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LIONEL H. OPIE | BERNARD J. GERSH

2 – Nitrates and newer antianginals

LIONEL H. OPIE,
JOHN D. HOROWITZ

> *"When the remedy is used for a long time, the dose requires to be increased before the effect is produced."*
>
> *Brunton, 1867*[1]

The nature of angina of effort

Besides the classic and well-described constricting chest pain with its characteristic radiation that is brought on by effort in those with symptomatic coronary artery disease (CAD), and its diagnostic relief by cessation of effort, there are a series of crescendo and decrescendo events that precede and follow the anginal pain (Fig. 2-1). The crescendo events constitute the ischemic cascade of Nesto,[2] to which must be added postischemic stunning,[3] often ignored.

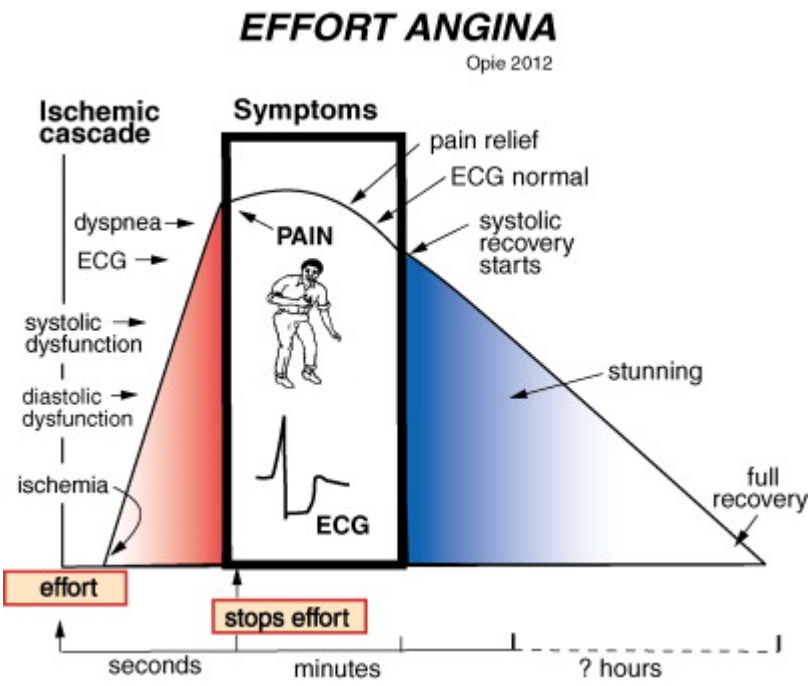

Figure 2-1 **The ischemic cascade** leading to the chest pain of effort angina followed by the period of mechanical stunning with slow recovery of full function. For basic concepts see Nesto.[2] *ECG,* Electrocardiogram.
(Figure © L. H. Opie, 2012.)

The initial imbalance between the oxygen supply and demand leads to inadequate myocardial blood flow (myocardial ischemia) that, in turn, sets off a series of metabolic changes. A deficit of high-energy phosphates leads to loss of potassium, gain of sodium and calcium, with rapid onset of diastolic dysfunction. A little later this is followed by systolic dysfunction, electrocardiogram (ECG) changes, shortness of breath, and then the onset of anginal chest pain that stops the effort. In the recovery period the ECG reverts to normal shortly after pain relief, but systolic recovery can be delayed for at least 30 minutes

(stunning).

This chapter focuses on the antianginal effects of nitrates, one of *four major classes of antianginals,* including β-blockers and calcium channel blockers (CCBs) (Fig. 2-2). Mechanistically, nitrates and CCBs are coronary vasodilators, with nitrates also reducing the preload and CCBs the afterload. β-blockers reduce oxygen demand by slowing the heart and by a negative inotropic effect. Metabolic antianginals constitute the new fourth class acting by metabolic modulation without major hemodynamic effects. Recent therapeutic developments have somewhat extended this classification, with the development of several agents with multiple effects or with totally novel mechanisms of action, such as the sinus node inhibitor ivabradine.

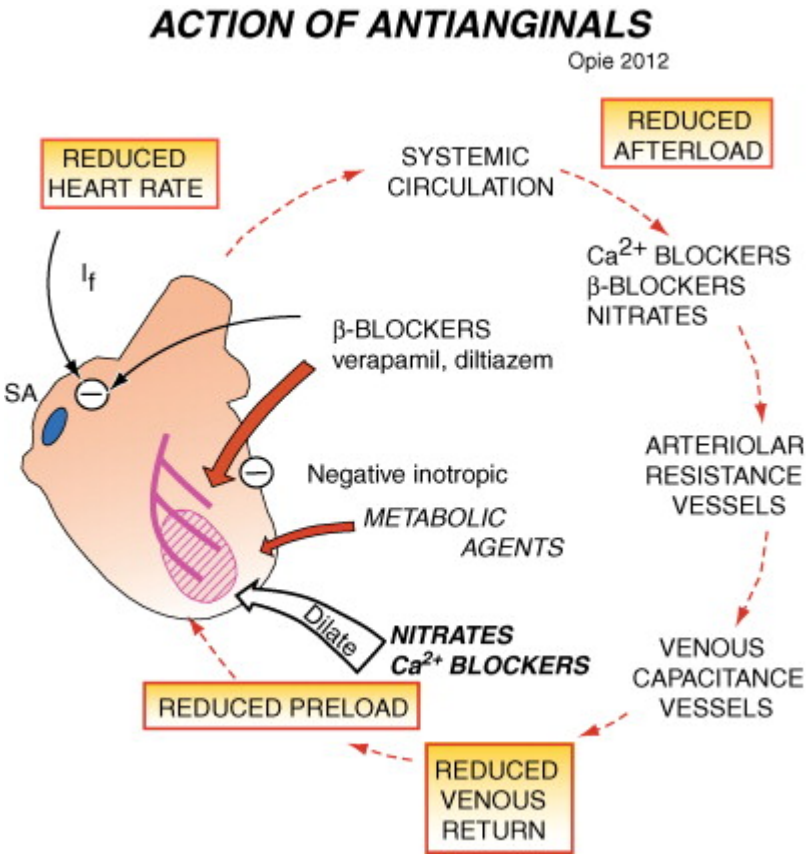

Figure 2-2 **Proposed antianginal mechanisms** for the major four classes of antianginal agents: nitrates, β-blockers, calcium channel blockers, and metabolic agents (for details of metabolic agents, see Figure 2-7). *SA,* Sinoatrial.
(Figure © L. H. Opie, 2012.)

This chapter reviews (1) the organic nitrates, both as regards their anitanginal effects and also their other therapeutic agents, and (2) recently developed novel agents with antianginal properties, including the metabolic modulators, ivabradine, allopurinol, and ranolazine. In this context, it is important to consider prophylactic antianginal therapy as only a component of therapy for patients with symptomatic myocardial ischemia, with other key considerations being the use of other agents that are both cardioprotective and antiatherosclerotic (aspirin, statins, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin receptor blockers [ARBs]) and the use of anti–heart failure drugs when necessary, whereas for some selected patients a considered invasive approach is appropriate.

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Mechanisms of nitrate action in angina

Nitrates provide an exogenous source of vasodilator nitric oxide (NO•, usually given as NO), a very short-lived free radical, thereby inducing coronary vasodilation even when endogenous production of NO• is impaired by CAD. Thus nitrates act differently from the other classes of antianginals (see Fig. 2-2). Chronic use of nitrates produces tolerance, a significant clinical problem. The main focus of current clinical work remains on strategies to minimize or prevent the development of tolerance, with the major emphasis on the adverse role of excess NO• that produces harmful peroxynitrite.[4] The thrust of basic work has shifted to endogenously produced NO• as a ubiquitous physiologic messenger, as described by Ignarro, Furchgott, and Murad,[5] the winners of the 1998 Nobel Prize for Medicine. Although endogenously produced NO• has many functions (such as a role in vagal neurotransmission) quite different from the NO• derived from exogenous nitrates, there are important shared vasodilatory effects.

Coronary and peripheral vasodilatory effects.

A distinction must be made between antianginal and coronary vasodilator properties. Nitrates preferentially dilate large coronary arteries and arterioles greater than 100 mcm in diameter [6] to (1) redistribute blood flow along collateral channels and from epicardial to endocardial regions and (2) relieve coronary spasm and dynamic stenosis, especially at epicardial sites, including the coronary arterial constriction induced by exercise. Thereby exercise-induced myocardial ischemia is relieved. Thus nitrates are “effective” vasodilators for angina; dipyridamole and other vasodilators acting more distally in the arterial tree are not, but rather have the risk of diverting blood from the ischemic area—a “coronary steal” effect.

