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The effects of nitroglycerin on regional myocardial contractile dysfunction produced by treadmill exercise or isoprenaline stimulation in dogs

W. Schneider, J.G. Grohs, G. Krumpl, N. Mayer & [1]G. Raberger

Institut für Pharmakologie der Universität Wien, Währingerstrasse 13A, A-1090 Wien, Austria

1 To compare different methods of cardiac stress testing that are clinically applied in the management of coronary heart disease, 2 groups of dogs each were chronically instrumented and subjected to treadmill exercise or isoprenaline infusion in the presence of coronary stenosis.

2 It was of interest to determine differences in haemodynamic and regional myocardial contractile parameters, the response to antianginal therapy (nitroglycerin $15\,\mu g\,kg^{-1}\,15\,min^{-1}$, i.v.), and, in particular, whether this response differed according to the mode of cardiac stimulation, i.e. treadmill exercise or isoprenaline infusion.

3 After stenosis of the circumflex branch of the left coronary artery which affected resting myocardial function only minimally, treadmill exercise or isoprenaline infusion induced transient regional contractile dysfunction. Heart rate, arterial blood pressure, left ventricular end-diastolic pressure and left ventricular dp/dt_{max} were registered and myocardial oxygen demand was calculated. Regional contractile performance was assessed by ultrasonic distance measurement in the underperfused and in a normally perfused area.

4 Treadmill exercise led to an increase in systolic arterial and left ventricular end-diastolic pressure. In contrast, isoprenaline-induced stimulation led to a decrease in diastolic arterial and left ventricular end-diastolic pressure. Regional contractile function in the critically underperfused area showed a deterioration during both modes of stress. Nitroglycerin completely abolished stress-induced contractile dysfunction only in the group where treadmill exercise was employed for stimulation.

5 The inability of nitroglycerin to prevent myocardial dysfunction in the isoprenaline group may be due to exhaustion of the arterial and/or venous vasodilator potency of nitroglycerin in the presence of adrenoceptor vasodilatation induced by isoprenaline.

6 These findings indicate that clinical antianginal drug testing and the evaluation of the course of disease in patients with coronary heart disease may be highly dependent on the test method chosen.

Introduction

Since the first report by Goldhammer & Scherf (1932), exercise stress testing has developed into an important tool in the management of coronary heart disease (Bruce *et al.*, 1963; 1974; Bruce & Hornsten, 1969; Blomquist, 1971; Bruce, 1971) for the differential diagnosis of angina pectoris, the evaluation of physical performance capacity before and after pharmacological or surgical treatment, and in rehabilitation control of patients with previous myocardial infarction. The manifold variety of exercise test methods developed over the years have in common that the patient has to be ambulatory, cooperative and properly motivated. Since these factors are disadvantages in patients who are unable to perform physical exercise and, moreover, the methods are generally unsuited for screening a larger population, different models have been developed using pharmacological stimulation of β-adrenoceptors as a method of stress testing (Wexler *et al.*, 1971; Combs & Martin, 1974; Schechter *et al.*, 1983; Yasuda *et al.*, 1987). The isoprenaline test and the adrenaline test are both highly sensitive and specific in diagnosing coronary heart disease (Combs & Martin 1974; Schechter *et al.*, 1983).

[1] Author for correspondence.

The present study was designed to assess differences not only in haemodynamic and regional contractile parameters, but, in particular, the response to antianginal therapy. Moreover, it appeared of interest to determine whether this response differed according to the mode of stimulation, i.e. whether treadmill exercise or isoprenaline infusion was used for stimulation. The investigation was based on a model of transient myocardial dysfunction in conscious dogs, using an ultrasonic distance measurement system (Brugge-Asperheim *et al.*, 1969; Gilly *et al.*, 1983) to assess regional shortening in the presence of impaired coronary flow reserve and treadmill exercise (Raberger *et al.*, 1986) or isoprenaline stimulation. The isoprenaline stimulation method has proved to be of value in investigations of changes in myocardial function in the presence of coronary stenosis in anaesthetized (Seitelberger & Raberger, 1984) and conscious dogs (Vatner *et al.*, 1974; 1976; Gallagher *et al.*, 1982). The model using treadmill exercise in the presence of impaired coronary flow reserve by transient stenosis of the circumflex branch has been used successfully in investigations on classical antianginal drugs such as propranolol (Mayer *et al.*, 1986), nitroglycerin (Schneider *et al.*, 1987a,b), verapamil (Schneider *et al.*, 1988) and more recently developed drugs like bepridil (Krumpl *et al.*, 1986b), alindine (Krumpl *et al.*, 1986a,c) and UL-FS 49 (Krumpl *et al.*, 1986a; Raberger *et al.*, 1987).

