Br J Clin Pharmacol 1996; **41**: 493–497

Pre- and afterload reduction in chronic mitral regurgitation: a double-blind randomized placebo-controlled trial of the acute and 2 weeks' effect of nifedipine or isosorbide dinitrate treatment on left ventricular function and the severity of mitral regurgitation

HENNING KELBÆK, JAN ALDERSHVILE, KNUD SKAGEN, PER HILDEBRANDT & STEEN L. NIELSEN
Medical Department B, Rigshospitalet, Department of Cardiology and Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, Department of Cardiology, Gentofte Hospital, University of Copenhagen, Denmark

1 The acute effect and effect of 14 days' treatment with isosorbide dinitrate (ISDN) and nifedipine (NIF) was evaluated by radionuclide cardiography in patients with chronic mitral regurgitation and sinus rhythm.

2 In 23 patients with clinically stable disease blood pressure was lowered by 15% and left ventricular volume was reduced by 16–20% after 20 mg sublingual ISDN causing combined pre- and afterload reduction. Afterload reduction alone induced by 10 mg NIF resulted in an acute 9% decrease in left ventricular endsystolic volume, whereas forward stroke volume increased by 30%, and regurgitation fraction tended to decrease. No haemodynamic effects could be detected after 14 days' treatment with 20 mg ISDN orally twice daily (preload reduction), whereas 20 mg NIF twice daily (afterload reduction) caused an increase in forward stroke volume (18%) and a decrease in both regurgitant volume (20%) and regurgitation fraction (22%) without affecting blood pressure or heart rate.

3 ISDN and NIF have beneficial acute haemodynamic effects in patients with chronic mitral regurgitation probably due to their pre- and afterload reducing properties. The reduction in regurgitation induced by NIF appears to be sustained after 14 days therapy.

Keywords mitral regurgitation radionuclide cardiography isosorbide dinitrate nifedipine

Introduction

Patients with mitral valve regurgitation may benefit from vasodilatation, whether or not the condition is secondary to congestive heart failure [1–3]. Isosorbide dinitrate (ISDN), a long-acting nitrate, is predominantly a venodilator with beneficial haemodynamic effects in patients with heart failure due to coronary artery disease [4]. Nifedipine (NIF), a dihydropyridine derivative and calcium blocking agent with a potent arterial dilatory effect may also be effective in the treatment of congestive heart failure [5–7], although some studies have shown a harmful longterm effect of this calcium blocker [8].

It was recently highlighted that in clinical decision making concerning the time for surgical treatment of patients with valvular disease, those with mitral regurgitation are the most difficult to handle [9]. In addition, the importance of non-invasive techniques for monitoring the course of mitral regurgitation has been stressed by several authors [10]. We have previously described a quantitative radionuclide method to determine the severity of mitral regurgitation [11].

In this study we used this radionuclide technique to evaluate changes in mitral valve regurgitation and left ventricular function by different treatment regimens. Firstly, the acute effects of combined pre- and afterload

Correspondence: Dr H. Kelbæk, Medical Department B 2013, Rigshospitalet, DK—2100 Copenhagen Ø, Denmark

© 1996 Blackwell Science Ltd

reduction induced by a high dose of sublingual ISDN was compared both with placebo and with the afterload reducing effect of a moderate dose of NIF. Secondly, the effect of 2 weeks' treatment with a moderate oral ISDN dose causing predominantly preload reduction was compared with placebo and with the effect of a moderate to high dose of oral NIF causing predominantly afterload reduction.

Methods

Study protocol

Prior medication (digitalis and diuretics) was continued throughout the study period. All patients were familiar with the investigation procedure. They attended the laboratory 3 h after a light breakfast for baseline measurements.

For the acute study patients were allocated by aid of a random numbers table to receive 20 mg sublingual ISDN (tablet to be chewed), 10 mg NIF (the content of a capsule with NIF in an oil solution to be swallowed) or placebo. All examinations were performed before and 20 to 30 min after drug administration, at a time when the acute haemodynamic effects of the two drugs were at maximum [12–14].

