardiovascular disease. According to the AHA (American Heart Association), each day over 2000 Americans will die of a cardiovascular disease (averaging one death every 39 seconds) and each year nearly 800,000 Americans will experience a stroke (averaging one cerebrovascular accident every 40 seconds). Therapeutic approaches to prevent cardiovascular disease include lifestyle modification (weight reduction, physical activity, smoking cessation), blood pressure control, fluid management, lipid-lowering treatment, and use of antiplatelet and antithrombotic agents [1].

Organic Nitrates
It represents the oldest class of Nitric Oxide donors applied clinically. Among them, Glyceryl Trinitrate (GTN) is the main representative of the class, which also includes isosorbide dinitrate (ISDN), isosorbide 5-mononitrate (ISMN) and pentaerythritol tetranitrate (PETN) [2]. Despite the benefits of these molecules in treating CVD like angina pectoris, pulmonary hypertension and heart failure, their continued use may cause tolerance, which is, in fact, the main limitation to the use of organic nitrates [3, 4].

Nitric oxide (NO)
It is a volatile, multifunctional free radical with a short life span. It is synthesized by one of three isoforms of nitric oxide synthase and exerts its effect by the activation of the soluble guanylate cyclase (sGC), which results in the production of cyclic guanosine monophosphate (cGMP) and the activation of the cGMP-dependent kinase (PKG) [5, 6]. It has been described that a reduction in NO bioavailability is involved in the pathophysiology of many cardiovascular diseases (CVD). In this context, the use of drugs capable of releasing NO is an effective approach while dealing with CVD [7].

Historical Perspective of Glyceryl Nitrates
Glyceryl trinitrate was the first organic nitrate which was discovered in 1847 by Ascanio Sobrero. At that time, it was also described that headaches were a side effect associated with this substance [8]. In 1879, the English physician William Murrel described, for the first time, the beneficial effects of the GTN against angina pectoris [9]. Since then, GTN was established as a drug for the treatment of chest pain, although the exact mechanism of action of this compound remained unanswered for about 100 years [10]. Then, Murad was a scientist and his colleagues described in 1977, that nitrates needed to release NO to present physiological effects [11]. Nitric oxide was only described as an endothelium- derived relaxing factor in middle 80s [12].
Then other nitro compounds with similar chemical properties have been developed. Most recent studies show that, in addition to angina, GTN and other organic nitrates such as ISDN and ISMN are able to improve left ventricular function in patients with congestive heart failure and pulmonary hypertension. Also, they show favourable effects on left ventricular remodelling after myocardial infarction and silent ischemia, in addition to reducing blood pressure alone or in combination with other drugs [13, 14].

Ischemic heart disease
It is an abnormal condition defined as a reduced blood supply to the heart [14-16]. Cardiac ischemia is caused by atherosclerosis, or hardening of the arteries, and can result in angina, heart attack and death. In developed countries, ischemic heart disease is one of the most frequently reported cardiovascular diseases and causes of death.

Angina pectoris
Angina pectoris can be defined as a chest pain or discomfort, usually attributed to myocardial ischemia. It is commonly

associated with coronary heart disease and atherosclerosis, although it can also be related to cardiomyopathy or aortic stenosis. The severity of the discomfort does not necessarily relate to the severity of the underling coronary disease [17]. Angina is considered stable when it shows a regular pattern, being elicited by exertion or emotional stress and the pain is relieved by a few minutes of rest or after the use of nitrates. Nitrates are the class of drugs to treat angina pectoris [18]. They have been used even before the cardiovascular properties of NO have been established [19]. Organic nitrates exert their maximal vasodilator effects on venous capacitance vessels and large and medium coronary arteries, while small arterioles are less affected. The vasodilation induced by these drugs increase the venous capacitance and reduce cardiac preload, which reduces left ventricular filling pressure and myocardium workload. The oxygen demand to myocardium decreases and this is the key mechanism involved in the use of this class of drugs in angina **[15]**. At high doses, nitrates exert arterial vasodilator effects, leading to dilation in epicardial arteries. This promotes a redistribution of coronary blood flow from healthy regions to ischemic areas [20].