A comparison of these two distinct models of regional myocardial dysfunction under identical experimental conditions, as undertaken in the present study, should prove of clinical importance in the judgement of different modes of stress testing in the management of coronary heart disease.

Methods

Experimental model

The study was carried out on 2 groups of 6 mongrel dogs each (25.7 ± 6.2 and 27.8 ± 2.6 kg, mean $\pm$ s.d.). The animals were vaccinated with Candivac DHL (distemper, hepatitis, leptospirosis, rabies) and Candur P (parvovirosis). The dogs recieved 'Loyal' dry food (Tagger & Co., Graz) as standard diet. Before instrumentation the dogs were trained to stand quietly and to run on a treadmill (Quinton model 1854). In order to keep the animals accustomed to the specific exercise performance, identical time protocols and working load changes (see experimental procedure) were used for training and for the investigations after instrumentation. The animals were fasted overnight, with free access to water. Morphine ($1\,mg\,kg^{-1}$, s.c.) was given as premedication 1 h before anaesthesia was induced with pentobarbitone ($25\,mg\,kg^{-1}$, i.v.). After endotracheal intubation with a cuffed Magill tube, the animals were ventilated with a $N_2O{:}O_2$ mixture (2:1) in a rebreathing system using an Engstroem respirator. Sterile thoracotomy was undertaken in the left fifth intercostal space and the pericardium was opened. A short section of the left circumflex coronary artery was dissected free near its origin to allow the placing of an hydraulic occluder around the vessel. A Konigsberg microtip manometer was inserted into the left ventricle via the apex. Subsequently, two pairs of piezoelectric ultrasonic crystals were implanted subendocardially, one pair in the perfusion area of the circumflex branch of the left coronary artery (henceforth referred to as the posterior wall), the other in the area supplied by the anterior descending branch of the left coronary artery (the anterior wall) (Figure 1). Measurement of arterial blood pressure was carried out by means of a Tygon catheter advanced into the descending aorta via the left carotid artery. A catheter advanced from the left jugular vein to the right atrium served for drug infusions. All catheters and wires were exteriorized between the scapulae. The animals were monitored postoperatively and propranolol, lidocaine, flunitrazepam and methadone were administered as required over night. Ampicillin was given for four days, 0.5 g twice a day, beginning on the day of surgery. The dogs recovered completely within a couple of days, but the investigations were started only 10 days after surgery to guarantee a stable haemodynamic state (Inou *et al.*, 1985). Subendocardial placement of ultrasonic transducers was confirmed at necropsy.

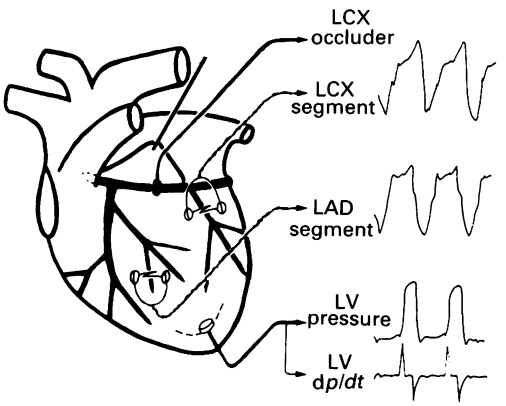

Figure 1 Instrumentation of dog heart.

Heart rate (derived from left ventricular pressure), systolic and diastolic arterial pressure (Statham pres-

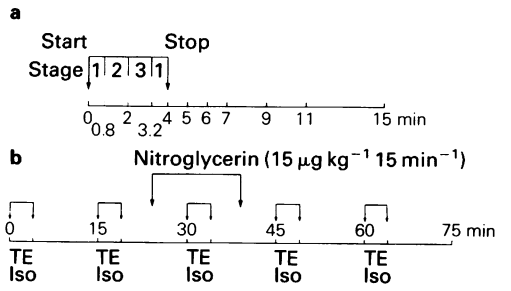

Figure 2 (a) One single test cycle with treadmill exercise or isoprenaline infusion: Stage 1: 6 km h^{-1}, 6% elevation or isoprenaline 0.13 μg kg^{-1} min^{-1}. Stage 2: 8 km h^{-1}, 8% elevation or isoprenaline 0.24 μg kg^{-1} min^{-1}. Stage 3: 10 km h^{-1}, 10% elevation or isoprenaline 0.325 μg kg^{-1} min^{-1}. (b) Time protocol of a complete experiment consisting of 5 test cycles. TE = treadmill exercise; Iso = isoprenaline infusion.

