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Nitrates: why and how should they be used today?

Current status of the clinical usefulness of nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate

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Summary. Nitrates are highly effective both in terminating acute attacks of angina pectoris and in the prophylaxis of symptomatic and asymptomatic myocardial ischemia. Preload reduction by venodilatation is the prevailing mechanism of nitrates in patients with chronic stable angina and is the unique feature distinguishing them from beta and calcium-channel blockers. Nitrates dilate coronary arteries not only in pre- and poststenotic vessels, but also in eccentric lesions. In patients with endothelial dysfunction, nitrates seem to be the physiological substitute for endothelium-derived relaxing factor. During the past decade, however, there has been substantial evidence of a clinically relevant loss of the anti-ischemic effects ("nitrate tolerance"). Many studies with oral dosing of isosorbide dinitrate or isosorbide-5-mononitrate at least three times daily have proven nitrate tolerance in patients with coronary artery disease and/or congestive heart failure. Complete loss of anti-ischemic effects after repetitive, continuous patch attachments has also been found. As we first showed in 1983, intermittent therapy with once-daily ingestion of high-dose sustained-release isosorbide dinitrate was successful in preventing the development of tolerance. Similarly, tolerance to isosorbide-5-mononitrate also does not develop when it is ingested once daily. It is now generally accepted that a daily low-nitrate interval is required to prevent tolerance development. Although the minimal patch-free interval required to prevent tolerance needs further investigation, a 12-h patch-free interval should prevent tolerance in most patients. The prolonged duration of action of once-daily high-dosage administration of sustained-release formulations, the improved patient compliance with a single daily administration, and the increased likelihood of maximal anti-ischemic effects are important reasons for recommending high single daily doses of isosorbide dinitrate or isosorbide-5-mononitrate.

Key words: nitrates, nitroglycerin; isosorbide dinitrate, isosorbide-5-mononitrate, angina pectoris

Since Sir Lauder Brunton's report on the use of amyl nitrite in 1867 [1] and William Murrell's description in 1879 of "Nitro-glycerine as a remedy for angina pectoris" [2], nitrates have been used for more than 100 years sublingually to treat, and for over 30 years in transdermal [3] and oral [4] preparations to prevent anginal pain.

Isosorbide dinitrate, synthesized in 1938, is a classic case of serendipity and today represents the major orally used nitrate. Since the early 1970s it has been known that isosorbide dinitrate is extensively denitrated in the liver [5–7]. This first-pass metabolism was erroneously thought to preclude the possibility of orally administered nitrates. Soon it became clear that the two denitrated metabolites, the isosorbide-2-mononitrate and the isosorbide-5-mononitrate, were also effective compounds [8, 9] and therefore the first-pass effect in the liver has to be considered a useful metabolism. In 1976, Michel compared the anti-ischemic effects of i.v. isosorbide dinitrate to those of i.v. isosorbide-2-mononitrate and i.v. isosorbide-5-mononitrate, revealing equipotent effects in dosages of 1:2:7 [9]. The main active metabolite, isosorbide-5-mononitrate [10, 11], became clinically available and was used primarily in Europe [12–16]. For oral therapy of myocardial ischemia, the equivalent doses of isosorbide dinitrate and isosorbide-5-mononitrate are 20 mg and 40 mg, respectively [17–19].

Towards the end of the last decade, however, there was substantial evidence of a clinically relevant attenuation or even loss of the anti-anginal (anti-ischemic) effects following oral and transdermal treatment ("nitrate tolerance"). These findings, [20–28] resulted in a declining use of nitrates. The following article summarizes the reasons why this "old drug", which is so unique, should still be used today and the strategies that have been established to avoid the development of tolerance.

What are the reasons for using nitrates?

There are a whole series of reasons why nitrates should be used as the fundamental drug in patients with ischemic heart disease (Table 1).

Table 1. Reasons for use of nitrates as fundamental drug therapy in patients with ischemic heart disease

Nitrates
1. Are highly effective in angina pectoris and silent myocardial ischemia
2. [a] Reduce preload by venodilatation, additionally useful in congestive heart failure
3. Dilate coronary arteries in prestenotic, stenotic and poststenotic segments, increase collateral blood flow
4. Homogenize flow imbalances
5. Show anti-platelet effects in vivo
6. [a] Are the physiologic substitutes for EDRF in "endothelial dysfunction"
7. Have minimal side effects
8. [a] Entail low costs

[a] Unique to nitrates, as opposed to beta and calcium-channel blockers

Highly effective in angina pectoris and silent myocardial ischemia

Nitrates are well known to be highly effective both in terminating acute attacks of *angina pectoris* and in its prophylaxis. Reports documenting the usefulness of nitrates for *silent ischemia* cover sublingual, oral, intravenous and transdermal administration. Winsor and Berger in 1975 published the effects of 2.6 mg oral nitroglycerin t.i.d. on Holter-detected episodes of ST-segment depression, without yet calling it silent ischemia [29]. The analysis of over 2000 ST-segment measurements showed that nitrate therapy significantly shifted the maximum ST changes from 2.0–2.5 mm to 1.0–1.5 mm. Using 10-h Holter monitoring, Schang and Pepine found that hourly administration of 0.4 mg sublingual nitroglycerin remarkably reduced the number of ischemic episodes from 3.7 to 0.6 [30]. The intravenous infusion of isosorbide dinitrate, 1.25 to 5.0 mg/h, in patients with vasospastic resting angina, as against placebo, significantly reduced the number of painless episodes of ST-segment changes [31]. In patients with severe coronary artery disease, Pepine et al. interpreted the reversibility of wall motion abnormalities with low-dose intravenous nitroglycerin as a sign of asymptomatic myocardial ischemia [32]. Recently, the reduction of silent episodes with isosorbide-5-mononitrate 20 mg t.i.d. or once-daily isosorbide-5-mononitrate 50 mg in sustained-release form has been reported [33]. Nitroglycerin patches were evaluated by Shell et al. in an open-label study (8 patients), titrating until all angina was abolished (mean dose of 10.4 mg/24 h). The reduction in the number of ischemic events from 5.3 to 0.8 per day (including both symptomatic and asymptomatic) as well as the reduction in duration of ischemia from 96 min per day to 17 min per day was impressive [34] and consistent with the results recorded in subsequent investigations [35–37].

From the presently published studies, it is clear that nitrates are as effective in silent myocardial ischemia as beta and calcium-channel blockers [38, 39]. However, prospectively designed, double-blind trials with stricter criteria are needed to further substantiate the usefulness of nitrates for the treatment of asymptomatic episodes.