Short Acting Nitrates should be administrated to patients during acute angina pectoris symptoms or immediately before physical exercise to prevent angina pectoris. On the other hand, long lasting nitrates are recommended for the treatment of patients who remain symptomatic despite the use of aspirin, statins, beta receptor blockers or calcium antagonists [21].

It is the most common symptom of ischemic heart disease and is characterized as chest pain which results from an imbalance in the coronary vessels where the oxygen demand in the heart is greater than the oxygen supply to the heart. The pain may be mild or intense and feel like a crushing, burning, or squeezing discomfort that can spread to the neck or arms. Typically, the pain lasts for 5-10 minutes and is relieved with sublingual nitroglycerin.

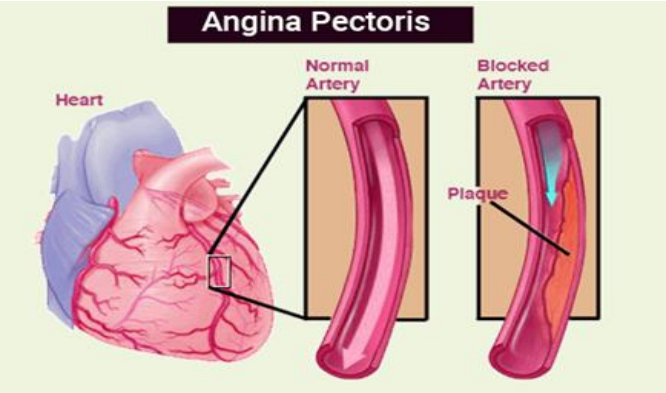

Fig 1

Symptoms: A heavy strangulation or pressure-like sensation, sometimes may feel like indigestion, usually located in retrosternal area, often radiating to the left shoulder, left arm, jaw, neck, epigastrium or back.

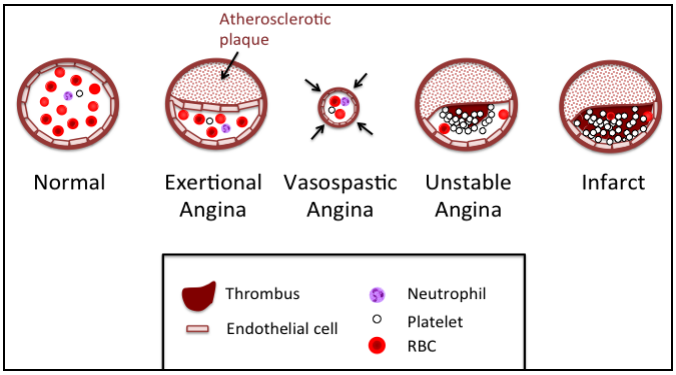

Fig 2

Angina pectoris is divided into three types

1. **Primary Angina or Variant Angina:** In this type of Angina, the ischemia causes spasm of the coronary vessels and chest pain without increases in cardiac demand. It is relieved by anti-anginal drugs.
2. **Secondary Angina or Effort Angina:** In this type of Angina, inadequate blood flow during exercise or times of stress results in chest pain. It is caused by narrowed arteries due to atherosclerosis. It occurs when there is exertion /effort Episodes of pain tend to be alike. It usually lasts a short time. It is relieved by anti- anginals.
3. **Unstable Angina:** In this type of Angina, a sudden worsening of the patient chronic angina occurs. It is more severe and lasts longer than stable angina. The episodes of pain tend to be changing in the character, i.e. increasing severity (crescendo angina), frequency and duration as well as precipitating factors. [22, 23].