The effects of 2 weeks' treatment were studied after random re-assignment of patients to a 2 week treatment period with either 20 mg ISDN taken orally as a plain tablet twice daily, 20 mg tablet NIF twice daily or placebo (double dummy principle). All 2 weeks' measurements were performed exactly 2 h after the morning dose of the medication.

A double-blind treatment design was used. Thus, all data processing was performed without knowledge of treatment pattern. The same observer performed all data processing in a given patient. The study protocol was approved by the local ethics committee and the Danish National Board of Health.

Patient group

Patients entered the study consecutively according to the following inclusion criteria: moderate to severe chronic mitral valve regurgitation as judged from contrast ventriculography or Doppler echocardiography in clinically stable patients (New York Heart Association Classification group II). For technical reasons (see below) only patients in sinus rhythm were included. Reasons for exclusion were pregnancy or lactation, other cardiac valve disease including concomitant mitral stenosis and treatment with calcium channel blockers, long acting nitrates or other vasodilatating drugs.

Investigations

All data were recorded at supine rest. Heart rate was measured by a 3-lead electrocardiogram and blood pressure by the sphygmomanometer technique with diastolic level corresponding to the Korotkoff phase 5.

Radionuclide cardiography was performed by combined first pass and multigated equilibrium technique after *in vitro* labelling of autologous red blood cells with ^{99m}Tc [17]. A bolus of approximately 500 MBq (14 mCi) was injected through an indwelling canula in the right basilic vein. First pass cardiographic data were acquired in list mode followed by a static image with a mobile gamma camera (Siemens) in the left anterior oblique projection, and processed with a dedicated computer to determine the *forward stroke volume*. Multigated cardiography was performed in the same projection with 16 frames per cardiac cycle, and left ventricular end diastolic volume was calculated as the end diastolic frame activity corrected for specific blood activity and attenuation. The *total (absolute) stroke volume* was determined as the product of the left ventricular end diastolic volume and ejection fraction as assessed by the multigated method, and the endsystolic volume as the difference between the end diastolic volume and the total stroke volume. The regurgitant volume was calculated as the difference between the total and the forward stroke volume. The regurgitation fraction was determined as the regurgitant volume divided by the total stroke volume [11]. The reproducibility of this method has recently been documented [16].

Statistical analysis

Data are presented by their means and s.d. Changes in data between the three groups were compared by the Kruskal–Wallis rank sum test. In addition, Mann–Whitney's test was applied when appropriate to compare differences between two groups. The 95% confidence intervals were calculated for differences between active and placebo treatment effects.

Results

Patients

Twenty-four patients were included in the study (13 men and 11 women). Their ages ranged from 27 to 82 years (mean, 58 years). Mitral regurgitation was due to mitral valve prolapse in nine patients and ischaemic heart disease in six other patients. In the remainder of patients rheumatic valve disease (3), ruptured chordae (2), endocarditis (2) and cardiomyopathy (2) were responsible. Two patients were excluded from the acute study, one due to technical problems, and one patient because a later echocardiogram showed aortic regurgitation in addition to the mitral valve disease. The latter patient was also excluded from the 2 week investigation in addition to two other patients, one because of lack of compliance in taking the study medicine (no adverse effects), and one because she developed rupture of a chorda during the study. Thus 22 patients participated in the acute study (seven in the ISDN group, eight in

Table 1 Haemodynamic parameters before and after treatment

	Placebo		*Isosorbide dinitrate*		*Nifedipine*	
	Before	*After*	*Before*	*After*	*Before*	*After*
Acute drug effects						
	$n=7$		$n=7$		$n=8$	
BPs (mmHg)	131(33)	133(27)	131(26)	109(25)*	123(18)	114(20)
BPd (mmHg)	77(16)	79(10)	81(10)	70(15)*	76(9)	72(7)
HR (beats min^{-1})	80(18)	79(18)	68(16)	68(14)	76(12)	82(8)
LVEF (%)	55(18)	55(17)	59(9)	63(9)	57(18)	60(17)
2 weeks' drug effects						
	$n=7$		$n=7$		$n=7$	
BPs (mmHg)	115(16)	119(13)	143(30)	133(13)	128(23)	116(13)
BPd (mmHg)	75(7)	79(7)	80(16)	78(7)	81(11)	74(7)
HR (beats min^{-1})	73(18)	70(19)	72(9)	68(9)	80(17)	82(16)
LVEF (%)	53(23)	53(23)	56(17)	58(17)	69(8)	69(7)