Preload reduction by venodilatation

It is well established that nitrates induce venodilatation, with subsequent reduction of the left ventricular end-diastolic pressure and end-diastolic volume (LVEDV) [40–48]. Preload reduction by venodilatation is the prevailing mechanism of nitrates in patients with chronic stable angina and reproducible, exercise-dependent ischemia, and is a unique feature of nitrates not shared by beta and calcium-channel blockers [49–51].

During resting conditions, the sublingual application of nitroglycerin resulted in a 25% decrease in LVEDV in healthy persons [52]. In patients with coronary artery disease, the LVEDV reduction observed was between 10% and 40% [53–56]. The sublingual and oral administration of isosorbide dinitrate at rest also led to a 16%–36% reduction in LVEDV [53, 57]. During exercise, a mean LVEDV reduction of 10% was reported in healthy persons after sublingual nitroglycerin [52]. The corresponding decrease in LVEDV in patients with coronary artery disease was in the range of 20% [56]. As we have shown, patients with good anti-ischemic nitrate response demonstrated an average LVEDV reduction at rest of 25%, and during exercise of 19% [58].

These volume changes are reflected by a mean increase in left ventricular ejection fraction (LVEF) at rest from 58% to 64% in healthy volunteers with sublingual nitroglycerin [59] and in patients with coronary artery disease from 43% to 63% [60]. During exercise, sublingual nitroglycerin increased LVEF from 50% to 60% [56] and from 36% to 48% [61]. In our studies, oral isosorbide dinitrate significantly incresed LVEF during exercise from 52% to 64% (Fig. 1).

In the treatment of congestive heart failure the first-line goal is to reduce elevated filling pressures and facilitate ventricular emptying. The acute favorable effects of reduction in pulmonary capillary pressure and increased cardiac output, accompanied by a remarkable decrease in systemic vascular resistance, are well known for nitro-

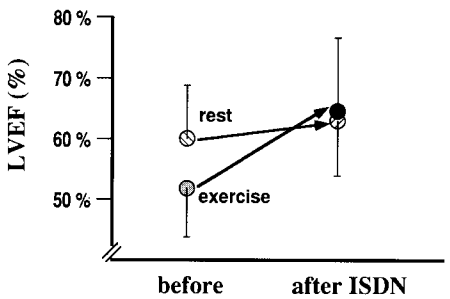

Fig. 1. Effects of isosorbide dinitrate (ISDN) on left ventricular ejection fraction *(LVEF)*. In our study in 22 patients with proven coronary artery disease, stable angina pectoris and reproducible ST-segment depression, a single oral dose of 80 mg isosorbide dinitrate in sustained-release form significantly ($P < 0.05$) increased the depressed LVEF during exercise from 52% to 64% at 2 h after the ingestion. At rest, there was a slight, but not significant trend of increasing LVEF from 60% to 63% [62, 63]

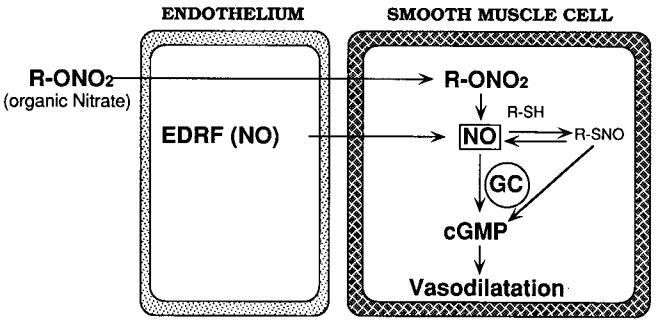

Fig. 2. Biochemical mechanism underlying the vasodilatative action of nitrates. The vasodilating effects of nitrates *(R-ONO$_2$)* are mediated by nitric oxide *(NO)* production, stimulating cyclic guanosine monophosphate *(cGMP)* via the activation of soluble guanylate cyclase *(GC)* in vascular smooth muscle cells. Nitrates also require sulfhydryl groups *(R-SH)* to produce *S*-nitrosothiols *(R-SNO)* to stimulate guanylate cyclase. Endothelium-derived relaxing factor *(EDRF)* is probably nitric oxide and therefore also leads to an increase of cyclic guanosine monophosphate, which relaxes vascular smooth muscle

glycerin, isosorbide dinitrate and isosorbide-5-mononitrate [64–73]. Therefore, nitrates are the ideal adjunct medication for patients with ischemic heart disease and pulmonary congestion.

Dilatation of coronary arteries

Since the early 1960s, it has been known that nitrates dilate major epicardial arteries [74–76]. Intracoronary (i.c.) administration of nitroglycerin increases the cross-sectional area of normal coronary arteries by approximately 40%, and sublingual nitroglycerin causes an increase of 20% [77]. Sublingual isosorbide dinitrate leads to similar effects [78, 79].

Furthermore, nitrates dilate coronary arteries not only in pre- and poststenotic vessels, but also in eccentric lesions with a dynamic component and variable myocardial ischemia [80, 81]. In moderately stenotic segments (mean 68%), i.c. nitroglycerin increased the area by 40%, in severely stenosed segments (mean 85%) by 36% [77]. Sublingually administered isosorbide dinitrate also led to remarkable dilatation in stenotic lesions, with even greater efficacy noted in the poststenotic vessels [79]. Isosorbide dinitrate demonstrated at least the same vasodilating properties as nitroglycerin, with the advantage of a longer duration of action [79]. In addition, nitrates also increase collateral blood flow [82, 83].

The usefulness of nitrates in unstable angina, e.g., variant angina with proven coronary spasm, is unquestioned (for review see [84]), and is as effective as nifedipine [85]. However, in patients with exercise-dependent ischemia and fixed threshold, the role of coronary dilatation still remains controversial [49, 50, 57, 77, 86–88].

Homogenization of flow imbalance

At rest, nitrates may reduce the global myocardial blood flow in healthy persons and patients with coronary artery disease by approximately 20%, following the decrease in oxygen demand [89–91]. In areas of reversible hypokinesia, the regional myocardial blood flow may increase after nitrates [91]. Changes in myocardial blood flow have also been explained on the basis of improved collateral blood flow [90]. During pacing-induced ischemia, a decrease in myocardial blood flow in both the normal and the poststenotic areas has been reported [92]. Nevertheless, the reduced oxygen demand (autoregulation, leading to "benign vasoconstriction"?) and the fact that the blood flow decreases more in the normal areas than in the poststenotic segments lead to a homogenization of the blood flow distribution [92–94]. This again shows that changes in myocardial blood flow (oxygen supply) should not be interpreted without changes in oxygen demand.