The additional peripheral hemodynamic effects of nitrates, originally observed by Lauder Brunton,[1] cannot be ignored. Nitrates do reduce the afterload, in addition to the preload of the heart (Fig. 2-3). The arterial wave reflection from the periphery back to the aorta is altered in such a way that there is “true” afterload reduction, with the aortic systolic pressure falling even though the brachial artery pressure does not change.[7]

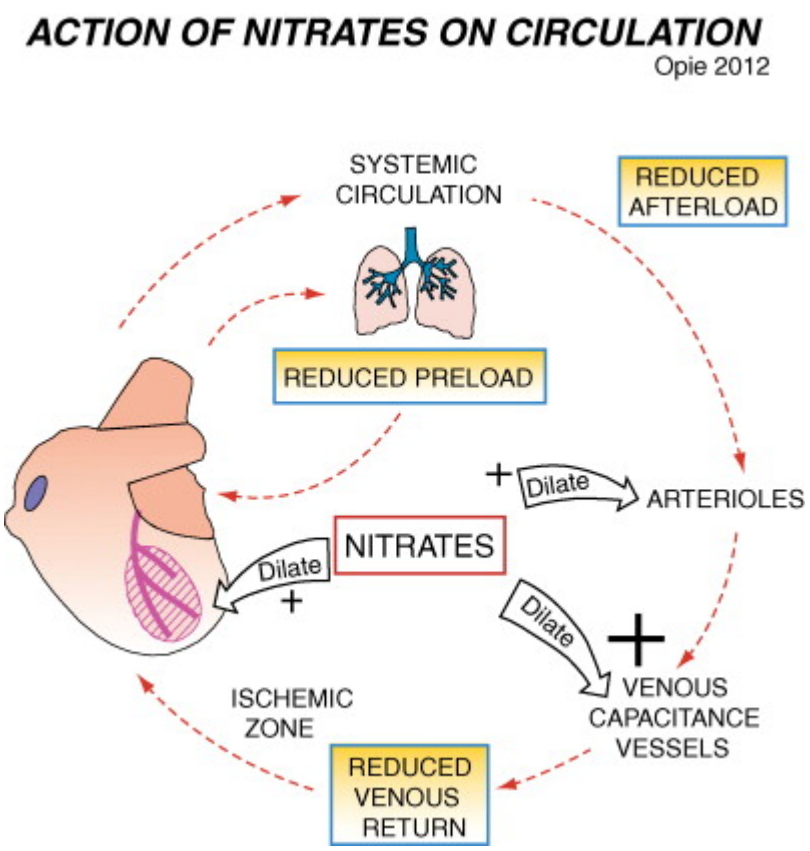

Figure 2-3 Schematic diagram of effects of nitrate on the circulation. The major effect is on the venous capacitance vessels with additional coronary and peripheral arteriolar vasodilatory benefits.
(Figure © L. H. Opie, 2012.)

Reduced oxygen demand.

Nitrates increase the venous capacitance, causing pooling of blood in the peripheral veins and thereby a reduction in venous return and in ventricular volume. There is less mechanical stress on the myocardial wall and the myocardial oxygen demand is reduced. Furthermore, a fall in the aortic systolic pressure also reduces the oxygen demand.

Endothelium and vascular mechanisms.

The fundamental mechanism of nitrate biological effect is the enzyme-mediated release of highly unstable $NO^{\bullet}$ from the nitrate molecule (Fig. 2-4).[8] An intact vascular endothelium is required for the vasodilatory effects of some vascular active agents (thus acetylcholine physiologically vasodilates but constricts when the endothelium is damaged). Nitrates vasodilate whether or not the endothelium is physically intact or functional. Prolonged nitrate therapy with formation of peroxynitrite may, however, inhibit endothelial nitric oxide synthase (NOS), which is one of several postulated mechanisms of nitrate tolerance. Similarly, long-term use of long-acting nitrates may cause endothelial dysfunction mediated by free radicals (see later, Fig. 2-5).[4],[9] Whether this problem extends to aggravation of preexisting endothelial dysfunction is uncertain. Thus nitrate tolerance and endothelial dysfunction have partially shared pathogenetic mechanisms.

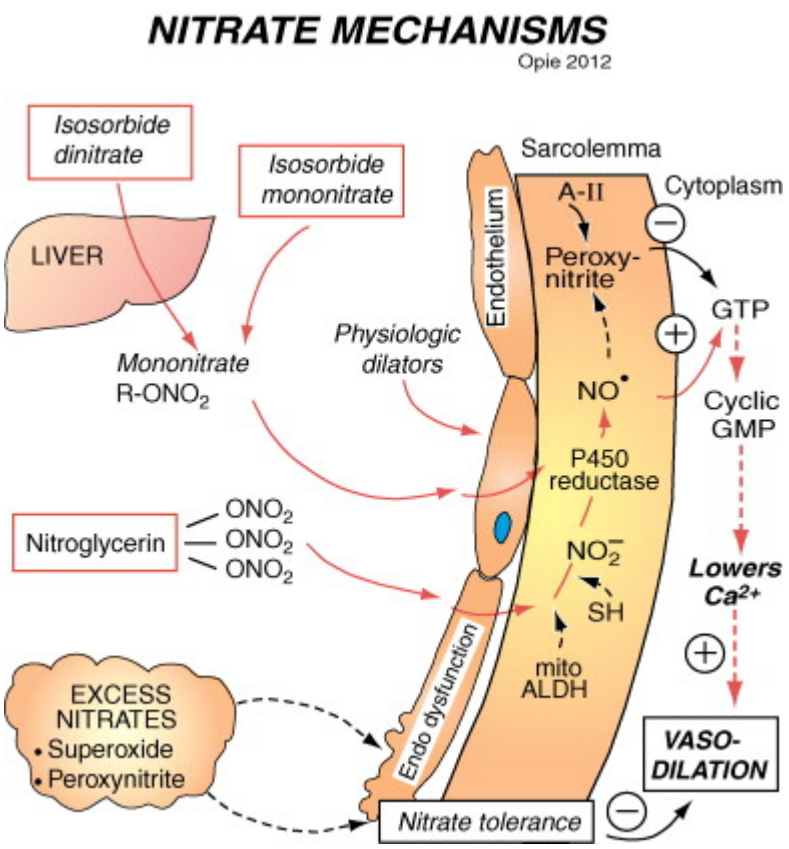

Figure 2-4 Effects of nitrates in generating nitric oxide (NO•) and stimulating guanylate cyclase to cause vasodilation. Nitrate tolerance is multifactorial in origin, including the endothelial effects of peroxynitrite and superoxide that ultimately inhibit the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (GMP). Note that mononitrates bypass hepatic metabolism and the mitochondrial aldehyde dehydrogenase-2 (mito ALDH) step required for bioactivation of nitroglycerin. Hence reduced or genetic lack of ALDH-2 may also be a cause of nitrate tolerance.[8] *SH,* Sulfhydryl.
(Figure © L. H. Opie, 2008.)

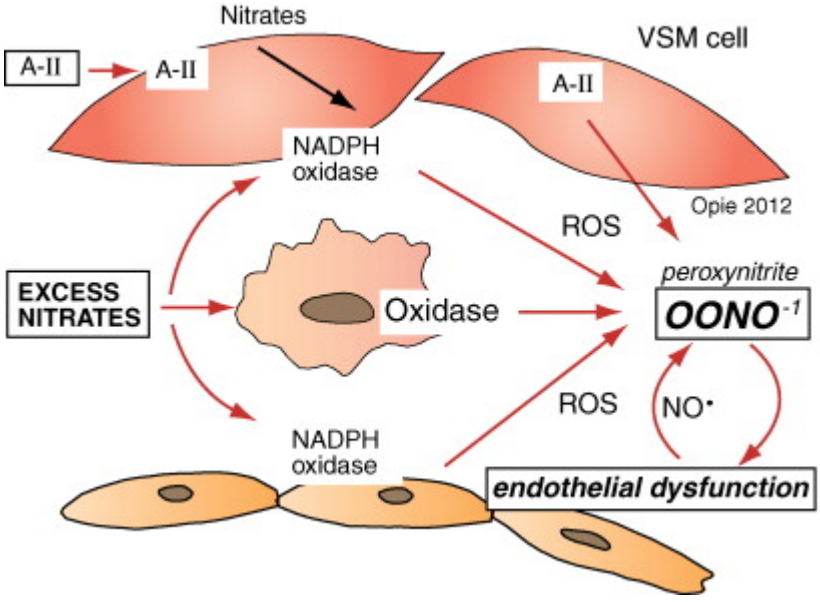

Figure 2-5 The formation of peroxynitrite and the role of oxidases in the process. Excess nitrate administration leads to stimulation of the oxidase system. The end result is increased endothelial dysfunction. Angiotensin II stimulates the vascular smooth muscle (VSM) cells to form peroxynitrite. Some of the procedures that diminish these processes, leading to endothelial dysfunction, include administration of carvedilol (strong data), high doses of atorvastatin (human volunteer data), and the

angiotensin receptor blocker telmisartan (experimental data). *NADPH,* Nicotinamide adenine dinucleotide phosphate; *NO•*, nitric oxide; *OONO,* peroxynitrite; *ROS,* reactive oxygen species.

Nitrates, after entering the vessel wall, are bioconverted to release NO•, which stimulates guanylate cyclase to produce cyclic guanosine monophosphate (GMP; see Fig. 2-4). In addition, NO• acts potentially via direct S-nitrosylation of a number of proteins, altering their physiologic properties via a posttranslational modification step. NO• may also be "scavenged" by the superoxide (O_2^-) radical, generating peroxynitrate ($ONOO^-$), which in high concentrations contributes to nitrate toxicity (Fig. 2-5) and the induction of nitrate tolerance. Conversely, low concentrations enhance the vasodilator effects of NO•.