Data are given as mean with s.d. in parentheses. BPs, systolic blood pressure; BPd, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; *$P<0.05$ *vs* other two treatments.

the NIF group, and seven in the placebo group), and 21 fulfilled the 2 week study (seven in each group).

Baseline data of the three groups did not show any statistical differences in either the acute or the 2 week study, and the patient groups were therefore comparable.

No patient complained of any adverse effect during the study of acute drug effects. During the 2 week study, three patients in the NIF group and two in the ISDN group developed transient headache, and two patients in the NIF group experienced a slight oedema of the feet for 1 day. One of the latter discontinued the medical treatment for 5 days but resumed the medication 3 days before the second investigation.

Acute haemodynamic effects of ISDN and NIF

ISDN 20 mg sublingually lowered the mean systemic blood pressure acutely by 18 mmHg (95% confidence intervals (95% CI) for the difference 7–28 mmHg), with no change in heart rate or left ventricular ejection fraction (Table 1). The left ventricular end diastolic volume was decreased by 16% from a mean value of 217–192 ml (95% CI for the difference 7–37 ml) and the end systolic volume by 20% from 89 to 71 ml (95% CI for the diffence 7–31 ml). No effects were recorded in forward stroke volume, regurgitant volume, or regurgitation fraction (Figure 1).

NIF 10 mg did not change the blood pressure, heart rate, or left ventricular ejection fraction significantly in the acute study (Table 1). No change was observed in total stroke volume or left ventricular end diastolic volume, whereas left ventricular end systolic volume was reduced by 9% (95% CI for the difference 1–18 ml). Forward stroke volume increased by 30% from 46 to 60 ml (95% CI for the difference 6–21 ml), while the regurgitation fraction tended to decrease. However, the reduction in regurgitation did not reach statistical significance.

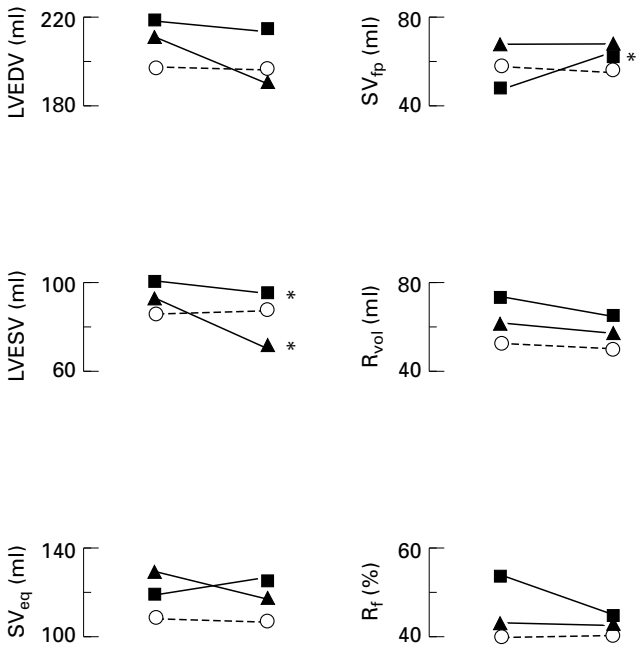

Figure 1 Absolute and relative left ventricular volumes before and after treatment of 22 patients with chronic mitral regurgitation with placebo (○), 20 mg isosorbide dinitrate (▲) sublingually, or 10 mg nifedipine (■) oil solution orally. Figures indicate mean values. LVEDV, left ventricular enddiastolic volume; LVESV, left ventricular endsystolic volume; SV_{eq}, total stroke volume (determined by the multigated equilibrium method); SV_{fp}, forward stroke volume (determined by the first pass technique); R_{vol}, regurgitant volume; R_f, regurgitation fraction. *$P<0.05$ *vs* placebo.