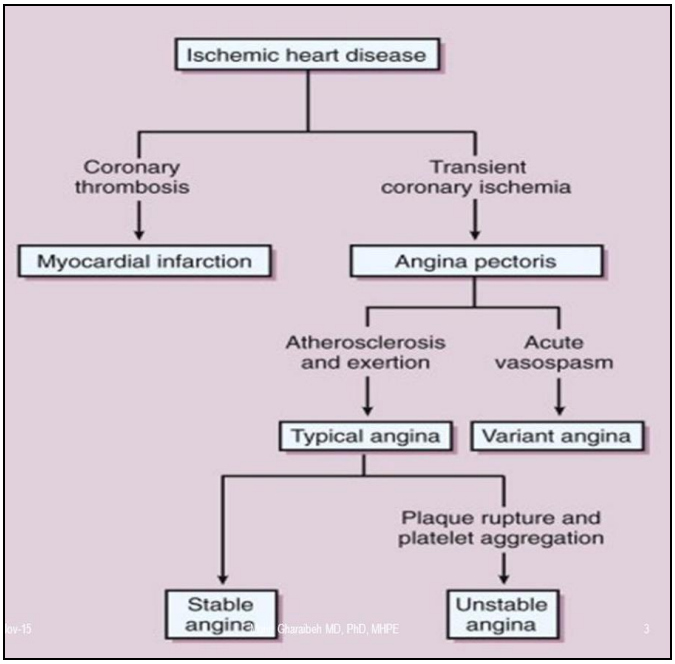

Fig 3

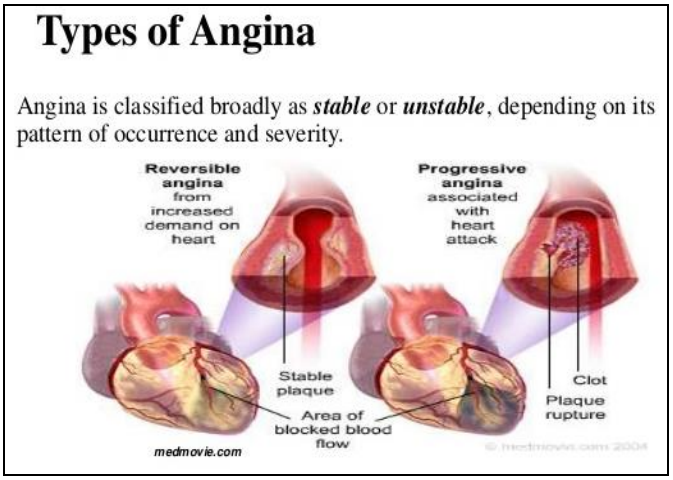

Fig 4

Overall, three drug classes are typically used in the treatment and prevention of angina: organic nitrates, calcium channel blockers and beta-blockers [24, 25].

Each of these therapeutic drug classes reduces myocardial oxygen requirements by decreasing heart rate, blood pressure and/or contractility.

Anti-angina agents

The use of nitrates & nitrites dates back to 1867 when nitrates & 1879 nitroglycerine were used for relieving pain of angina pectoris. Organic nitrtes are polyol esters of nitric acid, whereas organic nitrites are esters of nitrous acid. Nitrate ester (-C-O-NO_2) & nitrite ester (-C-O-NO) are characterized by a sequence of carbon-oxygen- nitrogen, whereas nitro compound possess carbon- nitrogen bonds (C-NO_2). The effect of nitrates on the heart is to reduce myocardial oxygen requirements relative to myocardial oxygen delivery. The arterial dilation produced by nitrates caused reduction in the mean systemic arterial pressure, which reduce the after load of the heart & thus diminishes the oxygen requirements of the heart. The venous dilation produced by nitrates results in increased peripheral pooling of blood, which decrease ventricular end- diastolic pressure & volume. This reduction in ventricular pressure & size results in a decreased myocardial wall tension & therefore, in decreased oxygen requirements. Nitrates are believed to dilate the larges epicardial & collateral coronary arteries selectively, an action that favours the distribution of blood to ischemic areas.

Isosorbide

The isosorbide agents are indicated in the prevention of angina pectoris and are not generally the agent of choice for acute angina episodes due to the slower onset of action (30- 60 minutes). Isosorbide is available in a dinitrate or mononitrate formulation, which is simply the active metabolite of isosorbide dinitrate. Both formulations are given once daily (with the extended release agents) or 2-3 times daily (with the immediate release formulations). Tolerance can be avoided by short periods of nitrate-free intervals (10-12 hours/day) [26, 30].