Overall the best known mechanism linked to clinical practice is that calcium in the vascular myocyte falls, and vasodilation results (see Fig. 2-4). Sulfhydryl (SH) groups are required for such formation of NO• and the stimulation of guanylate cyclase. Nitroglycerin powerfully dilates when injected into an artery, an effect that is probably limited in humans by reflex adrenergic-mediated vasoconstriction. Hence (1) nitrates are better venous than arteriolar dilators, and (2) there is an associated adrenergic reflex tachycardia[10] that can be attenuated by concurrent β-blockade.

Effects of NO• on myocardial relaxation and contractile proteins.

NO• has a fundamental role as a modulator of myocardial relaxation, mediated at least in part by cyclic GMP (see Fig. 2-4).[11] This effect is independent of the restoration of coronary blood flow that in turn can reverse ischemic diastolic dysfunction. Furthermore, NO• improves diastolic function in human heart muscle where it acts on the contractile proteins by increasing troponin I phosphorylation of the springlike cytoskeletal protein titin.[12] In long-term therapy, NO• donors may limit or reverse left ventricular hypertrophy (LVH).[13] These studies raise the possibility that organic nitrates may exert a role in the management of systemic hypertension, in which LVH is a marker and modulator of long-term cardiovascular risk. However, to date, there have been only sporadic clinical investigations.

Antiaggregatory effects.

Organic nitrates mimic the effects of endogenous NO• in inhibiting and potentially reversing platelet aggregation.[3],[14],[15] These effects are mediated primarily via the classical pathway of stimulation of activation of soluble guanylate cyclase (see Fig. 2-4).

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Pharmacokinetics of nitrates

Bioavailability and half-lives.

The various preparations differ so much that each needs to be considered separately. As a group, nitrates are absorbed from the mucous membranes, the skin, and the gastrointestinal (GI) tract. The prototype agent, nitroglycerin, has pharmacokinetics that are not well understood. It rapidly disappears from the blood with a half-life of only a few minutes, largely by extrahepatic mechanisms that convert the parent molecule to longer acting and active dinitrates.[16] Isosorbide dinitrate, on the other hand, must first be converted in the liver to active mononitrates (see Fig. 2-4) that have half-lives of approximately 4 to 6 hours with ultimate renal excretion. The mononitrates are completely bioavailable without any hepatic metabolism, with half-lives of 4-6 hours. In reality, knowledge of pharmacokinetics is of limited interest because of the highly variable relationship between the plasma concentrations of the nitrates, the levels of their active metabolites, and the onset and duration of pharmacologic action that matter most to the clinician.[16] Of the many nitrate preparations (Table 2-1), sublingual nitroglycerin remains the gold standard for acute anginal attacks.[17] In practice, patients are often also given long-acting nitrates. “No matter which long-acting preparation is used, physicians should prescribe the drug in a manner to decrease the likelihood of nitrate tolerance. This involves an on-off strategy of at least a 10-hour nitrate free interval each day.”[17] This policy does, however, entertain the risk of precipitation of angina during the nitrate-free interval, which is often at night.

Table 2-1 -- Nitrate Preparations: Doses, Preparations, and Duration of Effects

Compound	Route	Preparation and Dose	Duration of Effects and Comments
Amyl nitrite	Inhalation	2-5 mg	10 sec-10 min; for diagnosis of LV outflow obstruction in hypertrophic cardiomyopathy.
Nitroglycerin (trinitrin, GTN)	**(a)** Sublingual tablets	0.3-0.6 mg up to 1.5 mg	Peak blood levels at 2 min; t ½ approximately 7 min; for acute therapy of effort or rest angina. Keep tightly capped.
	(b) Spray	0.4 mg/metered dose	Similar to tablets at same dose.
	(c) Ointment	2%; 6 × 6 ins or 15 × 15 cm or 7.5-40 mg	Apply 2× daily; 6-h intervals; effect up to 7 h after first dose. No efficacy data for chronic use.
	(d) Transdermal patches	0.2-0.8 mg/h patch on for 12 h, patch off for 12 h	Effects start within minutes and last 3-5 h. No efficacy data for second or third doses during chronic therapy.
	(e) Oral; sustained release	2.5-13 mg 1-2 tablets 3× daily	4-8 h after first dose; no efficacy data for chronic therapy.
	(f) Buccal	1-3 mg tablets 3× daily	Effects start within minutes and last 3-5 h. No efficacy data for second or third doses during chronic therapy.
	(g) Intravenous infusion (discontinued in US)	5-200 mcg/min (care with PVC); Tridil 0.5 mg/mL or 5 mg/mL; Nitro bid IV 5 mg/mL	In unstable angina, increasing doses are often needed to overcome tolerance. High-concentration solutions contain propylene glycol; crossreacts with heparin.

Compound	Route	Preparation and Dose	Duration of Effects and Comments
Isosorbide dinitrate (sorbide nitrate) Isordil	**(a)** Sublingual **(b)** Oral tablets	2.5-15 mg 5-80 mg 2-3× daily	Onset 5-10 min, effect up to 60 min or longer. Up to 8 h (first dose; then tolerance) with 3× or 4× daily doses; 2× daily 7 h apart may be effective but data inadequate.
	(c) Spray	1.25 mg on tongue	Rapid action 2-3 min.
	(d) Chewable	5 mg as single dose	Exercise time increased for 2 min-2.5 h.
	(e) Oral; slow-release	40 mg once or 2× daily	Up to 8 h (first dose; 2× daily not superior to placebo).
	(f) Intravenous infusion	1.25-5 mg/h (care with PVC)	May need increasing doses for unstable angina at rest.
	(g) Ointment	100 mg/24 h	Not effective during continuous therapy.
Isosorbide 5-mononitrate	Oral tablets	20 mg 2× day (7 h apart); 120-240 mg 1× daily (slow release)	12-14 h after chronic dosing for 2 weeks. Efficacy up to 12 h after 6 weeks.
Pentaerythritol tetranitrate (not in US)	Sublingual	10 mg as needed	No efficacy data.

Available in the United States: Extended Release Isosorbide dinitrate, Isosorbide mononitrate.

GTN, glyceryl trinitrate; *IV,* Intravenous; *LV,* left ventricular; *PVC,* polyvinylchloride tubing; *t1/2;* half-life.

Long acting, available in the United States: Nitroglycerin Extended Release, nitroglycerin transdermal patch.

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Nitrate interactions with other drugs

Many of the proposed interactions of nitrates are pharmacodynamic, involving potentiation of vasodilatory effects, as with the CCBs. However, the chief example of vasodilator interactions is with the selective phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil as used for erectile dysfunction. PDE-5 inhibitors are increasingly used for the therapy of pulmonary hypertension (see Chapter 5) and their benefits in heart failure are being explored. As a group, these agents can cause serious hypotensive reactions when combined with nitrates (see Fig. 2-5). Hence the package insert of each agent forbids co-administration to patients taking nitrates in any form either regularly or intermittently. For example, sildenafil decreases the blood pressure (BP) by approximately 8.4/5.5 mm Hg, and by much more in those taking nitrates. The exertion of sexual intercourse also stresses the cardiovascular system further. As a group, these drugs should also not be given with α-adrenergic blockers. In case of inadvertent *PDE-5-nitrate combinations,* administration of an α-adrenergic agonist or even of norepinephrine may be needed.

An essential question for men with acute coronary syndrome (fig. 2-6

). Whenever a male patient presents with an anginal attack or acute coronary syndrome (ACS), whether or not precipitated by sexual intercourse, one essential question is whether the patient has recently taken sildenafil (Viagra), vardenafil (Levitra) or tadalafil (Cialis)? If so, how soon can a nitrate be given? In clinical practice nitrates may be started 24 hours after sildenafil.[17] A 24-hour interval for vardenafil can also be inferred from data in the package insert. For the longer-acting tadalafil the corresponding interval is 48 hours.[18]

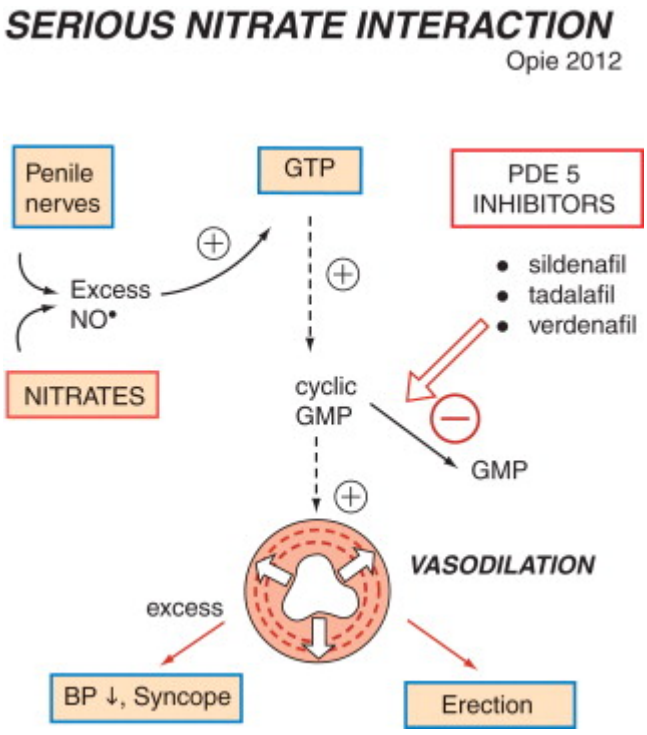

Figure 2-6 A serious nitrate drug interaction. The mechanism of normal erection involves penile vasodilation mediated by guanosine triphosphate (GTP) and cyclic guanosine monophosphate (GMP). The phosphodiesterase-5 inhibitors (PDE 5) such as sildenafil (Viagra) act by inhibiting the enzymatic breakdown of penile cyclic GMP to GMP with increased vasodilation. This is not confined to the penis and peripheral vasodilation added to that caused by nitrates, gives rise to an excess fall of blood pressure (BP) and possible syncope. Hence the use of PDE 5 inhibitors in any patient taking nitrates is contraindicated. *NO•*, Nitric oxide.