Anti-platelet effects in vivo

Several studies have reported remarkable anti-platelet effects of nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate [95, 96]. Interestingly, the in vivo anti-platelet efficacy of therapeutic dosages was found to be greater than in vitro [95, 97]. One possible explanation is a synergism with prostacyclin at sites of local prostacyclin production [95]. This hypothesis would not necessarily require the postulated but unconfirmed stimulation of prostacyclin [98–102]. As compared with aspirin, the inhibition of platelet function seems smaller, but the different underlying mechanisms suggest the possibility of additive effects [95]. Other explanations for the enhanced in vivo anti-platelet activity are related to the availability of reduced thiols [59], direct antiplatelet effects of the mononitrate metabolites [95], and the interaction with endothelium cells, postulating "endothelial cell-dependent anti-platelet nitrate properties" [103].

EDRF substitution

In 1987, Palmer et al. demonstrated that endothelium-derived relaxing factor (EDRF) is indistinguishable from nitric oxide (NO) [104]. EDRF, with its short half-life of 6–50 s, leads to an increase in cyclic guanosine monophosphate, which relaxes vascular smooth muscle (Fig. 2) [105]. Nitrates release NO, also leading to increased cyclic guanosine monophosphate (details will be discussed below). It is intriguing to consider EDRF as the "endogenous nitrate" that mediates vasodilatation induced by many vasoactive substances [106]. Shear stress also seems to release EDRF, explaining the marked vasodilatation that follows increased blood flow [107]. On the other hand, coronary arteries with damaged or absent endothelium react with a paradoxical vasoconstriction to "vasodilators" requiring intact endothelium, such as acetylcholine, histamine and 5-hydroxytryptamine [107, 108]. These inappropriate vasoconstrictor responses have been observed recently in patients and related to endothelial dysfunction in atherosclerotic regions, even without "significant" lesions [109, 110]. The dilator effect of nitrates, in contrast, is *independent* of endothelial integrity and may even be enhanced when endothelium is absent [111]. Therefore, in patients with endothelial dysfunction, nitrates may be considered as the physiologic substitute for EDRF (Fig. 2).

Minimal side effects

Headache is the most common adverse reaction and usually disappears (another form of nitrate tolerance) within a few days in a hyperbolic function [112], if the patients are highly compliant. Workers in the munitions industry learned to prevent "Monday-morning headache" by keeping a small pinch of powder in their hatbands to avoid the "nitrate-free weekend" [113, 114].

The less commonly encountered adverse reactions, such as nausea, vertigo, bradycardia and hypotension usually also disappear during long-term therapy. A few patients, even among those who are fully compliant, continue to suffer from these symptoms. The only contraindication for nitrates is arterial hypotension.

When does nitrate tolerance occur and how can it be circumvented?

Definition

Tolerance can be defined as the attenuation or loss of one or more effects during chronic administration. It must be strictly differentiated from a progression of the underlying disease, which is sometimes difficult in patients taking nitrates for years or in patients with unstable angina. Terms such as "partial" or "total" tolerance are sometimes confusing because they have been used with different meanings. On the one hand, they may refer to the attenuation of a single test parameter. Others have used it to describe the number of test parameters affected. Tolerance is only proven if the attenuation or loss is demonstrated despite the *same or even higher plasma levels.* Since many studies did not include the measurement of plasma levels, tolerance can only be suspected. As we know today, tolerance development regarding venous compliance may develop within 2 h [48]. Therefore, the term "tachyphylaxis" could be considered.

Induction of nitrate tolerance

Very soon after the introduction of nitroglycerin in clinical practice, Stewart published in 1888 a case of arterial hypertension entitled "Remarkable Tolerance of Nitroglycerin" [115] reporting "tolerance being so rapidly established". In 1905 he recommended to "temporarily discontinue the drug for two or more days, at intervals of two or three weeks", thus introducing "interval therapy" with nitrates [116]. Ever since, a large number of authors have corroborated these findings, and today there is unanimous agreement that tolerance develops with respect to the blood pressure effects of nitroglycerin [117, 118], isosorbide dinitrate [63, 68, 119–124] and isosorbide-5-mononitrate [125].

In contrast to the development of tolerance to headache, blood pressure and heart rate, the development of tolerance to the anti-anginal (anti-ischemic) effects were a matter of marked controversy.

Tolerance following oral administration

Many studies with at least thrice-daily oral dosing have proven nitrate tolerance. In 1969, Goldbarg et al. reported that after 4 weeks of treatment with 10 mg *isosorbide dinitrate* non-sustained release every 6 h, there was no difference between placebo and the nitrate with respect to anginal frequency and exercise capacity [126]. Similar studies were reported in 1970 and 1973 [127, 128]. In 1980, the total disappearance of the anti-ischemic effects during the administration of 20 mg, 40 mg and 60 mg isosorbide dinitrate in sustained-release form every 8 h was reported [121]. Another study revealed the same result for 40 mg isosorbide dinitrate every 6 h in non-sustained-release form [22]. In 1982, a complete loss of the anti-ischemic effects 4 h after the ingestion was reported when 15–120 mg isosorbide dinitrate was administered every 6 h in non-sustained-release form [122]. For *isosorbide-5-mononitrate* in non-sustained-release form, when given as 50 mg t.i.d., tolerance has also been established [125, 129].

Other studies with thrice-daily oral dosing did not reveal tolerance development. Another set of studies, applying oral *nitroglycerin* (2.6 mg every 8 h [29], 6.5 mg every 4–8 h [130]) or buccal nitroglycerin (3 mg, 3 times daily with a nitrate-free period of 10 h [131]) did *not* reveal tolerance development. Non-sustained-release *isosorbide dinitrate,* at variable dosages and intervals (5 mg every 1–4 h [132], 20 mg or 50 mg every 6 h [118], 40 mg every 8 h [133], and 40 mg every 4 h [134]) did *not* lead to an attenuation or loss of the anti-ischemic effects. These results were also shown with isosorbide dinitrate 20 mg sustained-release t.i.d. [18] and oral *isosorbide-5-mononitrate* 20 mg t.i.d. [18, 135–137] and 40 mg b.i.d. [138].