Haemodynamic changes after 2 weeks' treatment with ISDN and NIF

No significant haemodynamic changes were found after 2 weeks' treatment with 20 mg ISDN twice daily. No alterations were recorded in blood pressure, heart rate, ejection fraction, or absolute left ventricular volumes

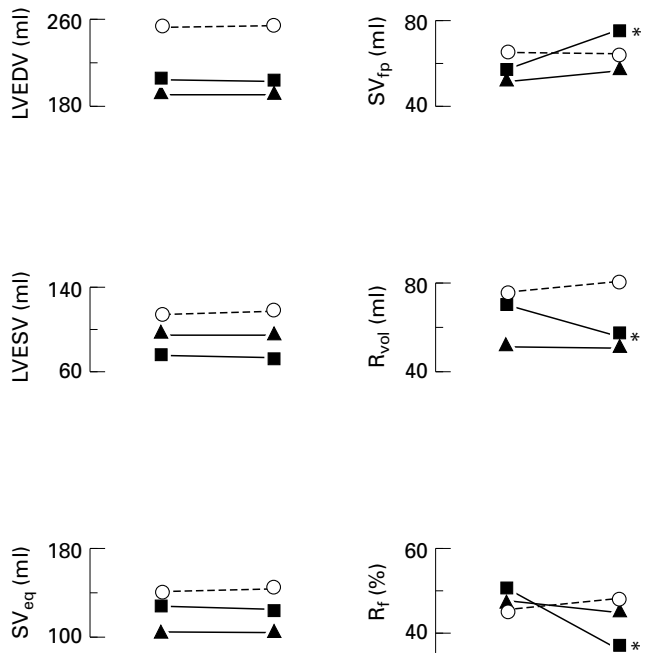

Figure 2 Absolute and relative left ventricular volumes before and after 2 weeks of treatment with placebo (○), 20 mg isosorbide dinitrate (▲) twice daily, or 20 mg nifedipine (■) twice daily in 21 patients with chronic mitral regurgitation. Figures indicate mean values. Abbreviations as in Figure 1. $*P<0.05$ *vs* placebo.

after 2 weeks' treatment with 20 mg NIF twice daily However, in the NIF group the mean forward stroke volume increased by 18% from 62 to 73 ml (95% CI for the difference 8–24 ml), the regurgitant volume decreased by 20% from 69 to 55 ml (95% CI for the diffence 6–31 ml), and the regurgitation fraction was reduced from 49 to 38% (95% CI for the difference 5–21%) (Figure 2).

Discussion

A moderate dose of sublingual ISDN has acute haemodynamic effects that last for at least 1 h [17]. Systemic and pulmonary blood pressure fall and cardiac output is reduced in patients with normal or low systemic vascular resistance [4, 12, 17] In this study high dose ISDN reduced both the blood pressure and left ventricular volume acutely by 15–20% without any influence on the regurgitant volume. Thus, taking the relation between systemic blood pressure and end systolic volume as an index of left ventricular contractility acute simultaneous pre- and afterload reduction reduces left ventricular volume without affecting contractility or severity of regurgitation.

In a study by Elkayam *et al.* [18] 2 months of treatment with ISDN alone or in combination with NIF resulted in a lower incidence of heart failure deterioration with ISDN compared with NIF. Exercise duration was increased after both treatment regimens in patients with congestive heart failure without affecting systolic blood pressure and heart rate, indicating that ISDN possesses physiological effects even after several weeks of treatment. Unfortunately, no placebo group was included to compare active treatment with the natural course of these patients.

The explanation for the discrepancy in acute and chronic haemodynamic effects recorded in the present study, is probably the difference in plasma levels induced by sublingual and oral ISDN administration. Development of nitrate tolerance is unlikely because this phenomenon has not been reported to occur with doses and intervals as those used in the present study. On the other hand, nitrate tolerance can not be ruled out, because no effect on central haemodynamics and blood pressure were recorded after 2 weeks' ISDN treatment.

