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The insufficient nitrate response: patients' characterization and response to beta and calcium blockade

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Little information has been published regarding the nitrate-induced changes of left ventricular volumes at rest and during exercise in relation to the degree of the anti-ischaemic response. Therefore we assessed the electrocardiographically defined nitrate response to a single tablet of 80 mg isosorbide dinitrate s.r. and compared it to the changes in end-diastolic volumes at rest and during exercise, as determined by radionuclide ventriculography. Thirty-four of the 63 patients were classified as good nitrate responders, whereas 29 patients showed insufficient nitrate response with regard to the reduction of exercise-induced ST-segment depression. The baseline characteristics were quite comparable. At rest the ISDN-induced decrease of the end-diastolic count rate was significantly less (−17%) in patients with insufficient ST-segment response when compared to patients with good ST-segment response (−25%). During exercise, in patients with good ST-segment response, ISDN reduced the end-diastolic volume significantly (−19%), whereas in patients with insufficient ST-segment response the end-diastolic volume remained unchanged. In this special subset of patients with insufficient nitrate response we further evaluated the effects of additional beta or/and calcium blockade. The benefits from verapamil were equivalent to propranolol. However, a considerable part of the patients investigated needed the combination of verapamil and propranolol for an optimal anti-ischaemic drug treatment.

Thus, our data support the concept that preload reduction plays a major role for the anti-ischaemic effects of ISDN in patients with exercise-dependent ischaemia. Since, a suboptimal therapeutic effect must be considered, objective control of the nitrate therapy (usually by exercise- and Holter-ECG) must be regarded as obligatory for each individual patient if optimal results are to be expected.

Nitrates are traditionally the basic drugs for the treatment of myocardial ischaemia and exert their anti-ischaemic effects predominantly by venodilatation with subsequent preload reduction[1–10]. There is, however, increasing evidence that a subgroup of patients with chronic stable coronary artery disease and exercise-dependent myocardial ischaemia respond poorly to nitrates with respect to their anti-ischaemic effect[11]. Since only anecdotical information has been obtained in such patients regarding the nitrate-induced changes of left ventricular volumes at rest[11] and no study has been reported so far investigating these changes during exercise, it is our purpose to present additional information. This article is focussed on the assessment of isosorbide dinitrate-induced changes of left ventricular end-diastolic volumes at rest and during exercise in relation to the degree of the anti-ischaemic effect. Furthermore, the response to additional beta or/and calcium blockade is described in a subset of patients who shared insufficient nitrate response.

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Patients and methods

All patients had angiographically proven coronary artery disease (≥75% stenosis of at least one of the three major coronary arteries), a left ventricular ejection fraction ≥35% in the contrast ventriculogram, a history of stable, exercise-dependent angina pectoris and a reproducible exercise-induced ST-segment depression of ≥0·15 mV (≥1·5 mm). Patients with inconclusive exercise ECGs (e.g. rest-

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ing ST-abnormalities, bundle-branch block, digitalis etc.) and those with atrial fibrillation, with complex and/or frequent arrhythmias, AV-blocks or a heart rate <50 beat min^{-1} during the washout phase were excluded as well as patients with a documented myocardial infarction within 3 months prior to inclusion. Informed consent was obtained from all patients.

Exercise tests were performed on a electronically braked bicycle-ergometer, which is self-adjusting and provides constant work-loads, in semi-upright position with the legs below heart level. The attending staff and environment was kept as constant as possible. Depending on the individual exercise capacity (as derived from previous stress tests), exercise was started with 50 or 80 W and, if possible, increased automatically by a programmable computer (ELP 500, Bosch) by 30 W every 3 minutes. The end-point of the control exercise test following the washout period (i.e. discontinuation of all antiischaemic medication for 4 days with only sublingual nitroglycerin allowed) was defined as angina pectoris associated with ST-segment depression of $\geq 1{\cdot}5$ mm. The subsequent exercise tests were performed until this individual work load had been reached. The 12-lead ECG (Schiller, Switzerland) was documented with a chart speed of 50 mm^{-1} at 1½ and 2½ minutes of each work load stage. ST-segment depression was measured 80 ms after the J-point in the precordial lead that showed maximal ST-depression during the control exercise test.