sure transducer), left ventricular pressure, left ventricular positive and negative dp/dt_{max} (Konigsberg microtip, HSE Physio Differentiator) and the two segmental signals were recorded on a Watanabe 6-channel recorder.

Myocardial function in the normally perfused area and in the region supplied by the stenosed vessel was assessed by determining the end-diastolic segment length at the point when the left ventricular pressure started to rise, and the end-systolic segment length at the point of maximal shortening during the ejection phase. Systolic shortening provides an accurate assessment of changes in regional myocardial performance (Battler *et al.*, 1980). Segment length values were normalized by dividing the observed length by the end-diastolic length, recorded immediately before stenosis of the left circumflex branch, and then multiplying by 10, according to Theroux *et al.* (1975).

Myocardial oxygen demand was calculated either as the double product or according to the 'Bretschneider equation' (Bretschneider, 1971; Hoeft *et al.*, 1984) as E_t:

$$E_t = E_0 + E_1 + E_2 + E_3 + E_4 \quad [\text{ml } O_2\,\text{min}^{-1}\,100\,\text{g}^{-1}]$$

$$E_0 = k_0 \qquad k_0 = 7.0 \times 10^{-1}$$

$$E_1 = TS \times HR \times k_1 \qquad k_1 = 3.0 \times 10^{-2}$$

$$E_2 = \frac{P_{syst\ max}^{1.5}}{dp/dt_{max}^{1/3}} \times TE \times HR \times k_2 \qquad k_2 = 1.4 \times 10^{-4}$$

$$E_3 = dp/dt_{max} \times HR \times k_3 \qquad k_3 = 1.2 \times 10^{-5}$$

$$E_4 = dp/dt_{max}^{1.5} \times HR \times k_4 \qquad k_4 = 8.0 \times 10^{-9}$$

Duration of systole (TS) and ejection time (TE) were calculated according to Hoeft *et al.* (1984) as follows:

$$TS = \frac{1}{(1.08 + HR \times 2.24 \times 10^{-2})}$$

$$TE = \frac{1}{(2.7 + HR \times 2.32 \times 10^{-2})}$$

Prior to experimentation all 12 dogs had been subjected to the protocol described below for 5 consecutive treadmill exercise cycles (Figure 2) using a constant degree of transient stenosis of the circumflex branch which had produced regional contractile dysfunction of comparable magnitude in the ischaemic area during all 5 exercise runs, with complete recovery in the intervening periods. This degree of stenois was used for the following investigations with treadmill exercise or isoprenaline infusion.

Treadmill exercise group

For the main experiment, the first group of 6 dogs was subjected to treadmill exercise as follows (Figure 2). Pre-exercise values were taken 0.5 min before starting the treadmill. The load was changed stepwise during the runs. The dogs were exercised for 0.8 min, running at a speed of 6 km h^{-1} and an elevation of 6% (stage 1), then for 1.2 min at 8 km h^{-1} and 8% (stage 2) and for another 1.2 min at 10 km h^{-1} and 10% (stage 3). In order to complete the exercise cycle of 4 min and for the technical purpose of resetting the programmer unit of the treadmill, the final 0.8 min was used to return to the initial speed of 6 km h^{-1} and elevation of 6%. Consequently, exercise parameters were recorded 0.8, 2, 3.2 and 4 min after the start. Haemodynamic and segmental data for the recovery period were registered 4.5, 5, 6, 7 and 9 min after initiation of exercise. Exercise runs of 4 min were followed by recovery periods of 11 min, giving exercise cycles of 15 min duration.

After a warm up exercise was carried out to exclude adaptation phenomena to physical stress (Williams *et al.* 1985) and stenosis of the circumflex branch, two control runs were performed. Nitroglycerin was administered intravenously at a dosage of 1 μg kg^{-1} min^{-1} for 15 min, whereby the infusion (15 ml 15 min^{-1}) was started 5 min after the end of the second run and finished 5 min after the end of the third run (Figure 2). This third run was not analysed because the infusion of nitroglycerin was not finished during the run. Subsequently two further runs were performed. The occluder was completely evacuated after each experiment.