(Figure © L. H. Opie, 2012.)

Beneficial combination with hydralazine.

There is a beneficial interaction between nitrates and hydralazine whereby the latter helps to lessen nitrate tolerance,[19] probably acting through inhibition of free radical formation. This may explain why the combination of nitrates and hydralazine is effective in heart failure[20] and is now approved for use in the United States as BiDil (Nitromed, Inc) for patients with heart failure who self-identify as black (see Chapter 6, page 198). Approval was based in part on results of the African-American Heart Failure Trial (A-HeFT) showing that BiDil gave a 43% reduction in death and a 39% reduction in hospitalizations.[21] The combination used was isosorbide dinitrate 20 mg and hydralazine 37.5 mg, both given three times daily.

Despite the proven efficacy of this combination in African Americans, much remains to be understood about the precise mechanism of interaction between isosorbide dinitrate and hydralazine, as well as understanding the optimal patient population. There could be a potentially incremental role of such combination therapy in other ethnic groups of patients with severe heart failure in whom other forms of pharmacotherapy are relatively contraindicated, for example, on the basis of renal dysfunction.

Short-acting nitrates for acute effort angina

Sublingual nitroglycerin is very well established in the initial therapy of angina of effort, yet may be ineffective, frequently because the patient has not received proper instruction or because of severe headaches. When angina starts, the patient should rest in the sitting position (standing promotes syncope, lying enhances venous return and heart work) and take sublingual nitroglycerin (0.3 to 0.6 mg) every 5 minutes until the pain goes or a maximum of four to five tablets have been taken. *Nitroglycerin spray* is an alternative mode of oral administration, which is more acceptable to some patients. It vasodilates sooner than does the tablet, which might be of special importance in those with dryness of the mouth.[22]

Isosorbide dinitrate may be given *sublingually* (5 mg) to abort an anginal attack and then exerts antianginal effects for approximately 1 hour. Because the dinitrate requires hepatic conversion to the mononitrate, the onset of antianginal action (mean time: 3.4 minutes) is slower than with nitroglycerin (mean time: 1.9 minutes), so that the manufacturers of the dinitrate recommend sublingual administration of this drug only if the patient is unresponsive to or intolerant of sublingual nitroglycerin. After oral ingestion, hemodynamic and antianginal effects persist for several hours. Single doses of isosorbide dinitrate confer longer protection against angina than can single doses of sublingual nitroglycerin (see Table 2-1).

Long-acting nitrates for angina prophylaxis

Long-acting nitrates are not continuously effective if regularly taken over a prolonged period, unless allowance is made for a nitrate-free or nitrate-low interval (Table 2-2).[23-26] Worsening of endothelial dysfunction is a potential complication of long-acting nitrates that should be avoided.[27] Hence the common practice of routine use of long-acting nitrates for patients with effort angina[28] may have to be reevaluated.

Table 2-2 -- Interval Therapy for Effort Angina by Eccentric Nitrate Dosage Schedules Designed to Avoid Tolerance

Preparation	Dose	Reference
Isosorbide dinitrate	30 mg at 7 am, 1 pm*	Thadani & Lipicky, 1994[23]
Isosorbide mononitrate (Robins-Boehringer-Wyeth-Ayerst; Pharma-Schwartz)	20 mg at 8 am and 3 pm	Parker, 1993[24]
Isosorbide mononitrate, Extended-release (Key-Astra)	120-240 mg daily	Chrysant, 1993[25]
Transdermal nitrate patches	7.5-10 mg per 12 h; patches removed after 12 h	DeMots, 1989[26]
Phasic release nitroglycerin patch	15 mg, most released in first 12 h[†]	Parker, 1989[‡]

* Efficacy of second dose not established; no data for other doses.

† No data for other doses.

‡ *Eur Heart J* 1989;10(Suppl. A):43-49.

Isosorbide dinitrate (oral preparation) is frequently given for the prophylaxis of angina. An important question is whether regular therapy with isosorbide dinitrate gives long-lasting protection (3-5 hours) against angina. In a crucial placebo-controlled study, exercise duration improved significantly for 6 to 8 hours after single oral doses of 15 to 120 mg isosorbide dinitrate, but for only 2 hours when the same doses were given repetitively four times daily.[29] Marked tolerance develops during sustained therapy, despite much higher plasma isosorbide dinitrate concentrations during sustained than during acute therapy.[29] With the extended-release formulation of isosorbide dinitrate *(Tembids),* eccentric twice-daily treatment with a 40-mg dose administered in the morning and 7 hours later was not superior to placebo in a large multicenter study.[23] Nonetheless eccentric dosing schedules of isosorbide dinitrate are still often used in an effort to avoid tolerance.

Mononitrates have similar dosage and effects to those of isosorbide dinitrate. Nitrate tolerance, likewise a potential problem, can be prevented or minimized when rapid-release preparations *(Monoket, Ismo)* are given twice daily in an eccentric pattern with doses spaced by 7 hours.[24] Using the slow-release preparation *(Imdur),* the dose range 30-240 mg once daily was tested for antianginal activity. Only 120 and 240 mg daily improved exercise times at 4 and 12 hours after administration, even after 42 days of daily use.[25] These high doses were reached by titration over 7 days. A daily dose of 60 mg, still often used, was ineffective.

Transdermal nitroglycerin patches are designed to permit the timed release of nitroglycerin over a 24-hour period. Despite initial claims of 24-hour efficacy, major studies have failed to show prolonged improvement.

Pentaerythritol tetranitrate may have the advantage of provoking less nitrate tolerance than other nitrates[30] but this drug is not widely available (also see section on “Prevention and Limitation of Nitrate Tolerance” page 52).

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Limitations: Side effects and nitrate failure

Side effects

Hypotension is the most serious and headache the most common side effect (Table 2-3). Headache characteristically occurs with sublingual nitroglycerin, and at the start of therapy with long-acting nitrates.[17] Often the headaches pass over while antianginal efficacy is maintained; yet headaches may lead to loss of compliance. Concomitant aspirin may protect from the headaches and from coronary events. In chronic lung disease, arterial hypoxemia may result from vasodilation and increased venous admixture. Occasionally, prolonged high-dose therapy can cause *methemoglobinemia* (see Table 2-3), which reduces the oxygen-carrying capacity of the blood and the rate of delivery of oxygen to the tissues. Treatment is by intravenous methylene blue (1-2 mg/kg over 5 min).

Table 2-3 -- Nitrate Precautions and Side Effects

Precautions
Need airtight containers.
Nitrate sprays are inflammable.
Common Side Effects
Headaches *initially* frequently limit dose; often respond to aspirin.
Facial flushing may occur.
Sublingual nitrates may cause halitosis.
Serious Side Effects
Syncope and hypotension may occur.
Hypotension risks cerebral ischemia.
Alcohol or other vasodilators may augment hypotension.
Tachycardia frequent.
Methemoglobinemia: with prolonged high doses. Give IV methylene blue (1-2 mg/kg)
Contraindications
In ***hypertrophic obstructive cardiomyopathy,*** nitrates may exaggerate outflow obstruction.
Sildenafil (or similar agents): risk of hypotension or even acute MI.
Relative Contraindications
Cor pulmonale: decreased arterial pO_2.
Reduced venous return risky in constrictive pericarditis, tight mitral stenosis.
Tolerance
Continuous high doses lead to tolerance that eccentric dosage may avoid.
Cross-tolerance between formulations.
Withdrawal Symptoms
Gradually discontinue long-term nitrates.

IV, Intravenous; *MI,* myocardial infarction.

Failure of nitrate therapy

In contrast to the marked beneficial effects of sublingual nitroglycerin in reversing attacks of angina pectoris,

long-acting nitrates are only moderately effective in reducing frequency of angina pectoris or in relieving symptoms in patients with heart failure. Apart from issues of noncompliance, the principal reason for limitation of therapeutic response to nitrates can be categorized as NO• resistance, “true” nitrate tolerance and nitrate “pseudo”-tolerance, alone, or in combination (Table 2-4).