The nitrate response was determined 2 hours after the ingestion of an 80 mg tablet isosorbide-dinitrate (ISDN, Isoket retard 80®, Pharma Schwarz, F.R.G.). The nitrate response was strictly defined according to electrocardiographic criteria: An 'insufficient' nitrate response was given, if the difference in ST-segment depression between the control- and the ISDN-values was ≤1 mm, at identical work loads, combined with a persistent pathologic ST-segment depression (≥1 mm). A 'good' nitrate response was defined as a Δ ST > 1 mm, combined with an absolute ST-segment depression of <1 mm.

Radionuclide ventriculography was performed at rest and simultaneously with the ECG during exercise. After standard stannous *in vivo* labeling of red blood cells with approximately 25 mCi (925 MBq) technetium-99m, the data were acquired using the equilibrium multiple-gated acquisition technique (MUGA). Left ventricular ejection fraction was calculated by a count-rate method applying a semi-automatic, clinically validated algorithm. This method is described in detail elsewhere[12].

To assess the changes of the left ventricular volumes, the left ventricular end-diastolic count-rate (specified as counts per second) was calculated, taking the number of actual acquired heart cycles as well as the halflife-time of technetium-99m into account. Since changes in end-diastolic volumes are proportional to changes in end-diastolic count-rates, the determination of absolute ventricular volumes with individual attenuation correction was not necessary.

Patients with insufficient nitrate response were investigated with regard to their response to beta or/and calcium blockade[13]. According to a randomized, double-blind and crossover protocol, propanolol (Dociton®, ICI), was administered as the standard beta-blocker and verapamil (Isoptin®, Knoll) as the standard heart rate decreasing calcium antagonist. The following dosages were prescribed for 3 weeks each in addition to the once-daily ingestion of ISDN: verapamil in non-sustained release form 120 mg q 8 h and propranolol in non-sustained release form 80 mg q 12 h (8 a.m. and 8 p.m.). The 2 dual combinations were compared according to a randomized, double-blind and crossover protocol, the triple combination was assessed in a single-blind manner and initiated in-hospital to survey possibly induced conduction disturbances[13].

Statistical analysis of the nitrate response was performed by the Mann–Whitney test. The 2-tailed-Wilcoxon's-test for matched pairs was applied for testing the response to beta or/and calcium blockade. Probabilities (P) were considered significant at the $P < 0{\cdot}05$ level ($^{*}P < 0{\cdot}05$; $^{**}P < 0{\cdot}01$; $^{***}P < 0{\cdot}001$). The P values were corrected using Bonferroni's adjustment[14]. The data are given as mean ± one standard deviation. The exercise parameters were compared at maximal intra-individually identical work loads.

Results

NITRATE RESPONSE

Nitrate response was determined in 63 non-consecutive patients with a mean age of 56 ± 8 (32–70) years. Thirty-four patients (including one female) were classified as good nitrate responders, 29 patients (also including one female) as insufficient nitrate responders. The baseline characteristics are listed in Table 1. Aside from the mean age and the number of patients with one-vessel disease, both groups did not differ with respect to the listed baseline parameters (Table 1).

Table 1 Baseline characteristics of the patients with good and with insufficient nitrate response

	Response	
	Good response	Insufficient response
No. of patients	34	29
Age (years)	53 ± 9	58 ± 7*
1 vessel disease	14	4*
2 vessel disease	12	11
3 vessel disease	8	14
Anterior wall infarction	3	4
Inferior wall infarction	4	4
Maximal comparable workload (W)	93 ± 27	86 ± 22
ST-segment depression (mm)	2·2 ± 0·7	2·6 ± 1·1
Resting heart rate (beats min^{-1})	71 ± 12	71 ± 11
Exercise heart rate (beats min^{-1})	126 ± 9	128 ± 19
Resting systolic blood pressure (mmHg)	136 ± 22	139 ± 11
Exercise systolic blood pressure (mmHg)	181 ± 20	174 ± 18
Resting pressure–rate product (mmHg min^{-1})	9677 ± 2266	9902 ± 1943
Exercise pressure–rate product (mmHg min^{-1})	22928 ± 4935	22402 ± 4570
Resting left ventricular ejection fraction (%)	58 ± 8	56 ± 9
Exercise left ventricular ejection fraction (%)	49 ± 13	52 ± 11

Aside from the mean age and the number of patients with one vessel-disease ($*P < 0·05$) both groups were comparable with respect to the listed baseline parameters.

The absolute values can be seen from Table 2, the relative changes from Table 3. In Table 2, statistical significance was calculated by comparing the values before and after ISDN in each response group separately, whereas Table 3 shows the statistical significance resulting from the comparison between the two response groups.