Isoprenaline stimulation group

The second group of 6 dogs was also tested on the treadmill. The observed values of myocardial oxygen demand during treadmill exercise were then mimicked by an infusion of isoprenaline in the resting animal. The speed of infusion was adjusted to achieve the value of oxygen demand observed during the control exercise as mentioned above. Isoprenaline doses were 0.13 $\mu g\,kg^{-1}\,min^{-1}$ for 0.8 min (stage 1), 0.24 $\mu g\,kg^{-1}\,min^{-1}$ for the following 1.2 min (stage 2) and 0.325 $\mu g\,kg^{-1}\,min^{-1}$ for the second 1.2 min (stage 3). After an isoprenaline stimulation cycle without stenosis, the circumflex branch was narrowed. When two stimulation cycles showed a comparable degree of regional dysfunction during isoprenaline infusion in the area supplied by the stenosed vessel, nitroglycerin was infused using the same dose and time protocol (Figure 2) as used with the treadmill exercise group. After ending the nitroglycerin infusion two further isoprenaline stimulation cycles were performed.

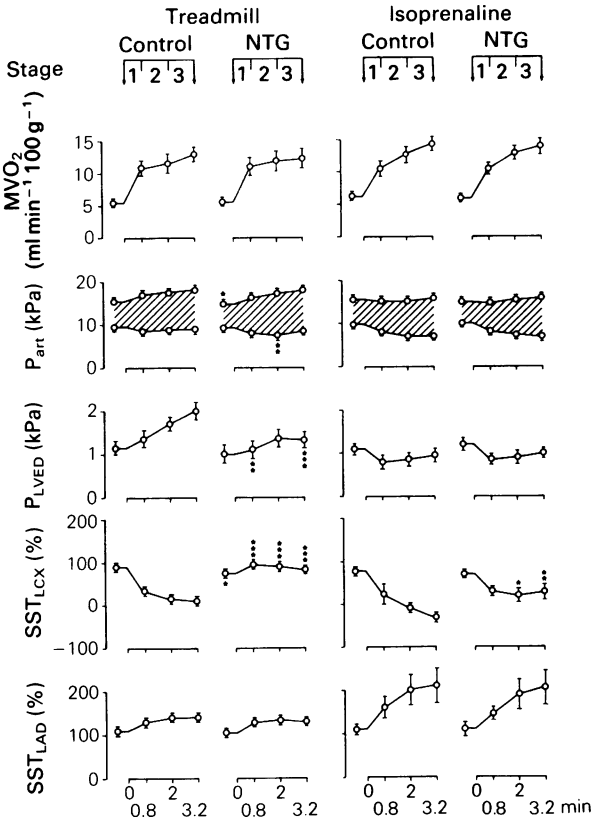

Figure 3 The first two columns show experiments with treadmill exercise before (Control) and after (NTG) nitroglycerin infusion (15 $\mu g\,kg^{-1}\,15\,min^{-1}$, i.v.); the second two columns show experiments with isoprenaline stimulation before and after nitroglycerin infusion. As the two pre-drug and post-drug test cycles did not differ significantly, they are expressed as one test cycle in each case. MVO_2 = calculated myocardial oxygen demand; NTG = nitroglycerin; P_{art} = arterial blood pressure; P_{LVED} = left ventricular end-diastolic pressure; SST_{LAD} = systolic shortening in the area perfused by the descending branch of the left coronary artery; SST_{LCX} = systolic shortening in the area perfused by the circumflex branch of the left coronary artery. Asterisks indicate significant differences from respective pre-drug values. Means ± s.e.mean; $n = 12$; t test for paired data; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Statistical analysis

Student's t test for unpaired data was used to compare the effects of treadmill exercise and isoprenaline stimulation before drug administration. Student's t test for paired data was used for statistical analysis within each model to evaluate significant differences between the corresponding pre- and post-drug values.

Results

There were no significant differences between base line values of any of the haemodynamic and functional parameters in the treadmill exercise group and in the isoprenaline stimulation group (Figure 3, Tables 1, 2). Comparing the values of heart rate and calculated oxygen demand at rest and values during exercise or isoprenaline stimulation, there was also no significant difference between the two groups in the control cycles.