There may be many different reasons why nitrate tolerance was not observed in these studies using frequent dosing. First, the study design has to be taken into consideration, since open studies may be sensitive to the inherent bias. Therefore, randomized, double-blind studies should be preferred. Whether a placebo control phase is mandatory or whether it increases the risk of cardiac events remains a controversial topic and one of ethical discussion [139, 140].

In some studies using t.i.d. regimens, the single dose and its duration of action might have been too small to generate constant plasma levels with oral nitroglycerin [29, 130] or oral isosorbide dinitrate/isosorbide-5-mononitrate in non-sustained-release form [18].

"Physiologic non-compliance" may be another reason, since tolerance develops rapidly and may be reversed within several hours [62, 141, 142]. Thus, the actual ingestion of each single tablet is pivotal. Unreliable or irregular ingestion of tablets may have blurred the problem of nitrate tolerance in many studies. Unfortunately, most of the studies omitted documentation of patients' compliance [118, 126, 127, 130]. Counting the tablets returned or the documentation of tablet intake on the basis of patients' diaries is not reliable. The assessment of plasma levels is not feasible in long-term studies on a day-by-day basis. A practical method for a daily compliance test is to determine the fluorescence in the patients' urine attribut-

able to the riboflavin added to the tablets. One should keep in mind that compliance not only refers to the fact of ingestion itself but also to the exact time of ingesting the prescribed dose. Obviously it is not easy to ingest the tablets t.i.d. every 8 h for several weeks. Thus, it is conceivable that patients may have introduced their own nitrate-poor interval by modifying the study protocol. In fact it was shown that a t.i.d. regimen with 30-mg dosages of isosorbide dinitrate with the last ingestion at 5 p.m. did not lead to the development of tolerance [143].

On the other hand, as we have seen, the individual analysis reveals that there might be a subset of patients who do not develop full tolerance despite high compliance [62]. Other data also suggest that tolerance is not a universal phenomenon, even considering that the time course of tolerance development may vary by up to 1 week between patients [124, 144, 145]. In some patients tolerance may develop only on the arterial side, with maintained venous response [28, 68].

Tolerance following transdermal application

For over 20 years, the transdermal application of nitroglycerin as ointments and cremes has been well established [146–148]. New transdermal delivery systems were designed to improve the nitroglycerin release, providing constant plasma levels for 24 h [149–151]. Indeed, the response of physicians and patients to the patches was "one of the most remarkable pharmaceutical stories" [152]. Preliminary studies showed encouraging results in patients with angina pectoris [153, 154] and congestive heart failure [155]. Subsequent trials, however, have revealed contradictory findings [27]. Recent studies assessing the anti-ischemic effects during 24 h of nitroglycerin infusion proved the concept of very rapid development of tolerance following constant nitroglycerin plasma levels [156–158]. In any discussion of the nitroglycerin patches, it is of essential importance to differentiate between the effects in the first hours after the first attachment, those in the 24 h after the first attachment, and the effects after repeated attachments.

First attachment. First 1–4 hours: The use of 5 mg per day has not consistently shown beneficial effects. Some authors reported significant anti-ischemic effects [154, 159–161], whereas others could not observe any anti-ischemic benefits [162–164]. Pooled data analysis of 17 trials in approximately 400 patients revealed a statistically significant increase of 77 s in exercise duration 4 h after attachment of a 5 mg per day dose [165]. Release of 10 mg/day nitroglycerin showed significant anti-ischemic effects in most studies [159–161, 164, 166–168]. For this dose, pooled analysis showed a highly significant increase of 114 s in exercise duration [165]. In most studies, 20 mg per day showed remarkable anti-ischemic effects [160, 163, 169, 170]. In patients with congestive heart failure, however, a minimal effective dose of 60 mg per day was postulated [171]. The comparison between oral therapy and nitroglycerin patches revealed considerably weaker effects for the patches [163].

First 24 hours: Although many authors have reported significant effects after 24 h [153, 155, 166, 170, 172], others have observed a loss of the initially beneficial effects for dosages between 5 and 30 mg per day [159–161, 163, 164, 167, 168]. For 24 h, the above-mentioned pooled analysis did not confirm a statistically significant increase in exercise duration, despite persistent decreases in systolic blood pressure and increases in heart rate [165]. The simultaneous determination of nitroglycerin plasma levels is important to differentiate between tolerance (same or higher plasma levels) and decreased effects due to lower plasma levels. Unfortunately, most of the studies did not include plasma level determinations. In 1986, Jordan et al. first proved that the rapid, i.e. within 18 h, attenuation of transdermal nitroglycerin in patients with congestive heart failure occurs despite persistently high, adequate plasma levels, and therefore can be attributed to development of tolerance [173]. These findings have recently been corroborated in patients with coronary artery disease (CAD), demonstrating a gradual decrease in exercise capacity in the presence of constant nitroglycerin plasma levels [158]. Thus, the maximal period of protection with nitroglycerin patches is up to 8 h [160, 163].

Repetitive attachments. Studies *without* acute testing do not allow differentiation between tolerance and insufficient nitrate response. Even if some statistically significant effects are demonstrable after repetitive attachments, the lack of acute testing still does not necessarily exclude an attenuation. A placebo-controlled study, testing 5, 10, and 20 mg per day after 1 week each, did not show any effects at any dose, 24 h after the attachment in 72 patients with stable angina and proven CAD [174]. In other studies, after 2 weeks of treatment with a 5 mg per day patch, small but statistically significant effects were observed 5 h after the attachment [35] as well as 4 h after 10 mg per day [175] and 3 and 24 h after 10 mg per day [176]. Placebo-controlled trials *with* initial responsiveness tests demonstrated a complete loss of the anti-ischemic effects after repetitive, continuous attachments even within the first hours after the second attachment in patients with CAD [159, 177, 178] and in patients with congestive heart failure as well [155, 179]. Therefore the clinical value of conventional nitrate patches has been seriously questioned [25, 152, 180].

Causes of tolerance development

To explain the phenomenon of nitrate tolerance, reduced absorption, enhanced metabolism or faster elimination of the administered nitrates or their active metabolites can be excluded on the evidence of increased plasma levels during long-term treatment [123, 181]. Venous pooling may lead to counter-regulatory mechanisms, by activation of the neurohormonal system resulting in vasoconstriction and sodium retention [182–184]. Whereas animal experiments have failed to demonstrate a further rise in plasma renin levels during long-term application of isosorbide dinitrate [185], in patients with severe congestive heart failure, neurohormonal activation (increased plasma renin activities and a slight increase in body weight) may play a role in tolerance development with the use of high dose nitroglycerin such as 6.4 μg/kg/min [71, 186, 187]. Although serious withdrawal phenomena may occur under

extreme, *nonclinical* conditions [113, 114], this has not been consistently observed in patients and is not considered to be a significant problem in clinical practice with the doses normally used during chronic administration [25, 184, 188–192].