Table 2-4 -- Factors Limiting Responsiveness to Organic Nitrates

Anomaly	Principal Mechanisms	Effects
NO resistance	“**Scavenging**” of NODysfunction of soluble guanylate cyclase	De novo hyporesponsiveness
“True” nitrate tolerance	**(1)** Impaired bioactivation of nitrates **(2)** Increased clearance of NO by O_2	Progressive attenuation of nitrate effectWorsening of endothelial dysfunction
Nitrate pseudotolerance	Increased release of vasoconstrictors (angiotensin II catecholamines, endothelin)	“Rebound” during nitrate-free periods

NO, Nitric oxide; O_2, oxygen.

Management of apparent failure of nitrate therapy.

After exclusion of tolerance and poor compliance (headaches), therapy is stepped up (Table 2-5)[31] while excluding aggravating factors such as hypertension, thyrotoxicosis, atrial fibrillation, or anemia.

Table 2-5 -- Proposed Step-Care for Angina of Effort

1. **General:** History and physical examination to exclude valvular disease, anemia, hypertension, thromboembolic disease, thyrotoxicosis, and heart failure. Check risk factors for coronary artery disease (smoking, hypertension, blood lipids, diabetes, obesity). Must stop smoking. Check diet.
2. **Prophylactic drugs.** Give aspirin, statins and ACE inhibitors. Control BP.
3. **Start-up.** *First-line therapy*. Short-acting nitrates are regarded as the basis of therapy, to which is added either a β-blocker or CCB (heart-rate lowering or DHP) β-blocker if prior infarct or heart failure. Otherwise level of evidence only C.[31] May use CCB (preferably verapamil as in INVEST[80] or diltiazem or long-acting dihydropyridine).
4. **Second-line therapy** is the combination of a short acting nitrate with a β-blocker plus a CCB (DHP).
5. **Third-line therapy.** The add-on choice is between long-acting nitrates, ivabradine, nicorandil, ranolazine, perhexiline (Australia and New Zealand), or trimetazidine (Europe). The European Guidelines, under review (2012), are expected to allow for any of these third-line drugs, except for long-acting nitrates, to be chosen as first-line agents.
6. **PCI with stenting** may be attempted at any stage in selected patients, especially for highly symptomatic single vessel disease.
7. **Consider bypass surgery** after failure to respond to medical therapy or for left main stem lesion or for triple vessel disease, especially if reduced LV function. Even response to medical therapy does not eliminate need for investigation.
8. **Nitrate failure** may occur at any of these steps. Consider nitrate tolerance or worsening disease or poor compliance.

ACE, Angiotensin-converting enzyme; *BP,* blood pressure; *DHP,* dihydropyridine; *LV,* left ventricular; *PCI,* percutaneous coronary intervention.

Nitrates for acute coronary syndromes

Large trials have failed to show a consistent reduction in mortality in either unstable angina and non-ST elevation myocardial infarction (MI) or in ST-elevation MI. Therefore the goal of nitrate therapy is pain relief or management of associated acute heart failure[32] or severe hypertension.

Intravenous nitroglycerin is widely regarded as being effective in the management of pain in patients with ACS, although without properly controlled trials. Nitroglycerin should be infused at an initial rate of 5 mcg/min (or even 2.5 mcg/min in patients with borderline hypotension), using nonadsorptive delivery systems. Although earlier studies used progressive uptitration of infusion rates to relief of pain (with eventual rates of >1000 mcg/min in some patients), this strategy should be limited in general because of the risks of tolerance induction and subsequent "rebound." Given that even 10 mcg/min nitroglycerin induces some degree of tolerance within 24 hours,[33] a maximal infusion rate of 16 mcg/min is recommended in most cases.[34] Nitrate patches and nitroglycerin ointment should not be used. Intravenous therapy, which can be titrated upward as needed, is far better for control of pain.

Percutaneous coronary intervention.

Intracoronary nitroglycerin is often used to minimize ischemia, for example, caused by coronary spasm. Some nitrate solutions contain high potassium that may precipitate ventricular fibrillation.

Nitrate contraindications.

With right ventricular involvement in acute myocardial infarction (AMI), a nitrate-induced fall in left ventricular (LV) filling pressure may aggravate hypotension. A systolic BP of less than 90 mm Hg is a contraindication. Recent ingestion of sildenafil or its equivalent means that nitrate therapy must be delayed or avoided (see "Nitrate Interactions with Other Drugs," page 43).

Acute heart failure and acute pulmonary edema

No clear guidelines exist regarding management of *acute decompensated heart failure.* In an observational study of more than 65,000 patients, intravenous nitroglycerin gave similar outcomes to the more modern and expensive intravenous nesiritide and better results than dobutamine.[35] However, the patients were not equally matched for BP at entry, so that randomized controlled trials are needed to develop practice guidelines.

In *acute pulmonary edema* from various causes, including AMI, nitroglycerin can be strikingly effective, with some risk of precipitous falls in BP and of tachycardia or bradycardia. Sublingual nitroglycerin in repeated doses of 0.8 to 2.4 mg every 5 to 10 minutes can relieve dyspnea within 15 to 20 minutes, with a fall of LV filling pressure and a rise in cardiac output.[36] Intravenous nitroglycerin, however, is usually a better method to administer nitroglycerin because the dose can be rapidly adjusted upward or downward depending on the clinical and hemodynamic response. Infusion rates required may be higher than the maximal use for AMI (i.e., above 200 mcg/min), but this is based on the idea of brief infusion when pulmonary edema is present without systemic hypotension. A similar approach has been validated with intravenously infused isosorbide dinitrate.[37]

On the other hand, the infusion rate of nitroglycerin at lower rates, in combination with N-acetylcysteine (NAC), was as effective as a diuretic-based treatment regimen in unselected patients with acute pulmonary edema.[38]

Congestive heart failure

Both short- and long-acting nitrates are used as unloading agents in the relief of symptoms in acute and chronic heart failure. Their dilating effects are more pronounced on veins than on arterioles, so they are best suited to patients with raised pulmonary wedge pressure and clinical features of pulmonary congestion. The combination of high-dose isosorbide dinitrate (60 mg four times daily) plus hydralazine was better than placebo in decreasing mortality, yet nonetheless inferior to an ACE inhibitor in severe congestive heart failure (CHF).[39] Dinitrate-hydralazine may therefore be chosen when a patient cannot tolerate an ACE inhibitor or it may be added to the therapy of heart failure, the latter indication being well validated in black patients.[21]

Nitrate tolerance remains a problem. Intermittent dosing designed to counter periods of expected dyspnea (at night, anticipated exercise) is one sensible policy.[40] Escalating doses of nitrates provide only a short-term solution and should be avoided in general. A third possible option is co-therapy with ACE inhibitors or hydralazine or both, which might blunt nitrate tolerance. *Nitrate patches* have given variable results in CHF.

Nitrate tolerance and nitric oxide resistance

Nitrate tolerance

Nitrate tolerance often limits nitrate efficacy. Thus longer-acting nitrates, although providing higher and better-sustained blood nitrate levels, paradoxically often seem to lose their efficacy with time. This is the phenomenon of nitrate tolerance (see Fig. 2-4). A number of hypotheses have been proposed to account for development of nitrate tolerance. These may be summarized as follows:

1. *Impaired nitrate bioactivation.* Several investigators have demonstrated that the induction of tolerance to nitroglycerin and to other organic nitrates is relatively nitrate-specific, with minimal cross-tolerance to more direct activators of soluble guanylate cyclase, including NO• itself.[41],[42] Infusion of nitroglycerin for 24 hours in patients with stable angina induced nitrate-specific tolerance, with simultaneous evidence of impaired bioactivation, via the enzymatic denitration of nitroglycerin and release of NO•.[42] As organic nitrate bioactivation is an enzymatic process, catalyzed by a large number of nitrate reductases, these findings have led to a search for a potential key "tolerance-inducing enzyme." Such an enzyme would be potentially inhibited after prolonged nitrate exposure.
2. *Aldehyde dehydrogenase (ALDH).* ALDH is an example of such an enzyme (see Fig. 2-4). Aldehydes are highly toxic compounds that generate reactive oxidative stress in the form of reactive oxygen species (ROS). Aldehydes physiologically result from numerous processes including the actions of catecholamines and are ubiquitously present in the environment. Normally their potentially noxious effects are kept at bay by the activity of the mitochondrial aldehyde dehydrogenase ($ALDH_2$). Inhibition of $ALDH_2$ by organic nitrates may remove a protective mechanism against oxidative stress.[43],[44] $ALDH_2$ is dysfunctional in up to 30% of Chinese and Japanese; this anomaly is thus estimated to involve at least 0.5 billion persons worldwide.[8] This enzyme modulates bioactivation of some organic nitrates, including nitroglycerin (see mito ALDH in Fig. 2-4). Conversely, nitroglycerin can potently and rapidly inactivate ALDH, including $ALDH_2$,[45] an effect that appears to occur prior to onset of nitrate tolerance. Moreover, induction of nitrate tolerance occurs more readily in $ALDH_2$-knockout mice.[8] Furthermore, pentaerythritol tetranitrate that is less reliant on $ALDH_2$ for bioactivation is consequently less subject to tolerance induction,[46],[47] in contrast to the endothelial dysfunction linked in normal subjects to the prolonged use of isosorbide-5-mononitrate.[9] However, it should also be noted that, apart from wide variability in the interactions between organic nitrates and various ALDH subtypes,[48] there are many other nitrate reductases: it therefore seems unlikely that inhibition of $ALDH_2$ is the single key mechanism underlying nitrate tolerance induction.[9]
3. *Free radical hypothesis*: *induction of oxidative stress and endothelial dysfunction.* A number of studies have linked the development of nitrate tolerance with increases in free radical release, oxidative stress and resultant induction of endothelial dysfunction.[49] Similarly, a number of studies in normal animal models and in normal humans[9] have demonstrated that induction of nitrate tolerance *may* be associated with the induction of vascular endothelial dysfunction. Based on the crucial role of $ALDH_2$ in limiting the harm of prolonged excess generation of ROS, any product that limits the generation of ROS may lessen the risk of nitrate tolerance. For example, agents stimulating guanylyl cyclase or the PDE 5 inhibitors with increased formation of vasodilatory cyclic GMP experimentally promote the activity of NO• (see Fig. 2-4).[50] Such mechanistic experimental data should not directly be translated into clinical practice because of the danger of excess vasodilation (see Fig. 2-4).