Haemodynamic and dimensional parameters during treadmill exercise before nitroglycerin infusion

The two control exercise cycles led to an increase in heart rate, myocardial oxygen demand, systolic arterial pressure, positive and negative left ventricular dp/dt_{max} and left ventricular end-diastolic pressure, reaching maximum values 3.2 min after starting the treadmill, i.e. at maximum work load. Diastolic arterial pressure decreased only slightly, with a maximum change only 0.8 min after the start of the treadmill (Figure 3, Table 1). All changes returned to pre-exercise control values by 3 min, indicating a rapid recovery after the end of each exercise run.

End-diastolic length increased in both the posterior wall segment and the anterior wall segment during treadmill exercise. However, while endsystolic segment length decreased in the anterior wall, which

Table 1 Haemodynamic and regional functional data during treadmill exercise before and after nitroglycerin (15 $\mu g\,kg^{-1}\,15\,min^{-1}$ i.v.)

	Treadmill exercise before nitroglycerin				*Treadmill exercise after nitroglycerin*			
	0 min	0.8 min	2 min	3.2 min	0 min	0.8 min	2 min	3.2 min
HR (beats min^{-1})	112 ± 23	183 ± 33	193 ± 32	203 ± 29	117 ± 23	178 ± 33	192 ± 27	193 ± 32
PAS (kPa)	15.6 ± 1.9	17.0 ± 2.4	174 ± 2.7	18.0 ± 2.6	14.7 ± 1.3*	16.3 ± 1.7	17.2 ± 2.1	17.9 ± 1.6
PAD (kPa)	9.5 ± 1.2	8.6 ± 1.3	8.9 ± 1.4	9.1 ± 1.5	9.3 ± 0.9	8.2 ± 1.7	7.6 ± 1.8**	8.3 ± 1.8
PAM (kPa)	12.6 ± 1.4	12.8 ± 1.8	13.1 ± 1.9	13.5 ± 1.8	12.0 ± 1.0	12.2 ± 1.6	12.4 ± 1.7**	13.1 ± 1.4
$dp/dt +_{max}$ (kPa s^{-1})	343 ± 58	488 ± 135	511 ± 153	544 ± 140	330 ± 55	506 ± 170	527 ± 162	543 ± 154
$dp/dt -_{max}$ (kPa s^{-1})	340 ± 77	377 ± 87	396 ± 78	407 ± 82	317 ± 60**	365 ± 82	404 ± 101	422 ± 95*
PLVED (kPa)	1.16 ± 0.57	1.37 ± 0.69	1.69 ± 0.56	2.01 ± 0.62	1.02 ± 0.73	1.08 ± 0.74**	1.34 ± 0.76	1.32 ± 0.58***
MVO_2 (ml O_2 min^{-1} 100 g^{-1})	5.54 ± 1.41	10.68 ± 3.77	11.61 ± 4.39	12.69 ± 4.06	5.56 ± 1.30	10.86 ± 4.71	11.77 ± 4.14	12.22 ± 4.24
DP (kPa min^{-1})	1743 ± 411	3119 ± 816	3355 ± 788	3617 ± 641	1717 ± 353	2914 ± 689	3274 ± 548	3452 ± 590
LED_{LCX} (mm)	10.28 ± 0.23	10.35 ± 0.37	10.50 ± 0.46	10.48 ± 0.40	10.30 ± 0.28	10.27 ± 0.40	10.40 ± 0.46*	10.38 ± 0.47
LES_{LCX} (mm)	9.20 ± 0.30	9.93 ± 0.51	10.36 ± 0.57	10.43 ± 0.55	9.38 ± 0.33	9.08 ± 0.51***	9.32 ± 0.75***	9.37 ± 0.72***
SST_{LCX} (mm)	1.09 ± 0.33	0.42 ± 0.39	0.13 ± 0.22	0.05 ± 0.21	0.92 ± 0.27*	1.19 ± 0.52***	1.07 ± 0.52***	1.01 ± 0.49***
LED_{LAD} (mm)	10.20 ± 0.31	10.08 ± 0.28	10.31 ± 0.31	10.32 ± 0.28	9.99 ± 0.23*	9.94 ± 0.23*	10.05 ± 0.30*	10.07 ± 0.32*
LES_{LAD} (mm)	8.07 ± 0.30	7.46 ± 0.57	7.53 ± 0.57	7.54 ± 0.53	7.95 ± 0.34*	7.42 ± 0.62	7.42 ± 0.55**	7.49 ± 0.54
SST_{LAD} (mm)	2.14 ± 0.53	2.61 ± 0.65	2.78 ± 0.78	2.78 ± 0.69	2.04 ± 0.43	2.52 ± 0.65	2.63 ± 0.63	2.58 ± 0.60