The fundamental *mechanism* of tolerance development following long-term therapy with nitrates has been attributed to a loss of its effect on the vessel's smooth muscle, which was observed in isolated vessel specimens [193, 194]. It is well established today that nitrate-induced vasodilatation is not related to prostaglandin synthesis [99–101, 195]. The vasodilator action of nitrates is mediated by nitric oxide (NO) production, stimulating cyclic guanosine monophosphate via the activation of soluble guanylate cyclase in vascular smooth muscle (Fig. 2), [196–199]. Since in vitro, despite the induction of nitrate tolerance, the vessels remain responsive to cyclic guanosine-monophosphate, the loss of the effects during long-term nitrate application can be traced back to the reduced activation of guanylate cyclase [199]. Nitrates also require sulfhydryl groups to produce *S*-nitrosothiols to stimulate guanylate cyclase [5]. As cysteine represents the main sulfhydryl-donor [200, 201], the development of nitrate tolerance may be due to a rapidly occurring exhaustion of the "cysteine pool" (deficiency of reduced sulfhydryl groups in vascular smooth muscle, [202]) with a subsequently reduced production of *S*-nitrosothiols [199, 203]. This theory is supported by the clinical observation of potentiated nitroglycerin efficacy in patients with coronary artery disease when used in conjunction with *N*-acetylcysteine, which is converted to cysteine in vivo [201, 204, 205].

Whether the administration of sulfhydryl donors will reverse or prevent the development of tolerance is still unclear. May et al., after inducing tolerance with a 24-h infusion of nitroglycerin, reported a restored effect of intracoronary nitroglycerin on coronary sinus blood flow measured 5 min after the infusion of 100 mg/kg *N*-acetylcystein over 15 min [206]. In patients with severe congestive heart failure, Packer et al. observed the reversibility of induced nitroglycerin tolerance (6.4 µg/kg/min over 48 h) 30 min after addition of high-dose (200 mg/kg) oral *N*-acetylcysteine [71]. However, in patients with CAD and exercise-induced ischemia, Parker et al. were not able to reverse tolerance to oral isosorbide dinitrate 15 min after the infusion of 100 mg/kg *N*-acetylcysteine [207]. Recently, Bertel et al. indicated that the *N*-acetylcysteine-induced enhanced responsiveness during nitroglycerin tolerance is not a reversal but rather a nonspecific effect, which was similar before and after the induction of tolerance [208]. These findings support the hypothesis that nitroglycerin may react with *N*-acetylcysteine extracellularly to form an guanylate cyclase-stimulating intermediate compound (*S*-nitrosocysteine?), independent of tolerance [208–210]. Furthermore, the possible role of other mechanisms, such as nitrate-induced direct inactivation of the guanylate cyclase with the subsequent need for its de novo biosynthesis, is still undetermined.

It is apparent that the degree of fluctuation in plasma levels is more important for the development of tolerance than the total of daily administered doses (Tables 2, 3). Therefore, counter-regulatory mechanisms should be more intensively considered again to explain nitrate tolerance and its possible prevention by ACE inhibitors [187, 225]. Perhaps the development of tolerance occurring within 24 h results from different mechanisms than tolerance developing within weeks.

Although the mechanisms which cause tolerance development and its reversal are not completely understood and require further investigation, it is clear today that constant nitrate plasma levels arising from oral isosorbide dinitrate or isosorbide-5-mononitrate ingested every 8 h (or more frequently) and from continuous attachment of conventional patches lead to a considerable attenuation of the initially beneficial anti-ischemic effects in the majority of patients.

Strategies to avoid tolerance development

The established strategies for oral and transdermal therapy to avoid tolerance development are summarized in Tables 2 and 3.

Table 2. Established strategies for avoiding development of tolerance with oral isosorbide dinitrate (ISDN) or oral isosorbide-5-mononitrate (IS-5-MN) in patients with coronary artery disease (CAD) or congestive heart failure (CHF)

Total daily dose (mg)	Single dose (mg)	Release formulation	Intake regimen	Disease	Reference
ISDN					
40	20	Non-sustained	8 am & 1 pm	CAD	[22]
60	30	Non-sustained	7 am & 12	CAD	[143]
80	80	Sustained	Once daily (8 am)	CAD	[62]
90	30	Non-sustained	7 am, 12 & 5 pm	CAD	[143]
120	120	Sustained	Once daily (8 am)	CAD	[23, 211–213]
160	80	Sustained	8 am & 2 pm	CAD	[63]
120	120	Sustained	Once daily (8 am)	CHF	[214]
IS-5-MN					
40	40	Sustained	Once daily	CAD	[15]
50	50	Sustained	Once daily	CAD	[215–218]
60	60	Sustained	Once daily	CAD	[15, 219, 220]
100	100	Sustained	Once daily	CAD	[13, 16, 216, 218]

Table 3. Established strategies for avoiding development of tolerance with transdermal nitroglycerin patches in patients with CAD or CHF

Total daily dose (mg)	Patch-free interval	Disease	Reference
5, 10, 15, 20	12 h	CAD	[224]
10	12 h	CAD	[221, 222]
10	10 h	CAD	[223]
10–20	10 h	CAD	[192]
10	8 h	CAD	[178]
10	8 h	CHF	[191]

Strategies for oral therapy

Once-daily intermittent intake of high dosages. Since no studies prior to 1982 assessed nitrates with less than t.i.d. dosing, we investigated the hemodynamic and anti-ischemic effects of isosorbide dinitrate taken according to once- and twice-daily regimens [62, 63]. The goal of our studies, applying isosorbide dinitrate in different dosage intervals, was to determine whether a new regimen might prevent the development of tolerance. In order to achieve the longest possible duration of action of a single tablet, we administered the highest single dosage of isosorbide dinitrate in sustained-release form available at that time (80 mg). Patients were selected according to our standard objective criteria for anti-ischemic studies, and only patients with a high likelihood of excellent compliance were enrolled. In addition, we assessed the ingestion of each individual tablet by adding riboflavine to the study medication and checking two urine specimens per day. The determined compliance was 95%, meaning that 95% of all tablets prescribed were actually taken.