In chronic mitral regurgitation, the left ventricle faces a considerable increase in afterload during systole, despite the enlarged low impedance left atrium; this seems to be most pronounced when the left ventricle is dilated [19], and the influence of afterload reduction on acute mitral regurgitation has been ascribed entirely to the reduction in left ventricular volume [20]. The findings of this study is somewhat at variance with this concept. The afterload reducing effect of NIF decreased left ventricular volume, but only at endsystole, while a considerable increase in the forward functional stroke volume was demonstrated. No change was recorded in blood pressure and the decrease in regurgitant volume and regurgitation fraction was not significant until the completion of the 14 days study. The afterload reducing effects of NIF seems to increase contraction, and it is possible that the lack of concomitant preload reduction is of importance for the decrease in severity of regurgitation. The haemodynamic beneficial effects of NIF in these patients seem to be maintained after weeks.

Hamilton *et al.* [21] evaluated the effect of tailored afterload reduction in patients with severe congestive heart failure and secondary mitral regurgitation using Doppler echocardiographic measures. They found a decrease in atrial volumes in addition to a marked reduction in mitral regurgitation.

Although the present study is the first to evaluate haemodynamic effects of ISDN and NIF in patients with chronic mitral regurgitation in a double-blind controlled design, the conclusions reached may be limited due to the size of the study population. Nevertheless, the cross-over design was avoided because of the inherent methodological disadvantages of this kind of study, especially problems with exclusion of carry-over effects [22]. In spite of the above mentioned limitations, the study population was large enough to demonstrate significant and clinically important haemodynamic changes. The limitation in patient allocation was the reason for choosing the dose regimens known to cause characteristic haemodynamic effects with the smallest side effects. Transient head ache, flushing and tachycardia were experienced by a few patients in each group.

The severity of mitral regurgitation can be determined by different non-invasive methods [23, 24]. The main advantage of the radionuclide technique employed in the present study is that a quantitative measure of regurgitation is obtained by combining two methods using identical principles for delineation of regions of

interest and background subtraction, and thereby diminishing weaknesses of the methods that are of major importance when the techniques are singly applied. One disadvantage of the method is that it is cumbersome unless restricted to patients with sinus rhythm, and patients without sinus rhythm were therefore not included in the present study.

This study illustrates that pre- and afterload reduction induced by ISDN reduces blood pressure and left ventricular volume acutely without affecting regurgitation in patients with chronic mitral regurgitation and sinus rhythm. These effects disappear or are undetectable after 2 weeks of oral treatment, probably because ISDN administered in a dosage that predominantly causes preload reduction does not influence left ventricular haemodynamics in patients with mitral valve regurgitation. NIF causes acute afterload reduction in the same patients resulting in an increased forward stroke volume. This effect is maintained together with a decrease in regurgitant volume and regurgitation fraction after two weeks of treatment with an oral dose of NIF.

We thank the laboratory staff of the Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, led by chief technician Kirsten Bülow for skilled assistance in the accomplishment of this work.

References

1 Greenberg BH, Massie BM, Brundage BH, Botvinick EH, Parmley WW, Chatterjee K. Beneficial effects of hydralazine in severe mitral regurgitation. *Circulation* 1978; **58:** 273–279.

2 Keren G, Bier A, Strom JA, Laniado S, Sonnenblick EH, LeJemtel TH. Dynamics of mitral regurgitation during nitroglycerin therapy: A Doppler echocardiographic study. *Am Heart J* 1986; **112:** 517–525.

3 Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M. Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. *Am J Cardiol* 1991; **67:** 259–263.

4 Rabinowitz B, Tamari I, Elazar E, Neufeld HN. Intravenous isosorbide dinitrate in patients with refractory pump failure and acute myocardial infarction. *Circulation* 1982; **65:** 771–778.

5 Klugman S, Salvi A, Camerini F. Haemodynamic effects of nifedipine in heart failure. *Br Heart J* 1980; **43:** 440–446.