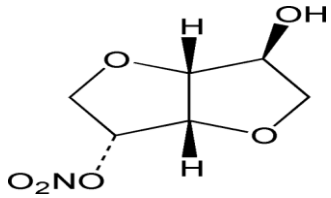

Fig 5: Isosorbide

Mechanism of Action

It's action involves the formation of free radical nitric oxide (NO), which interacts with & activates guanylate cyclase.

Also a nitrosothiol intermediate is implicated by a reaction of the nitrate with glutathione, which enhances formation of cyclic guanine nucleotide, which relax smooth muscles. Within the cell, nitrite ion is converted to nitric oxide (NO) which after forming a reductive nitrothiol intermediate activates a soluble cytosolic form of the enzyme guanylate cyclase. cGMP formation is thereby increased. The guanylate cyclase increase the synthesis of guanosine 3', 5'-monophosphate (cycli GMP), which activates a protein kinase. The protein kinase mediate dephosphorylation of myosine which is responsible for the maintenance of the contractile state in smooth muscle. These compounds also decrease peripheral arterial resistance & reduce venous tone, thereby increasing venous capacitance & decreasing venous return to the heart [3, 4].

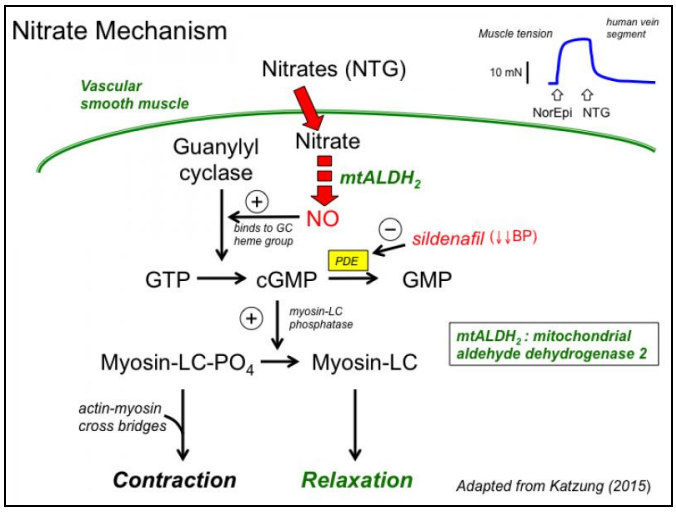

Fig 6

Conclusion

Angina pectoris can be defined as a chest pain or discomfort, usually attributed to myocardial ischemia. It is commonly associated with coronary heart disease and atherosclerosis, although it can also be related to cardiomyopathy or aortic stenosis. The isosorbide agents are indicated in the prevention of angina pectoris. It's action involves the formation of free radical nitric oxide (NO), which interacts with & activates guanylate cyclase. Also a nitrosothiol intermediate is implicated by a reaction of the nitrate with glutathione, which

enhances formation of cyclic guanine nucleotide, which relax smooth muscles. These compounds also decrease peripheral arterial resistance & reduce venous tone, thereby increasing venous capacitance & decreasing venous return to the heart.