Even with dosing every 12 h, development of tolerance occurred. The isosorbide-5-mononitrate trough plasma levels were 386 ng/ml, those of isosorbide-2-mononitrate 37 ng/ml and those of isosorbide dinitrate of 7 ng/ml [63]. The high plasma levels of isosorbide dinitrate after 12 h may be explained by an inhibited metabolism of isosorbide dinitrate due to its metabolites [7].

As we first showed in 1983, intermittent therapy with once-daily ingestion of 80 mg isosorbide dinitrate sustained release prevented the development of tolerance [23, 62, 63]. The peak plasma levels were 485 ng/ml for isosorbide-5-mononitrate, 96 ng/ml for isosorbide-2-mononitrate and 25 ng/ml for isosorbide dinitrate [63]. The trough levels for isosorbide dinitrate and isosorbide-2-mononitrate were essentially zero and for isosorbide-5-mononitrate below 100 ng/ml [63, 226]. Since then, several other groups have corroborated our concept of once-daily high dosage of isosorbide dinitrate sustained release and shown that the use of once-daily 120 mg doses of isosorbide dinitrate in sustained-release form does not induce the development of tolerance during chronic treatment and cumulation of plasma levels does not occur (Table 1) [211–214]. An alternative regimen, particularly in countries where those formulations are not available, is 'eccentric' or 'asymmetric' dosing. As we have demonstrated, the ingestion of 80-mg tablets of isosorbide dinitrate in sustained-release form at 08.00 h and 14.00 h results in the best compromise between circumvention of tolerance and maximal possible duration of anti-ischemic protection [62].

Similarly, *isosorbide-5-mononitrate* ingested once daily in 40-mg or 50-mg doses in sustained-release form prevented tolerance development with trough levels of 90 ng/ml after 3 weeks and longer [15, 215–218]. The once-daily ingestion of 60 mg [15, 219] and even 100 mg of isosorbide-5-mononitrate in sustained-release form [13, 16, 216, 218] did not reveal tolerance development. Conversely, Thadani et al. reported tolerance development for 50 and 100 mg isosorbide-5-mononitrate in sustained-release form after once-daily intake for 1 week (measured 4 h after ingestion) with comparable trough levels [218, 227]. There is currently no reasonable explanation for these controversial findings, unless the development of unstable angina and remarkable shifts in the control group are taken into consideration [227].

Frequent intermittent intake of low dosages. The nitrate plasma level valleys resulting from 20 mg *isosorbide dinitrate* in non-sustained-release form administered at 08.00 h and 13.00 h effectively prevented tolerance development [22]. Ingestion of 30 mg isosorbide dinitrate in non-sustained-release form b.i.d. at 07.00 h and noon or t.i.d. at 07.00 h, 12.00 h and 17.00 h did not lead to tolerance [143]. *Isosorbide-5-mononitrate,* ingested as 20-mg doses in non-sustained-release form every 12 h over 4 weeks did not lead to tolerance development, as evidenced by testing 1 h after the ingestion [228]. However, in another study, the same 12-h-interval regimen led to a considerably shorter duration of anti-anginal effects [229]. Ingestion of 40 mg isosorbide-5-mononitrate every 12 h also caused "partial tolerance" [144]. These data are consistent with our previous findings recorded with the same dosing regimen with isosorbide dinitrate sustained release [62, 63]. Therefore, the intake of 20 or 40 mg isosorbide-5-mononitrate every 12 h cannot be recommended.

Arguments for the usage of high single dosages

Increased duration of action. To characterize the duration of action, it is not only important to describe the total time range of statistically significant changes, but also to define the duration of the *maximal* effects obtained [230, 231]. Thus, although single dosages of 15–30 mg non-sustained isosorbide dinitrate showed statistically significant anti-ischemic effects for 8 h, the maximal effects were observed for only 2–3 h [122, 131, 232, 233]. Also, a single dose of 40 mg isosorbide dinitrate in non-sustained-release form demonstrated considerably less anti-ischemic effects 6 h than 1 h after ingestion [234].

Since there was much evidence that sustained-release formulations prolong the duration of action of a single dose of *isosorbide dinitrate* [120, 121, 133, 235, 236], a capsule of 120 mg isosorbide dinitrate was developed. As we have demonstrated, this 120-mg capsule which effects an approximately six-fold change of isosorbide-5-mononitrate plasma levels is able to maintain significant anti-ischemic effects for up to 12 h, with its 6-h effects identical to those after 2 h [237]. A similar behavior with regard to duration of action and degree of anti-ischemic response can also be assumed for *isosorbide-5-mononitrate* in doses ranging from 20 mg in non-sustained-release form to 100 mg in sustained-release form [17, 129, 135–138, 215, 216, 228, 238].

Increased nitrate response. High plasma levels increase the likelihood of achieving the maximal possible anti-ischemic effect. As we have seen, there is no predictable inter-individual relationship between the plasma levels of isosorbide dinitrate, isosorbide-2-mononitrate or isosorbide-5-mononitrate and the degree of the anti-ischemic effect (Fig. 3). Thus, low plasma levels may be associated with an either small or even optimal anti-ischemic effect.

This leads to the question of whether patients with relatively small effects at low plasma levels may benefit from increasing dosages. This intra-individual dose response relationship was thoroughly investigated by Schneider et al. and Kenedi (Fig. 4) [124, 216]. They both found that increasing oral dosages of isosorbide dinitrate (5 mg, 20 mg, 40 mg and 80 mg in non-sustained-release form), as well as increasing oral dosages of isosorbide-5-mononitrate (25 mg, 50 mg and 100 mg in sustained-release form), remarkably enhanced the anti-ischemic effects in those patients who experienced a relatively limited response at lower plasma levels (Fig. 4). Akhras et al. reported a progressive reduction of angina pectoris with increasing dosages of isosorbide-5-mononitrate [239].

Since it is impossible to predict the anti-ischemic response from plasma levels, and repetitive stress tests to titrate the optimal dose are very time-consuming, it makes sense to recommend intermittently *high* plasma levels. Fortunately, nitrates reveal an extremely large therapeutic range.