6 Elkayam U, Roth A, Weber L, *et al*. Effects of nifedipine on hemodynamics and cardiac function in patients with normal left ventricular ejection fraction already treated with propranolol. *Am J Cardiol* 1986; **58:** 536–540.

7 Thomson A, Fletcher PJ, Harris PJ, Freedman B, Kelly DT. Regional distribution of cardiac output at rest and during exercise in patients with exertional angina pectoris before and after nifedipine therapy. *J Am Coll Cardiol* 1988; **11:** 837–842.

8 Packer M. Calcium channel blockers in chronic heart failure. *Circulation* 1990; **82:** 2254–2257.

9 Frankl WS. Valvular heart disease: the technologic dilemma. *J Am Coll Cardiol* 1991; **17:** 1037–1038.

10 Cheitlin MD. Valvular heart disease: Management and intervention. *Circulation* 1991; **84** (suppl I): I-259 to I-264.

11 Kelbæk H, Aldershvile J, Svendsen JH, Folke K, Nielsen SL, Munck O. Combined first pass and equilibrium radionuclide cardiographic determination of stroke volume for quantitation of valvular regurgitation. *J Am Coll Cardiol* 1988; **11:** 769–773.

12 Badger RS, Brown BG, Gallery CA, Bolson EL, Dodge HT. Coronary artery dilation and hemodynamic responses after isosorbide dinitrate therapy in patients with coronary artery disease. *Am J Cardiol* 1985; **56:** 390–395.

13 Harten JV, Burggraaf K, Danhof M, Brummelen PV, Breimer DD. Negligible sublingual absorption of nifedipine. *Lancet* 1987; **ii:** 1363–1364.

14 Elkayam U, Roth A, Mehra A, *et al*. Randomized study to evaluate the relation between oral isosorbide dinitrate dosing interval and the development of early tolerance to its effect on left ventricular filling pressure in patients with chronic heart failure. *Circulation* 1991; **84:** 2040–2048.

15 Kelbæk H, Bülow K, Aldershvile J, Møgelvang J, Nielsen SL. A new ^{99m}Tc-red blood cell labeling procedure for cardiac blood pool imaging: clinical results. *Eur J Nucl Med* 1989; **15:** 333–335.

16 Kelbæk H, Aldershvile J, Skagen K, Hildebrandt P, Nielsen SL. Mitral regurgitation determined by radionuclide cardiography: dependence of posture and exercise. *Br Heart J* 1994; **72:** 156–160.

17 Sweatman T, Strauss G, Selzer A, Cohn KE. The long-acting hemodynamic effects of isosorbide dinitrate. *Am J Cardiol* 1972; **29:** 475–480.

18 Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. *Circulation* 1990; **82:** 1954–1961.

19 Corin WJ, Monrad ES, Murakami T, Nonogi H, Hess OM, Krayenbuehl HP. The relationship of afterload to ejection performance in chronic mitral regurgitation. *Circulation* 1987; **76:** 59–67.

20 Yoran C, Yellin EL, Becker RM, Gabbay S, Frater RWM, Sonnenblick EH. Mechanism of reduction of mitral regurgitation with vasodilator therapy. *Am J Cardiol* 1979; **43:** 773–777.

21 Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Woo M. Acute reduction of atrial overload during vasodilator and diuretic therapy in advanced congestive heart failure. *Am J Cardiol* 1990; **65:** 1209–1212.

22 Altman DG. Clinical trials. In *Practical statistics for medical research*, First Edition; Ed. Altman DG, London: Chapman and Hall, 1991: 440–476.

23 De Zuttere D, Touche T, Saumon G, Nitenberg A, Prasquier R. Doppler echocardiographic measurement of mitral flow volume: validation of a new method in adult patients. *J Am Coll Cardiol* 1988; **11:** 343–350.

24 Rigo P. Quantification of mitral insufficiency by radionuclide techniques. *Eur Heart J* 1991; **12** (Suppl B): 15–18.

(*Received 8 June 1995, accepted 3 January 1996*)