According to the definition of nitrate response, the mean ST-segment depression in patients with good response was significantly reduced from 2·2 ± 0·7 mm to 0·4 ± 0·5 mm (−82%) and in patients with insufficient nitrate response from 2·6 ± 1·1 mm to 2·1 ± 1·1 mm (−19%).

At rest, patients with insufficient nitrate response, as defined by ST-segment criteria, demonstrated similar changes in heart rate (+21% *vs* +21%), systolic blood pressure (−8% *vs* −7%), diastolic blood pressure (−2% *vs* −4%) and left ventricular ejection fraction (+11% *vs* +8%) as compared to the patients with good ST-segment response. Only the ISDN-induced decrease of the end-diastolic count rate was significantly less in patients with insufficient ST-segment response (−17%) as compared to patients with good ST-segment response (−25%).

During exercise, patients with insufficient ST-segment response showed a similar reaction to those patients with good ST-segment response with respect to heart rate and diastolic blood pressure. Whereas systolic blood pressure in patients with good ST-segment response was essentially unchanged, patients with insufficient ST-segment response showed a significant decrease of 5%. Therefore, the ISDN-induced increase in pressure–rate product was significantly less in patients with insufficient ST-segment response as compared to the patients with good ST-segment response (+2% *vs* +7%). The highest significance was found for the ISDN-induced change in left ventricular end-diastolic count rates: Whereas ISDN in patients with good ST-segment response reduced the end-diastolic volume significantly for 19%, the change in patients with insufficient ST-segment response (−4%) was not significant.

Angina pectoris

Twenty-nine/thirty-four patients with good ST-segment response no longer experienced anginal pain at the same workload after ISDN, while the

Table 2 Results before and 2 hours after the ingestion of a single tablet of 80 mg isosorbide dinitrate (ISDN) at rest and during maximal, comparable workload

	Response							
	Good response				Insufficient response			
	At rest		During exercise		At rest		During exercise	
	Before ISDN	After ISDN	Before ISDN	After ISDN	Before ISDN	After ISDN	Before ISDN	After ISDN
ST-segment depression (mm)	—	—	2·2 ± 0·7	0·4 ± 0·5***	—	—	2·6 ± 1·1	2·1 ± 1·1**
Heart rate (beats min^{-1})	71 ± 12	86 ± 15***	126 ± 19	133 ± 21***	71 ± 11	86 ± 13***	128 ± 19	137 ± 18**
Systolic blood pressure (mmHg)	136 ± 22	127 ± 17***	181 ± 20	184 ± 22	139 ± 11	127 ± 11***	174 ± 18	166 ± 16**
Diastolic blood pressure (mmHg)	90 ± 9	86 ± 10*	108 ± 12	100 ± 13***	86 ± 8	84 ± 8	105 ± 17	95 ± 11**
Pressure–rate product (mmHg min^{-1})	9677 ± 2266	10860 ± 2384**	22928 ± 4935	24607 ± 5196**	9902 ± 1943	10934 ± 1805*	22402 ± 4570	22740 ± 4014
End-diastolic count rate (counts s^{-1})	1225 ± 350	923 ± 279***	1558 ± 390	1261 ± 277	1223 ± 328	1012 ± 291**	1425 ± 279	1372 ± 372
Left ventricular ejection fraction (%)	58 ± 8	63 ± 8***	49 ± 73	63 ± 12***	56 ± 9	62 ± 10***	52 ± 11	59 ± 14***

Patients with insufficient reponse to ISDN are per definition differentiated from those with good response by the effect on exercise-induced ST-segment depression (see text). Statistical significance relates to the comparison of the measurements before and after ISDN.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 3 Relative changes of the parameters listed in Table 2

	Response			
	At rest		During exercise	
	Good	Insufficient	Good	Insufficient
ST-segment depression (Δ%)	—	—	−82	−19***
Heart rate (Δ%)	+21	+21	+6	+7
Systolic blood pressure (Δ%)	−7	−8	+2	−5**
Diastolic blood pressure (Δ%)	−4	−2	−8	−10
Pressure–rate product (Δ%)	+12	+10	+7	+2*
End-diastolic count rate (Δ%)	−25	−17*	−19	−4***
Left ventricular ejection fraction (Δ%)	+8	+11	+29	+13**

The difference between the results before as well as after ISDN is given as percentage of the baseline value. The statistical significance is calculated for the comparison between good and insufficient nitrate response, respectively. For explanation, see Table 2 and text.

remaining 5 patients complained about angina pectoris at the same exercise level. Twenty-four/twenty-nine patients with insufficient ST-response described anginal pain at the same exercise level after ISDN; however, angina disappeared in the remaining 5 patients after ISDN despite insufficient ST-segment response.