The reasons why some patients, despite high dosages, do not respond to nitrates are still unclear. It seems to happen more frequently in patients with severe congestive heart failure than in patients with CAD [57, 240]. The degree of anti-anginal response has been related to the acute reaction of the adrenergic and renin-aldosterone system with higher levels of plasma catecholamines, plasma renin activity and plasma aldosterone in nonresponders [241]. Since only little information has been obtained regarding the nitrate-induced changes in left ventricular volumes at rest in coronary patients with insufficient nitrate response [57], and no study has been reported so far investigating these changes during exercise, we investigated the isosorbide dinitrate-induced changes in LVEDV at rest and during exercise in relation to the degree of the anti-ischemic effect [58]. Patients with insufficient anti-ischemic effects were characterized by the absence of LVEDV changes during exercise, supporting the concept that preload reduction plays the major role for the anti-ischemic nitrate effects in patients with exercise-dependent ischemia [49, 50]. Others have claimed a lack of coronary dilatation as the explanation for insufficient nitrate response [57]. Overall, with adequate high dosing of oral nitrates in patients with CAD, the anti-anginal response rate in clinical practice is quite high.

The prolonged duration of action of once-daily high-dosage sustained release, the improved patient compliance with single daily administration, and the increased likelihood of maximal anti-ischemic effects are striking reasons for the therapeutic approach recommending high single daily doses of isosorbide dinitrate or isosorbide-5-mononitrate.

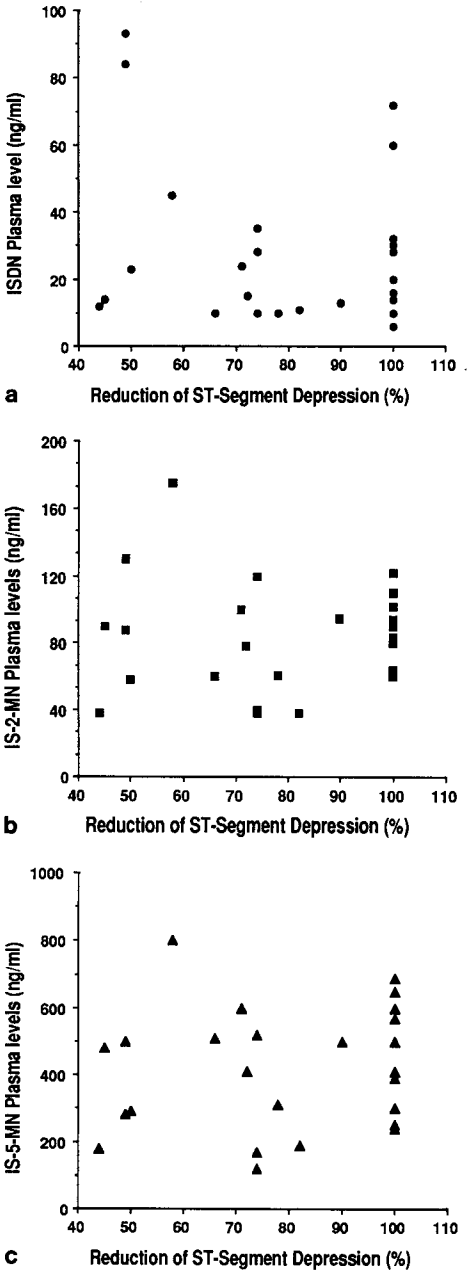

Fig. 3. Lack of *inter*-individual correlation between nitrate plasma levels and the degree of anti-ischemic effects. In our studies, the amount of anti-ischemic response was assessed by percent reduction of exercise-induced ST-segment depression, with 100% as the optimal effects (normalization of ST-segment depression at comparable workload). Comparison of 25 patients at 2 h after the ingestion of 80 mg ISDN, revealed no relation between the improvement of exercise-induced ST-segment depression and the ISDN **(a),** isosorbide-2-mononitrate (IS-2-MN) **(b)** and isosorbide-5-mononitrate (IS-5-MN) **(c)** plasma levels. Thus, low plasma levels may be associated with a small or optimal anti-ischemic effect

Strategies for transdermal therapy

For transdermal delivery systems, various "patch-free intervals" have been investigated. The following strategies were *not* successful in preventing tolerance development: a 2-h patch-free interval using 10 mg per day in patients with congestive heart failure [191], a 6-h patch-free interval, using the same dose in patients with CAD [223], and a 8-h "infusion-free" interval in patients with congestive heart failure receiving 6.4 μg/kg/min [242]. With 15 mg per day, even a 10-h patch-free interval was not helpful [243] and in a recent study assessing everyday activities in patients receiving a mean dose of 52 mg per day, even a 12-h patch-free interval did not prevent tolerance development [37].

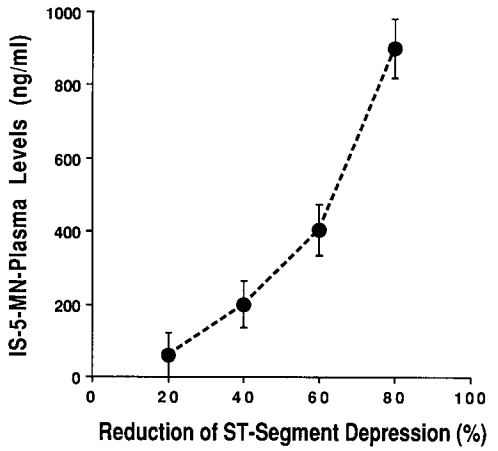

Fig. 4. *Intra*-individual dose-response relationship. Increasing plasma levels of IS-5-MN following increasing oral doses of ISDN or IS-5-MN remarkably enhanced the anti-ischemic effects in those patients who experienced a limited response at lower plasma levels. (Adopted from 124 and 216)

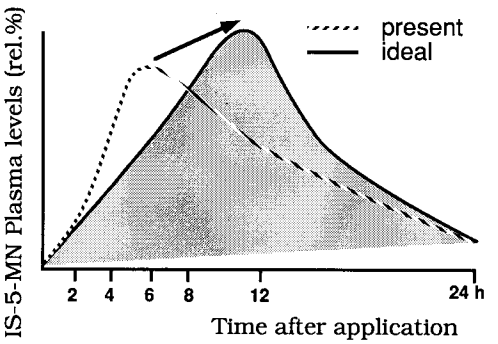

Fig. 5. Ideal plasma level profile to prevent tolerance development combined with maximal duration of action. Currently available sustained-release ISDN or IS-5-MN formulations show peak plasma levels at approximately 6 h after ingestion. The ideal profile, however, would provide a *later* peak, mimicking the plasma level curves obtained with our asymmetric 08.00 h + 14.00 h regimen [63]. These gradually increasing plasma levels would counteract the very rapid development of tolerance during the first hours after intake. Recommendations for the ideal profile of transdermal use of nitroglycerin would be similar

In contrast, the removal of a 10-mg patch for 12 h was effective in patients with CAD when tested after 3 days [222] and after 1 week [221] (Table 3). These findings are corroborated by the prevention of tolerance interrupting a nitroglycerin infusion for 12 h in patients with exercise-induced ischemia (1.5 mg/h [156]) or congestive heart failure (6.4 µg/kg/min [71]). In other studies, a 10-h patch-free interval was effective in patients with CAD using 10 mg per day [223] or a mean of 16 mg per day [192]. An 8-h patch-free interval assured full response to 10 mg per day after 1 week in patients with CAD [178] and after 1 month in patients with congestive heart failure [191].