HR = heart rate; PAS, PAD, PAM = systolic, diastolic and mean arterial pressure; dp/dt_{max} = first derivative of left ventricular pressure; PLVED = left ventricular end-diastolic pressure; MVO_2 = myocardial oxygen demand; DP = rate-pressure product; $LED_{LCX,LAD}$ = end-diastolic segment length in the area supplied by the left circumflex branch or left anterior descending branch respectively; LES = end-systolic segment length; SST = systolic shortening.
As the two pre-drug and the two post-drug runs did not differ significantly, they are expressed as one run in each case. Means ± s.d.; $n = 12$. Asterisks indicate significant differences from respective pre-drug values; t test for paired data; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

signifies an increase in systolic shortening and is the normal myocardial response to work load, end-systolic segment length in the critically perfused posterior wall increased with treadmill exercise, leading to a decrease in systolic shortening (Figure 3, Table 1). This reduction in systolic shortening indicates myocardial dysfunction in the area perfused by the stenosed circumflex branch. All changes returned to pre-exercise values by 3 min at the latest after the end of each exercise cycle.

Haemodynamic and dimensional parameters at rest and during treadmill exercise after nitroglycerin infusion

No clear nitroglycerin-induced changes were seen at rest. Haemodynamic changes induced by treadmill exercise after nitroglycerin infusion were similar to those before nitroglycerin infusion, except that the increase in left ventricular end-diastolic pressure was significantly less pronounced. While the increase in end-diastolic segment length in the normally perfused anterior wall was slightly, although not significantly diminished, i.e. systolic shortening was reduced compared with pre-drug data, the endsystolic length in the posterior wall perfused by the stenosed circumflex branch showed a highly significant reduction at maximum work load, indicative of an increase in systolic shortening, so that myocardial contractile dysfunction in the critically perfused area was completely prevented by nitroglycerin infusion (Figure 3, Table 1). Calculated myocardial oxygen demand showed a slight and insignificant decrease at maximum work load after nitroglycerin compared to pre-drug values.

Haemodynamic and dimensional parameters during isoprenaline stimulation before nitroglycerin infusion

Isoprenaline stimulation led to an increase in heart rate, myocardial oxygen demand, rate-pressure product and positive left ventricular dp/dt_{max}, reaching maximum values 3.2 min after starting the infusion, but negative left ventricular dp/dt_{max} remained unchanged. Diastolic arterial pressure showed a distinct decrease, while systolic arterial pressure was nearly unchanged during isoprenaline infusion. Left ventricular end-diastolic pressure decreased on isoprenaline stimulation. The change was significant only at the beginning of stimulation.

End-diastolic segment length decreased in both the posterior and the anterior wall segment during isoprenaline infusion. End-systolic segment length showed a decrease in the anterior wall, resulting in an increase in systolic shortening, indicative of enhanced contractile function in this area. End-systolic segment length in the posterior wall perfused by the stenosed circumflex branch increased during isoprenaline stimulation, leading to a severe reduction in systolic shortening, indicating myocardial dysfunction during stimulation (Figure 3, Table 2). All changes returned to pre-stimulation values by 3 min at the latest after the end of the isoprenaline infusion.

Haemodynamic and dimensional parameters at rest and during isoprenaline stimulation after nitroglycerin infusion

No nitroglycerin-induced changes were observed at rest. The pattern of haemodynamic and dimensional values was very similar to values before nitroglycerin infusion. There were only isolated significant differences between pre- and post-nitroglycerin values with regard to haemodynamic parameters, but no uniform tendency throughout the whole stimulation period. The only clear effects after nitroglycerin infusion consisted in an almost unchanged end-systolic segment length in the posterior wall during isoprenaline stimulation so that systolic shortening in this area showed a slight increase as compared with values before nitroglycerin infusion (Figure 3, Table 2).