RESPONSE TO BETA OR/AND CALCIUM BLOCKADE

As 3 patients discontinued the combination therapy[13], the results regarding response to beta or/and calcium blockade are based on 26 completed cases. Their mean age was 54 ± 16 (range 49–69), including one female patient. Four patients had one-vessel disease, 10 patients two-vessel disease and 12 patients three-vessel disease. Previous myocardial infarctions were documented in 8 patients (4 in anterior and 4 in inferior localization). According to cardiac catheterization, 17 patients had normal left ventricular ejection fractions and 9 patients' EF was <55%, including 2 patients with an EF between 35% and 40%. The mean work load during control conditions was 87 ± 23 W.

The results for the combinations ISDN plus propranolol, ISDN plus verapamil as well as for the triple combination are listed in Table 4. The values before and after ISDN in these 26 patients are essentially the same as compared to the total group of 29 patients with insufficient nitrate response.

Angina pectoris during exercise

According to the above-mentioned criteria for anginal response, both dual combinations proved to be superior to ISDN alone in 5 patients. ISDN plus verapamil was superior to ISDN alone and to ISDN plus propranolol in another 5 cases. In 2 patients ISDN plus propranolol was more effective than ISDN alone and ISDN plus verapamil, respectively. Ten patients had no anginal improvement during either dual combination as compared to ISDN alone. Altogether, 12 patients showed remarkable improvement on either dual combination. Triple therapy, as compared to both dual combinations, led to an additional effect in 8 patients, whereas 2 patients even on this medication did not feel a relevant improvement as compared to ISDN alone. None of the patients worsened on triple therapy.

Angina frequency according to the diaries

Ten of the 26 patients did not feel any pain during all three trial phases. The mean angina frequency in the remaining group did not differ when taking ISDN plus verapamil or ISDN plus propranolol (12 *vs* 14 attacks per each phase). During triple therapy there was a significant reduction to 4 attacks per 3 weeks. Since patients nearly always took only 1 nitroglycerin-capsule per anginal attack, the results for nitroglycerin consumption are identical.

Side effects and preference for therapy

During the combination ISDN plus verapamil 6 patients reported mild constipation and 2 developed mild ankle oedema without congestive heart failure. While taking ISDN plus propranolol, 8 patients complained of fatigue, 6 patients of cold fingers/toes, 2 of insomnia, 1 of fear, 1 of dizziness and 1 of constipation. During triple therapy, 3 patients complained of constipation, 5 of fatigue and 1 patient developed

Table 4 Results before as well as 2 hours after the ingestion of a single tablet of isosorbide dinitrate (ISDN) alone or in combination with verapamil or/and propranolol in patients with insufficient nitrate response

	Control	ISDN	ISDN + verapamil	ISDN + propranolol	Triple therapy
At rest					
Heart rate (beats min^{-1})	71 ± 11	86 ± 14***	67 ± 10	56 ± 6***	53 ± 6***
Systolic blood pressure (mmHg)	138 ± 11	127 ± 12***	126 ± 9***	124 ± 12***	118 ± 12***
Diastolic blood pressure (mmHg)	85 ± 7	85 ± 9	79 ± 7**	77 ± 6**	77 ± 7***
Pressure–rate product (mmHg min^{-1})	9796 ± 1882	10907 ± 1896*	8513 ± 1480*	6874 ± 716**	6317 ± 974**
Left ventricular ejection fraction (%)	56 ± 100	60 ± 9**	60 ± 12*	59 ± 10*	57 ± 8
During Exercise					
ST-segment depression (mm)	2·6 ± 1·1	2·1 ± 1·2	0·9 ± 0·9***	0·9 ± 0·7***	0·2 ± 0·4***
Heart rate (beats min^{-1})	128 ± 20	137 ± 19**	117 ± 16**	96 ± 12***	91 ± 13***
Systolic blood pressure (mmHg)	175 ± 17	166 ± 17*	165 ± 16*	159 ± 17**	147 ± 19**
Diastolic blood pressure (mmHg)	105 ± 16	95 ± 11*	94 ± 13*	100 ± 14	87 ± 13***
Pressure–rate product (mmHg min^{-1})	22406 ± 4678	22756 ± 4237	19337 ± 3866*	15277 ± 2438**	13432 ± 2811***
Left ventricular ejection fraction (%)	53 ± 11	59 ± 14***	59 ± 10**	60 ± 10**	56 ± 10*

Statistical significance relates to the comparison of the drug values with the control measurements. For explanation see Table 2 and text.

dyspnoea. None of these side-effects forced discontinuation. At the end of the 2 dual combination (double-blind) phases, 14 patients preferred the combination ISDN plus verapamil whereas 8 patients felt better on ISDN plus propranolol. Four patients were indecisive. Comparing all 3 study-phases, 12 patients were in favour of the triple combination.