In a recently published study, patches delivering 5, 10, 15 and 20 mg per day remained effective for over 4 weeks when intermittently removed for 12 h [224]. However, just before patch application, the placebo group was able to exercise longer than either active treatment group ("zero hour effect"). The clinical relevance of these unexpected findings require further investigation.

Although the minimal patch-free interval required to prevent tolerance development seems to be dose-dependent and needs further investigation, the recommendation of a 12-h patch-free interval should prevent tolerance in most patients using conventional patches.

Future expectations for oral and transdermal therapy

All available sustained-release formulations for *oral* treatment with isosorbide dinitrate or isosorbide-5-mononitrate show a similar release profile, peaking at 6 h after the intake and gradually waning for the rest of the day (Fig. 5) [63, 226, 244]. The ideal profile for a single ingestion, however, would provide a *later* peak, mimicking the plasma level curves obtained with our asymmetric (08.00 h and 14.00 h) regimen [63]. These gradually increasing plasma levels would counteract the very rapid development of tolerance during the first hours after intake (Fig. 5). Such a formulation, however, is currently not available.

The recommendations for the ideal profile for *transdermal* use of nitroglycerin would be similar (Fig. 5). The development of this type of patch, with increasing, late-peaking plasma levels is rather difficult. The role of the "phased release" patches remains to be investigated [245].

As pointed out, nitrates cannot protect for 24 h. Fortunately, in most patients angina pectoris and silent ischemia occur predominantly during the day [246–249]. In order to *optimize* the anti-ischemic treatment (see below), beta-blocking or calcium-channel-blocking agents should be added whenever possible.

What are the goals of anti-ischemic treatment and how should therapy be monitored?

The treatment of patients with CAD is primarily focused on symptomatic relief, i.e. reduction or abolition of angina pectoris (and its equivalents) and life prolongation. Quality of life also has to be taken into consideration and the patient should be free of symptoms at his or her individually desired activity levels. A good quality of life, however, does not only mean freedom from pain; even minor side effects of medication and the number of tablets to be ingested each day must be taken into account when quality of life is assessed.

For the treatment of angina, coronary bypass surgery and balloon angioplasty have their well-defined role, particularly in patients desiring higher levels of physical activity. In general, bypass surgery has shown to improve quality of life more markedly than medical treatment, but with diminishing differences after 5 years and similar activity limitations between the two groups after 10 years [250]. The other indication for coronary revascularization is life prolongation. The three major bypass trials have characterized well-defined subgroups of patients who live longer after bypass surgery as opposed to medical treatment (for overview see [251]). For PTCA, similar data

have not yet been obtained; we have to wait for the results of the BARI and EAST trials.

Do nitrates prolong life?

Nitrates are far from having been so thoroughly investigated regarding their impact on prognosis as beta and calcium-channel blockers (for overview see [251]). There is, unfortunately, no major prospective trial assessing life prolongation with nitrates. Several minor studies revealed positive effects on mortality, most of them related to reduction of infarct size [252–259]. A retrospective analysis for a period of 11 months in comparable groups of patients with CAD revealed a mortality of 26% in those without nitrates and of 10% in those receiving nitrates (predominantly isosorbide dinitrate) [260]. Yusuf et al. published the pooled analysis of seven trials in patients with acute myocardial infarction, reporting a 49% reduction in the probability of death during hospitalization with i.v. nitroglycerin [261]. These data should reinitiate the discussion about the use of nitrates in patients with acute myocardial infarction for prognostic indication. The prospective, randomized V-HeFT trial was the first to prove life prolongation by vasodilators [262]. Since, however, a combination of isosorbide dinitrate and hydralazine was used, the question of a prognostic effect of isosorbide dinitrate alone cannot be answered.

Thus, in many studies a beneficial trend toward nitrate-related life prolongation was observed. It is now of major importance to conduct a prospective, randomized trial to prove the beneficial effects of nitrates on mortality in secondary prevention and/or in congestive heart failure.

Is it mandatory to treat silent myocardial ischemia?

It cannot be questioned that silent myocardial ischemia, provoked by high and low levels of physical activities as well as by mental stress, is an important clinical problem [263–265]. Although the pathophysiologic mechanisms responsible for the absence of pain are still not clear (role of endorphins? generally increased pain threshold? [266–268]), it is apparent that transient episodes of considerable, asymptomatic ischemia are frequent and occur in many patients with CAD [264, 269]. As mentioned above, nitrates are as effective in the treatment of silent ischemia as beta and calcium-channel blockers [38, 39, 264]. The treatment of silent ischemia would become mandatory if it would positively affect prognosis. Recently, several studies have shown that silent mycardial ischemia is related to an increased risk of nonfatal and fatal events, and that Holter-detected ischemic episodes identify patients at higher risk, as compared to the exercise test alone [270–273]. Whether the treatment of silent episodes improves prognosis, however, has not yet been shown. Although the CASS trial, using retrospective analysis, showed improved prognosis of patients with painless and positive treadmill tests who underwent bypass surgery [274], we will have to wait for prospective trials before this important issue can be answered. Since intermittent episodes of ischemia have a cumulative effect and may cause myocardial necrosis [275], abolition of the "total ischemic burden" has been recommended [269].

How should anti-ischemic therapy be monitored?

Once patients with angina pectoris have been correctly identified [276], the abolition of symptoms should be only the first step. After the patient has been assigned to revascularization and/or medical treatment (for overview see [251]), and is then asymptomatic, an exercise test, preferably with thallium-201 or technetium-99m-MIBI scintigraphy, is indicated. If exercise-inducible ischemia is still present, ST-segment Holter monitoring should be considered, since the presence of silent ischemia in this subset of patients reflects a markedly poorer prognosis [272, 273, 277]. For ST-segment Holter monitoring, on-line, digital, full disclosure systems should be preferred [278, 279]. The ultimate goal of anti-ischemic therapy is the identification and abolition of all ischemic episodes related to a poor prognosis (ischemia at risk), while maintaining the patients' quality of life.

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