The problems with the free radical hypothesis include (1) the paucity of supporting data in tolerance occurring in the presence of preexistent coronary disease and thus of endothelial dysfunction,[33] (2) the finding that some nitrates may reduce oxidative stress,[51] and (3) the preservation of endothelial function in some models of tolerance.[52] Nevertheless, the free radical hypothesis would explain why nitrate tolerance can be lessened acutely in some models by concurrent therapy by vitamin[9],[53],[54] or hydralazine.[55-57] Other agents that reduce oxidative stress include statins, ACE inhibitors, and ARBs.[55]

Prevention and limitation of nitrate tolerance

In effort angina, many studies now show that symptomatic tolerance can be lessened by interval dosing. Eccentric twice-daily doses of isosorbide mononitrate (Monoket, Ismo) or once-daily treatment with 120 or 240 mg of the extended-release formulation of mononitrate (Imdur) maintain clinical activity but may

nonetheless lead to endothelial dysfunction.[9] There is considerable evidence that nitrate effects on blood vessels and platelets are SH-dependent.[58-60] Concomitant therapy with SH donors such as NAC potentiates nitroglycerin effects, both hemodynamically[61] and on platelet aggregation.[62] Concomitant nitroglycerin-NAC therapy may also limit tolerance induction clinically[63] while improving outcomes in unstable angina pectoris.[64] Simple procedures that might be tried are folic acid supplementation, supplemental L-arginine,[65] and vitamin C.[9] Rapidly increasing blood nitrate levels may overcome tolerance. Although there is strong evidence that nitrate-free intervals limit tolerance, they may be associated with "rebound" or the "zero-hour phenomenon."

Concomitant cardiovascular co-therapy (fig. 2-7):

Carvedilol has strong experimental and clinical support. It can attenuate nitrate tolerance induced in rodents by preventing free-radical generation and CYP depletion, and therefore maintaining the activity of the NO–cyclic GMP pathway (see Fig. 2-4).[66] Clinically, carvedilol prevents nitrate tolerance better than a β-blocker. As β-blockade is commonly used in effort angina, carvedilol may be the β-blocker that is preferred. To be sure would require more high-quality comparative trials in the modern era.

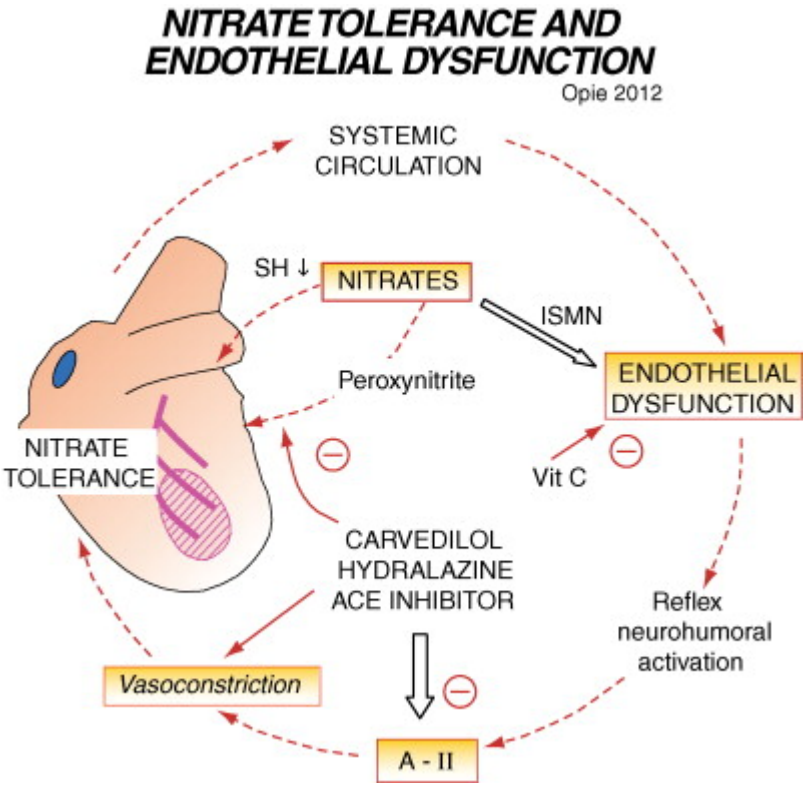

Figure 2-7 Current proposals for therapy of nitrate tolerance. For cellular mechanisms of peroxynitrite, see Figure 2-3. Carvedilol, vitamin C, and hydralazine may all lessen free radical formation. Isosorbide dinitrate and hydralazine have proven long-term effects in heart failure patients. Angiotensin-converting enzyme inhibitors oppose the neurohumoral activation that is thought to occur as a result of nitrate-induced vasodilation, possibly involving reflex arterial constriction and impaired renal blood flow. *ISMN,* Isosorbide mononitrate; *SH,* sulfhydryl.
(Figure © L. H. Opie, 2012.)

Nebivolol is a β-blocker that somewhat paradoxically, is also a β_3-adrenoceptor *agonist,* whereby it activates NOS, thus releasing NO•.[67] This unusual property should theoretically help to limit nitrate tolerance.

Hydralazine is logical, especially in CHF because (1) there are strong trial data favoring the nitrate-hydrazine combination, and (2) the hydralazine may overcome the effect of free radical formation.

Experimental nitroglycerin-induced endothelial dysfunction in humans can be prevented by high-dose *atorvastatin* (80 mg/day) for 7 days.[48] The proposed mechanism is statin-induced decrease of the nitroglycerin-induced oxidative stress.

Experimentally, telmisartan, an *ARB,* counters nitrate-induced vascular dysfunction.[68]

Choice of nitrate medication.

Pentaerythritol tetranitrate (not in the United States) is relatively resistant to tolerance induction.[30] Experimentally, pentaerythritol tetranitrate improves angiotensin II–induced vascular dysfunction caused by stimulation of nicotinamide adenine dinucleotide phosphate oxidase activity (see Fig. 2-4) and formation of ROS (see Fig. 2-5).[47] Likewise, in experimental diabetes, vascular function is maintained.[69] In a small study on patients with CAD, treatment for 8 weeks with oral pentaerythritol tetranitrate 80 mg three times daily did not induce endothelial dysfunction.[70] Taken together, these observations suggest that pentaerythritol tetranitrate could be used more often (where it still is available). Decisive evidence from a prospective double-blinded clinical trial versus a standard nitrate is still required for proof of concept.

Nitrate cross-tolerance

Short- and long-acting nitrates are frequently combined. In patients already receiving isosorbide dinitrate, addition of sublingual nitroglycerin may give a further therapeutic effect, albeit diminished. Logically, as discussed in previous editions of this book, tolerance to long-acting nitrates should also cause cross-tolerance to short-acting nitrates, as shown for the capacitance vessels of the forearm, coronary artery diameter, and on exercise tolerance during intravenous nitroglycerin therapy.

Nitrate pseudotolerance and rebound

Rebound is the abrupt increase in anginal frequency during accidental nitrate withdrawal (e.g., displacement of an intravenous infusion) or during nitrate-free periods.[71],[72] Nitrate pseudotolerance probably accounts for the "zero-hour phenomenon," whereby patients receiving long-acting nitrate therapy experience worsening of angina just prior to routine administration of medication.[26] The underlying mechanisms are unopposed vasoconstriction (angiotensin II, catecholamines, and endothelin) during nitrate withdrawal with attenuation of net vasodilator effect of NO•.[56]

Nitric oxide resistance

NO• resistance may be defined as *de novo* hyporesponsiveness to NO• effects, whether vascular or antiaggregatory. It also occurs with other "direct" donors of NO•, such as sodium nitroprusside. The occurrence of NO• resistance accounts for the finding that some patients with heart failure respond poorly to infused NO• donors, irrespective of prior nitrate exposure.[73] The mechanisms of NO• resistance in platelets relate primarily to incremental redox stress mediated by superoxide anion release.[74] There is a close association between NO• resistance and endothelial dysfunction as in ACS.[75] Platelet resistance to NO• is an adverse prognostic marker.[76]

Step-care for angina of effort

The National Institute for Clinical Excellence (NICE) in the United Kingdom is an impartial body of experts drawn from the United Kingdom who aim to produce an impartial and high-quality document. Their full-length document on the management of stable angina, comprising 489 pages, is summarized in abridged format.[77] Each of the recommendations is supported by a table of all the relevant studies, which are graded into low, medium, and high quality. For example, comparison between β-blockers and CCBs covers 18 analyses.