Reference

1. AHFS Drug Information, ed AHFS. Drug Information. Bethesda, MD: American Society of Health- System Pharmacists, 2014.
2. Wang PG, Xian M, Tang X, Wu X, Wen Z, Cai T, Janczuk AJ. Nitric oxide donors: Chemical activities and biological applications. Chem. Rev. 2002; 102:1091-1134.
3. Miller MR, Wadsworth RM. Understanding organic nitrates—A vein hope? Br. J. Pharmacol. 2009; 157:565-567.
4. Münzel T, Daiber A, Mülsch A. Explaining the phenomenon of nitrate tolerance. Circ. Res. 2005; 97:618-628.
5. Moncada S, Higgs A. Mechanisms of disease: The L-arginine-nitric oxide pathway. N. Engl. J. Med. 1993; 329:2002-2012.
6. Rudolph V, Freeman BA. Cardiovascular consequences when nitric oxide and lipid signalling converge. Circ. Res. 2009; 105:511-522.
7. Pörsti I, Paakkari I. Nitric oxide-based possibilities for pharmacotherapy. Ann. Med. 1995; 27:407-420.
8. Follmann M, Griebenow N, Hahn MG, Hartung I, Mais FJ, Mittendorf J, *et al*. The chemistry and biology of soluble guanylate cyclase stimulators and activators. *Ange*w. Chem. Int. Ed. Engl. 2013; 52:9442-9462.
9. Murrel W. Nitroglycerine as a remedy for angina pectoris. Lancet. 1879; 1:80-81.
10. Marsh N, Marsh A. A short history of nitroglycerine and nitric oxide in pharmacology and physiology. Clin. Exp. Pharmacol. Physiol. 2000; 27:313-319.
11. Arnold WP, Mittal CK, Katsuki S, Murad F. Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations. *Proc. Natl. Acad. Sci. USA.* 1977; 74:3203-3207.
12. Furchgott RF. Endothelium-derived relaxing factor: discovery, early studies, and identification as nitric oxide. Biosci. Rep. 1999; 19:235-251.
13. Bode-Böger SM, Kojda G. Organic nitrates in cardiovascular disease. Cell. Mol. Biol. 2005; 51:307-320.
14. Münzel T, Daiber A, Gori T. Nitrate therapy: New aspects concerning molecular action and tolerance. Circulation. 2011; 123:2132-2144.
15. Lexi-Comp I. ed Drug Information Handbook. 21st ed. Hudson, OH: Lexi-Comp, 2014.
16. Wilson PW. Prediction of cardiovascular disease events. *Cardiol Clin.* 2000; 29(1):1-13.
17. Srikanth S, Deedwania P. Primary and secondary prevention strategy for cardiovascular disease in diabetes mellitus. Cardiol Clin. 29(1):47-70.
18. Lardizabal JA, Deedwania P. Lipid-lowering therapy with statins for the primary and secondary prevention of cardiovascular disease. Cardiol Clin. Feb; 29(1):87-103.
19. Heidenreich PA, Trogdon JG, Khavjou OA, *et al*. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation.* 1; 123(8):933-944.
20. Gupta R, Deedwania P. Interventions for cardiovascular disease prevention. *Cardiol Clin.* 29(1):15-34.
21. Franco M, Cooper RS, Bilal U, Fuster V. Challenges and opportunities for cardiovascular disease prevention. Am J Med. 124(2):95-102.
22. Ketchum K, Peterson K, Thakurta S, Low A, McDonagh MS. Drug class review: Newer Antiplatelet Agents. Update 2. Oregon Health and Science University 2011.
23. De Lemos JA, Rourke RA, Harrington R. Chapter 59. Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. In: Fuster V, Walsh RA, Harrington RA, eds. Hurst's the heart. 13th ed. New York: McGraw-Hill, 2011.
24. Weitz JI. Chapter 30. Blood Coagulation and Anticoagulant, Fibrinolytic, and Antiplatelet Drugs. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill, 2011.
25. Weitz JI. Chapter 118. Antiplatelet, Anticoagulant, and Fibrinolytic Drugs. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medecine. 18th ed. New York: McGraw-Hill, 2012.
26. Katzung BG. Vasodilators & the Treatment of Angina Pectoris. In: Katzung BG, Trevor AJ, eds. *Basic & Clinical Pharmacology*. 13th ed. New York, NY: McGraw-Hill, 2015.
27. Michel T, Hoffman BB. Treatment of Myocardial Ischemia and Hypertension. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York, NY: McGraw-Hill; 2011.
28. Depre C, Vatner SF, Gross GJ. Coronary Blood Flow and Myocardial Ischemia. In: Fuster V, Walsh RA, Harrington RA, eds. Hurst's The Heart. 13th ed. New York, NY: McGraw-Hill, 2011.
29. Fihn SD, Gardin JM, Abrams J, *et al*. uideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2012; 126(25):3097-3137.
30. McEvoy GK, Snow EK, Kester L, Litvak K, Miller J, Welsh OH, eds. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 2014.