Discussion

THE INSUFFICIENT NITRATE RESPONSE

Although it is generally accepted that coronary dilatation plays an important role in the mechanism underlying the anti-ischaemic action of nitrates in patients with dynamic stenoses and variable myocardial ischaemia[15–17], the prevailing mechanism in patients with chronic stable angina and reproducible, exercise-dependent myocardial ischaemia remains a matter of discussion: Whereas several authors found preload reduction (decreased oxygen demand) to represent the major mechanism for the beneficial nitrate effects[1–3], others claim the dilatation of coronary stenoses (increased oxygen supply) to be responsible for the nitrates' effects in this form of ischaemia too[11,17].

It is well established that nitrates induce venodilatation with subsequent reduction of the left ventricular end-diastolic volume (LV-EDV): During resting conditions, the sublingual application of nitroglycerin resulted in a 25% decrease of LV-EDV in healthy persons[18]. In patients with coronary artery disease, the LV-EDV reduction observed was between 10% and 40%[19–23]. The sublingual and oral administration of isosorbide dinitrate (ISDN) at rest, also led to a 16%–36% reduction of LV-EDV[11,19]. During exercise, a mean LV-EDV reduction of 10% was reported in healthy persons after sublingual nitroglycerin[18]. The corresponding decrease of LV-EDV in patients with coronary artery disease was in the range of 20%[20]. Unfortunately, these studies did not differentiate between patients with good and insufficient anti-ischaemic nitrate response. Furthermore, there are no data published addressing the changes of LV-EDV during exercise in patients with coronary artery disease following ISDN.

As we have seen, patients with good ST-segment response to ISDN demonstrated an average LV-EDV reduction during exercise of 19% (Table 3). In contrast, patients with insufficient ST-segment response were characterized by the absence of LV-EDV changes during exercise following ISDN (Table 3). Our data support the concept that preload reduction still plays the major role for the anti-ischaemic effects of ISDN in patients with exercise-dependent ischaemia[1–3]. In contrast to our findings, Kaski *et al.* claim coronary dilatation and not preload reduction to be responsible for the anti-ischaemic action of 10 mg sublingually administered ISDN in patients with chronic stable, exercise-dependent ischaemia[11]. However, the number of nitrate nonresponders investigated for changes of LV-EDV was quite small ($N = 4$). Furthermore, they did not report the changes of LV-EDV during exercise. As it can be deducted from our data in 29 patients with insufficient nitrate response, it is, however, not permissible to extrapolate from the presence of LV-EDV changes at rest to LV-EDV changes during exercise: Even despite a significant reduction in LV-EDV of 17% following ISDN at rest, the changes of this parameter during exercise were meaningless (Table 3).

Although this was not a prospective, double-blind, randomized and stratified study, the differences between patients responding and nonresponding to ISDN cannot be explained on the basis of the severity of coronary artery disease, basal exercise capacity or baseline heart rate, blood pressure or left ventricular ejection fraction at rest and during exercise, respectively (Table 1). The lack of anti-ischaemic response was demonstrable even despite a significant lower increase of the rate–pressure product, as compared to the patients with good anti-ischaemic response (Table 3). Our findings underline that in the case of nitrates the pressure–rate product is not related to the anti-ischemic effects[24]. This may be explained by the fact that reductions in ventricular volumes are not reflected by the pressure–rate product. Therefore the rate–pressure product should only be taken as an index for myocardial oxygen demand if changes of LV-EDV can be ruled out[25].

RESPONSE TO BETA OR/AND CALCIUM BLOCKADE

The equity of the anti-ischaemic properties of propranolol and verapamil has been well established[26–29]. As we have seen in this special subset of patients with insufficient anti-ischaemic response to ISDN, the benefits from verapamil are to the same extent as those of propranolol (Table 4). Since, however, the net negative inotropic and chronotropic effects of verapamil are less pronounced than those of propranolol[30], the dilatation of coronary stenoses following verapamil are a matter of controversy[31]. As verapamil does not act via dilatation of the collateral vessels[32], additional

mechanisms must be taken into consideration to explain the well documented anti-ischaemic potency of verapamil: an improvement of myocardial acidosis in ischaemic zones, independent of tissue blood flow, thus influencing zones, independent of tissue blood flow, thus influencing the metabolism at the molecular level, has been reported[33,34]. The exact mechanisms of the anti-ischaemic effects of verapamil, however, are not yet completely understood[35].