First-line therapy.

Short-acting nitrates are regarded as the basis of therapy, to which either a β-blocker or CCB is added.

Second-line therapy.

Second-line therapy is the combination of a short acting nitrate with a β-blocker plus a CCB (dihydropyridine [DHP]) such as long-acting nifedipine, amlodipine, or felodipine. The NICE investigation could find no evidence of the difference in cardiac mortality or rate of nonfatal MI between patients treated with this combination compared with either of the two agents alone. However, there was objective evidence that during exercise testing the combination increased exercise time and time to ST depression in the short term when compared with one of the two agents alone. This beneficial effect of combination treatment was not matched by improved symptom control, as assessed by the frequency of episodes of angina and use of nitroglycerin. The short-term improvement in exercise tolerance would, however, translate to a subjective benefit for the patient.

Third-line therapy.

The add-on choice is between long-acting nitrates, ivabradine, nicorandil, and ranolazine. We add perhexiline (Australia and New Zealand) and trimetazidine (Europe). The European Task Force for the management of stable angina, presently preparing its report for the European Guidelines, will also allow for any of these third-line drugs, except for long-acting nitrates, to be chosen as first-line agents according to the judgment and experience of the practicing physician or cardiologist.

Overall care.

A full history and physical examination is required to exclude all remediable factors (see Table 2-5), not forgetting aortic stenosis that may be occult in older adults. Risk factors such as hypertension and lifestyle must be vigorously managed and aspirin, statins, and an ACE inhibitor given if there are no contraindications.[78] Percutaneous coronary intervention (PCI) and bypass surgery are increasingly taken as escape routes when coronary anatomy is appropriate. However, conservative management gives outcome results as good as PCI.[79] There are no long-term outcome studies on the benefits of nitrates alone in angina pectoris.

Combination therapy for angina

Existing data are inadequate to evaluate the overall efficacy of combinations of nitrates plus β-blockers and CCBs when compared with optimal therapy by each other or by any one agent alone. The COURAGE study reflects current American practice.[79] Almost all received a statin and aspirin, 86% to 89% a β-blocker, and 65% to 78% an ACE inhibitor or ARB. Nitrate use declined from 72% at the start to 57% at 5 years. However, only 43% to 49% were given a CCB, even though first-line therapy in those with effort angina or prior infarction by the CCB verapamil was identical in outcome with β-blockade by atenolol.[80]

β-blockade and long-acting nitrates are often combined in the therapy of angina (see Table 2-5). Both β-blockers and nitrates decrease the oxygen demand, and nitrates increase the oxygen supply; β-blockers block the tachycardia caused by nitrates. β-blockade tends to increase heart size and nitrates to decrease it.

CCBs and short-acting nitroglycerin are often combined. In a double-blind trial of 47 patients with effort angina, verapamil 80 mg three times daily decreased the use of nitroglycerin tablets by 25% and prolonged exercise time by 20%.[81] No outcome data have been reported. *CCBs and long-acting nitrates* are also often given together, however, again without support from outcome trial data.

Nitrates, β-blockers, and CCBs may also be combined as triple therapy. The ACTION study was a very large outcome study in which long-acting nifedipine gastrointestinal therapeutic system (GITS; Procardia XL, Adalat CC) was added to preexisting antianginal therapy, mostly β-blockers (80%) and nitrates (57% nitrates as needed, and 38% daily nitrates).[28] The CCB reduced the need for coronary angiography or bypass surgery, and reduced new heart failure. In hypertensive patients added nifedipine gave similar but more marked benefits plus stroke reduction.[82] There are two lessons. First, dual medical therapy by β-blockers and nitrates is inferior to triple therapy (added DHP CCBs); and second, hypertension in stable angina needs vigorous antihypertensive therapy as in triple therapy. However, we argue that “optimal medical therapy” should consider a metabolically active agent.

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Metabolic and other newer antianginal agents

The metabolic antianginal agents and ranolazine have antianginal activity not mediated by nor associated with hemodynamic changes (Fig. 2-8). Their protective mechanisms oppose the basic metabolic mechanisms operative in the myocardial ischemia that is the basis of angina.

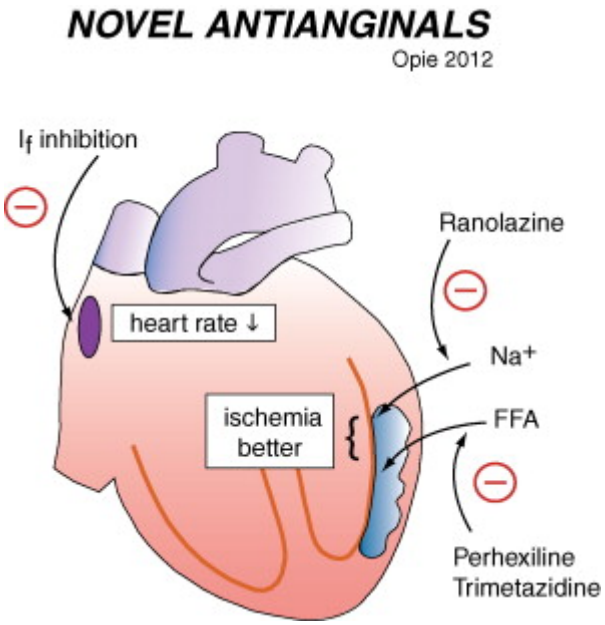

Figure 2-8 Novel antianginal agents work in different ways. If inhibition by ivabradine increases myocardial oxygen demand by decreasing the heart rate. Ranolazine decreases the inflow of sodium by the slow sodium current during ischemia and thereby lessens the intracellular sodium and calcium load. Perhexiline inhibits free fatty acid (FFA) oxidation at the level of the enzyme CPT-1. Trimetazidine inhibits fatty acid oxidation at the level of the mitochondrial long-chain oxidation and, in addition, improves whole-body insulin sensitivity.
(Figure © L. H. Opie, 2012.)

Ranolazine (ranexa).

Ranolazine is approved by the Food and Drug Administration for chronic effort angina, and may be used in combination with amlodipine, β-blockers, or nitrates. It is a metabolically active antianginal, originally thought to act by inhibition of oxygen-wasting fatty acid metabolism, thereby increasing the metabolism of protective glucose.[83] Currently, however, the favored mechanism is inhibition of the slow inward sodium current whereby sodium enters the ischemic cells, then dragging in calcium ions by sodium-calcium exchange with their proischemic effects. Controversy continues as to whether the antianginal effects of ranolazine, including a possibly beneficial effect in suppressing atrial fibrillation, might partially depend on improvement in myocardial energetics.[84] A metabolic mechanism is particularly relevant because of the recent findings that ranolazine lowers fasting plasma glucose and hemoglobin A1c in patients with non-ST elevation ACS and hyperglycemia.[85] Ranolazine helps in poorly controlled diabetes and may also improve symptomatic status in systolic heart failure by reducing calcium overload.[86]

Ranolazine cautions.

Although the US packet insert warns about prolongation of the QT_c interval, in a recent large trial on patients with ACS no proarrhythmic effects were noted.[87] However, ranolazine should still be avoided in

those with prior QT prolongation, or with other drugs that prolong the QT interval (see Fig. 8-6). Because it is metabolized by the hepatic enzyme CYP3A, drugs inhibiting this enzyme (ketoconazole, diltiazem, verapamil, macrolide antibiotics, human immunodeficiency virus protease inhibitors, and grapefruit juice) and chronic liver disease may all increase ranolazine blood levels and hence QT prolongation.

Trimetazidine.

Trimetazidine is widely used as an antianginal drug in Europe but not in the United States or United Kingdom. It is a partial inhibitor of fatty acid oxidation without hemodynamic effects. Short-term clinical studies have demonstrated significant benefits including a reduction in weekly angina episodes and improved exercise time, but large, long-term trials are needed.[88] In diabetic patients with CAD trimetazidine decreased blood glucose, increased forearm glucose uptake, and improved endothelial function.[89] An interesting proposal is that, because it acts independently of any BP reduction, it could be used as an antianginal in those with erectile dysfunction in place of nitrates to allow free use of sildenafil and similar agents.

There is increasingly strong evidence that trimetazidine may also be useful in the treatment of chronic systolic heart failure[90] secondary to improvements in myocardial energetics. In heart failure added trimetazidine gives benefit to conventional therapy including β-blockades and RAS inhibition.[91] In a small series of neurologic patients, treatment with trimetazidine worsened previously diagnosed Parkinson disease,[92] which should become a contraindication to its use.

Perhexiline.

Perhexiline inhibits fatty acid oxidation at the level of CPT-1, the enzyme that transports activated long-chain fatty acids into the mitochondria. Once widely used, hepatotoxicity and peripheral neuropathy became limitations in the 1980s. The subsequent realization that these side effects resulted mainly from slow hepatic hydroxylation and that their incidence could be reduced by measuring blood levels and lowering doses if needed, has led to a resurgence for use in refractory angina in Australia and New Zealand.[7],[93-96] Elsewhere, perhexilene is not widely used. It should theoretically be ideal for the combination of angina and heart failure.[93]

Use in heart failure.

Perhexiline improves symptoms and energetics in moderate systolic heart failure refractory to other therapy.[97] Perhexiline also improves nonobstructive hypertrophic cardiomyopathy.[98] The latter major finding, it must be emphasized, represents the first demonstration by a controlled trial that symptoms in heart failure caused by this condition are amenable to pharmacologic therapy.

Other newer antianginal agents

Ivabradine.

Ivabradine (Procoralan) is a blocker of the pacemaker current I_f, and hence does not act directly on the metabolism but indirectly by decreasing the heart rate and thus the metabolic demand of the heart. Its antianginal potency is similar to that of β-blockade[99] and amlodipine.[100] There is no negative inotropic effect nor BP reduction as with β-blockers, nor any rebound on cessation of therapy.[94] Ivabradine is licensed in the United Kingdom and other European countries for use in angina when β-blockers are not tolerated or are contradicted. In practice, it may be combined with β-blockade with clinical benefit,[101] but in this study the β-blocker was not upwardly titrated to achieve maximal heart rate reduction. Theoretically there is less risk of severe sinus node depression than with β-blockade because only one of several pacemaker currents is blocked, whereas β-blockade affects all. The downside is that the current I_f is also found in the retina, so that there may be disturbance of nocturnal vision with flashing lights (phosphenes)[102] that could impair driving at night and is often transient.

Use in heart failure.

The SHIFT study established the clinical benefits of ivabradine in a group of patients with moderate systolic heart failure whose heart rates remained elevated despite β-blockade.[103] Ivabradine reduced cardiovascular mortality and hospital admissions, and also substantially improved quality of life. However, the findings of SHIFT have been challenged. In the *Lancet* editorial accompanying the SHIFT study, Teerlink questioned whether adequate β-blocker doses had been used.[104] Only 23% of the patients were at trial-established target doses and only half were receiving 50% or more of the targeted β-blocker dose (also see Chapter 6, page 196).

European approval.

In December 2011 The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the approval of the license of ivabradine. The license now includes the treatment of chronic heart failure New York Heart Association level II to IV with systolic dysfunction in patients in sinus rhythm and whose heart rate is 75 bpm or more, in combination with standard therapy including b-blocker therapy or when b-blocker therapy is contraindicated or not tolerated. The CHMP contraindications to use in heart failure are unstable or acute heart failure or pacemaker-dependent heart failure (heart rate imposed exclusively by the pacemaker).

Nicorandil.

Nicorandil (not in the United States) has a double cellular mechanism of action, acting both as a potassium channel activator and having a nitratelike effect, which may explain why experimentally it causes less tolerance than nitrates. It is a nicotinamide nitrate, acting chiefly by dilation of the large coronary arteries, as well as by reduction of pre- and afterload. It is widely used as an antianginal agent in Japan. In the IONA study, 5126 patients with stable angina were followed for a mean of 1.6 years. Major coronary events including ACS were reduced.[105]

Allopurinol.

Allopurinol may have a double energy-conserving mechanism. First, it might reduce myocardial oxygen consumption via inhibition of xanthine oxidase. Second, in heart failure allopurinol may act by promoting transfer of high-energy phosphate from creatine phosphate to adenosine triphosphate.[106] In keeping with these energy-enhancing concepts, Norman et al.[107] performed a double-blind placebo crossover study of high-dose allopurinol (600 mg/day) in patients with stable angina pectoris. They found a moderate increase in time to chest pain and to significant ST depression, thereby establishing an antianginal effect of

high-dose allopurinol. Furthermore, this dose of allopurinol reduced vascular oxidative stress and improved endothelial function in patients with CAD.[108]

Despite the considerable interest arising from these findings, a number of important issues remain unclear. First, the mechanism of action is not clear. Favorable effects on myocardial energetics might underlie the increases in exercise tolerance.[106],[109] Second, little information is currently available as to the dose-response characteristics of allopurinol in angina, its potency in otherwise refractory cases, or its long-term safety in the high dose used in the study performed by Norman et al.[107]

Are nitrates really safe?

In contrast to the reasonable data for the safety of β-blockers and CCBs in effort angina,[110] logic would say that nitrate therapy that leads to excess production of free radicals, endothelial dysfunction, tachycardia, and renin-angiotensin activation may not be safe.[111] Analyses of two large databases showed that nitrate use was associated with increased mortality with hazard ratios of 1.6 and 3.8.[112] Prolonged nitrate therapy given to Japanese patients for vasospastic angina increased serious cardiac events in a descriptive study.[113] At present the best policy may lie in adding short-acting nitrates to β-blockers or CCBs plus the standard cardioprotective drugs such as aspirin, ACE inhibitors, and statins,[57] as in the EUROPA study (see Chapter 5).

Summary

1. ***Mechanisms of action.*** Nitrates act by venodilation and relief of coronary vasoconstriction (including that induced by exercise) to ameliorate anginal attacks. They are also arterial dilators, and reduce aortic systolic pressure. Their unloading effects also benefit patients with CHF with high LV filling pressures.
2. ***Intermittent nitrates for effort angina.*** Sublingual nitroglycerin remains the basic therapy, usually combined with a β-blocker, a CCB, or both with careful assessment of lifestyle, BP, and blood lipid profile. As the duration of action lasts for minutes, nitrate tolerance is unusual because of the relatively long nitrate-free intervals between attacks. Intermittent isosorbide dinitrate has a delayed onset of action because of the need for hepatic transformation to active metabolites, yet the duration of action is longer than with nitroglycerin.
3. ***For anginal prophylaxis.*** Some newer nitrate preparations are not substantial advances over the old. We support the NICE recommendations for initial use of a short-acting nitrate plus either a β-blocker or CCB, then adding both the β-blocker and a DHP CCB, then adding a third-line agent, with some latitude in allowing the “third-line” agent (ivabradine, nicorandil, ranolazine, trimetazidine; or perhexiline in Australia and New Zealand) to be used as the initial combination with short-acting nitrates.
4. ***Nitrate tolerance.*** The longer the duration of nitrate action, the more tolerance is likely to develop. Thus it effectively turns into a balancing act between duration of action and avoidance of tolerance. Down-grading long-acting nitrates to a third-line choice as recommended by NICE, instead of a first-line choice as it is still often used, should lessen the risk of tolerance. Increasing data show that endothelial dysfunction, in which aldehyde formation plays a role, is incriminated in nitrate tolerance. Co-therapy with carvedilol or possibly nebivolol as the β-blockers of choice should help to prevent or delay tolerance, yet prospective clinical trials are lacking.
5. ***For unstable angina at rest.*** A nitrate-free interval is not possible, and short-term treatment for 24 to 48 hours with intravenous nitroglycerin is frequently effective; however, escalating doses are often required to overcome tolerance.
6. ***Early phase AMI.*** We suggest that intravenous nitrates be specifically reserved for more complicated patients.
7. ***Treatment of CHF.*** Tolerance also develops during treatment of CHF, so that nitrates are often reserved for specific problems such as acute LV failure, nocturnal dyspnea, or anticipated exercise. However, isosorbide dinitrate combined with hydralazine is now licensed for heart failure in self-defined black subjects.
8. ***Acute pulmonary edema.*** Nitrates are an important part of the overall therapy, acting chiefly by preload reduction.
9. ***Nitrate tolerance.*** The current understanding of the mechanism tolerance focuses on free radical formation (superoxide and peroxynitrite) with impaired bioconversion of nitrate to active $NO^{\bullet}$. During the treatment of effort angina by isosorbide dinitrate or mononitrate, substantial evidence suggests that eccentric doses with a nitrate-free interval largely avoid clinical tolerance, but endothelial dysfunction remains a long-term hazard. Besides addition of hydralazine (see previous discussion) other less well-tested measures include administration of antioxidants, statins, ACE inhibitors, and folic acid.
10. ***Serious interaction with sildenafil-like agents.*** Nitrates can interact very adversely with such agents, which are now often used to alleviate erectile dysfunction. The latter is common in those with cardiovascular disease, being a manifestation of endothelial dysfunction. The co-administration of these PDE-5 inhibitors with nitrates is therefore contraindicated. Every man presenting with ACS should be questioned about recent use of these agents (trade names: Viagra, Levitra, and Cialis). If any of these agents has been used, there has to be an interval of 24-48 hours (the longer interval for

Cialis) before nitrates can be given therapeutically with reasonable safety but still with great care.

11. ***Newer antianginal agents.*** Newer antianginal agents other than nitrates are being increasingly tested and used. These include ivabradine, ranolazine, trimetazidine, perhexiline, and allopurinol. These directly or indirectly help to preserve the myocardial energy balance. There are relatively few significant side effects.

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