Since a considerable part of our patients needed the combination of verapamil plus propranolol for an optimal anti-ischaemic drug treatment, the reduction of heart rate and contractility seems to be the key for an effective anti-ischaemic drug regimen in this special subset of patients.

LIMITATIONS OF THE STUDY

Data regarding the incidence of nitrate-nonresponders cannot be derived from our studies, since they were not performed to address this question. For this purpose a great number of patients must be tested on a consecutive basis. Kaski *et al.* reported that 46 out of 217 consecutive investigated patients with stable angina, positive exercise test and angiographically proven coronary artery disease did not increase their coronary reserve following the administration of 10 mg of sublingual ISDN[11]. Although we have not performed a similar study, we feel that the figure of 21% nonresponders is relatively high.

It must be emphasized that the borderline between good and insufficient nitrate response must be an arbitrary definition, depending on the choice of drug (nitroglycerin, isosorbide dinitrate or isosorbide-5-mononitrate), the route of administration (intravenous, sublingual, oral, transdermal) and the dosage administered. Furthermore, the response can be measured by subjective (angina pectoris) or objective (e.g. ST-segment depression, thallium-scintigraphy, radionuclide ventriculography) methods. We think that the single dosage of 80 mg ISDN chosen in our studies is quite high not to be criticized as underdose. Furthermore, the objective parameter of exercise-induced ST-segment depression is more reliable, especially when used for testing the intra-individual response rather than the subjective parameter angina pectoris.

Unfortunately, we have no measurements of plasma levels in the patients with insufficient nitrate response. However, impaired absorption is not known as a major problem concerning oral ISDN-therapy. Since insufficient ST-segment response was demonstrable despite significant changes in heart rate, blood pressure, end-diastolic volume and left ventricular ejection fraction (Table 2), it is justified to assume adequate plasma levels in our patients.

The count-derived method chosen in this study has the great advantage of being independent of possibly erroneous corrections for attenuation of radiation. It is restricted, however, only to the use of calculating short-term volume changes after a single injection rather than the comparison of absolute volumes. It is not permissible to compare the count-rates of different groups. Since the calculation of volume changes after separate injections of technetium-99m can be misleading, numbers for changes of the left ventricular end-diastolic volumes during the combination therapy (with tests performed at different days[13]) were not obtained (Table 4).

Our data are indicative that the lack of preload reduction may be taken as explanation for the absence of anti-ischaemic benefit from ISDN. However, the exact measurement of preload requires the additional measurement of pressures and wall-thickness. For the exact differentiation between preload-reduction and coronary vasomotion in clinical circumstances, tip-manometry, contrast-ventriculography and quantitative coronary angiography before and after ISDN at rest and during exercise is necessary. Since we have not performed such measurements, one might still argue that a lack of coronary vasodilatation cannot be ruled out and the end-diastolic volume did not decrease as a consequence of persisting ischaemia.

PRACTICAL IMPLICATIONS

Although nitrates are the basic treatment for all forms of myocardial ischaemia, an insufficient therapeutic effect when used as monotherapy must be taken into consideration. Therefore, in each individual patient, even if a reduction of anginal pain is achieved, an objective control of the nitrate therapy (usually by exercise- and Holter-ECG) must be recommended. In patients with insufficient nitrate response, the reduction of heart rate and contractility seems to play the major role. However, most of our patients needed the combination of verapamil plus propranolol for an optimal anti-ischaemic drug treatment. This regimen could be administered even without a deterioration of LV-ejection fraction (EF) at rest or during exercise in our patients with an initial EF of $\geq 35\%$. Thus, we could confirm other findings reporting no relevant EF changes when combining propranolol with verapamil[30,36–38]. Although the

inherent danger of such a combination must be kept in mind, in experienced hands it has been proven safe[30,39–44]. Care must always be taken about the possible induction of heart block[44] or symptomatic sinus bradycardia[37] which we observed in two patients[13]. Therefore, this therapy should be initiated inside the hospital. It is recommended to begin with verapamil, subsequently titrating the beta-blocker until the optimal necessary and tolerated dose has been reached.

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