Discussion

Today, many different methods of stress testing are used in the quantification and follow up of coronary heart disease and also in the evaluation of antianginal drugs. Two main principles can be distinguished: physical exercise and pharmacologically induced stress, especially stimulation of adrenoceptors. This study was designed to assess differences in haemodynamic and regional contractile parameters and especially differences in response to antianginal therapy depending on the mode of stimulation. Graded treadmill exercise and isoprenaline infusion were selected as representative models.

Comparability of the treadmill exercise group and the isoprenaline stimulation group

In order to evaluate haemodynamic and regional myocardial contractile differences between stimulation by treadmill exercise and stimulation by isoprenaline infusion, steady state values of parameters representing myocardial energy demand had to be simulated exactly. Since normally used parameters for quantification of stress testing, such as heart rate or rate-pressure product may be non-uniformly influenced by different modes of stimulation, myocardial oxygen demand calculated according to the 'Bretschneider equation' (Bretschneider 1971; Hoeft

Table 2 Haemodynamic and regional functional data during isoprenaline infusion before and after nitroglycerin (15 $\mu g\,kg^{-1}\,15\,min^{-1}$, i.v.)

	Isoprenaline infusion before nitroglycerin				*Isoprenaline infusion after nitroglycerin*			
	0 min	0.8 min	2 min	3.2 min	0 min	0.8 min	2 min	3.2 min
HR (beats min^{-1})	123 ± 10	169 ± 19	185 ± 14	193 ± 12	123 ± 13	170 ± 14	187 ± 17	195 ± 15
PAS (kPa)	15.5 ± 1.0	15.3 ± 1.0†	15.3 ± 1.0†	16.0 ± 1.1†	15.1 ± 0.7	14.8 ± 0.7	15.6 ± 0.8	15.8 ± 1.0
PAD (kPa)	9.7 ± 0.6	7.8 ± 0.8	7.1 ± 0.8†††	7.0 ± 0.8†††	9.8 ± 0.6	8.1 ± 0.8	7.3 ± 0.8	6.8 ± 1.0
PAM (kPa)	12.6 ± 0.7	11.5 ± 0.6†	11.2 ± 0.7††	11.5 ± 0.8††	12.4 ± 0.6	11.5 ± 0.6	11.4 ± 0.6	11.3 ± 0.7
$dp/dt +_{max}$ (kPa s^{-1})	369 ± 82	525 ± 108	603 ± 117	662 ± 126†	354 ± 74*	525 ± 96	627 ± 97	660 ± 104
$dp/dt -_{max}$ (kPa s^{-1})	382 ± 76	382 ± 69	388 ± 81	387 ± 83	367 ± 75**	373 ± 81	377 ± 85	368 ± 94
PLVED (kPa)	1.07 ± 0.42	0.81 ± 0.47†	0.86 ± 0.51†††	0.94 ± 0.57†††	1.18 ± 0.49	0.86 ± 0.42	0.88 ± 0.44	0.99 ± 0.40
MVO_2 (ml O_2 min^{-1} 100 g^{-1})	6.22 ± 1.07	10.48 ± 2.77	12.61 ± 2.73	14.23 ± 3.15	6.01 ± 1.05	10.44 ± 2.17	13.19 ± 2.63	14.31 ± 2.92
DP (kPa min^{-1})	1917 ± 173	2581 ± 364†	2823 ± 291†	3101 ± 347†	1854 ± 211	2514 ± 229	2908 ± 280	3076 ± 316
LED_{LCX} (mm)	10.19 ± 0.37	9.45 ± 0.81††	9.65 ± 0.83††	9.60 ± 0.92††	10.18 ± 0.37	9.35 ± 0.64	9.44 ± 0.71*	9.44 ± 0.76
LES_{LCX} (mm)	9.40 ± 0.34	9.25 ± 0.78††	9.75 ± 0.91	9.87 ± 0.97	9.46 ± 0.43	9.10 ± 0.57	9.33 ± 0.80*	9.27 ± 0.88**
SST_{LCX} (mm)	0.79 ± 0.37	0.20 ± 0.77	−0.10 ± 0.33	−0.26 ± 0.23††	0.72 ± 0.33	0.25 ± 0.39	0.11 ± 0.39*	0.16 ± 0.35***
LED_{LAD} (mm)	10.08 ± 0.63	9.37 ± 0.60††	9.49 ± 0.68†††	9.56 ± 0.54†††	9.96 ± 0.51	9.14 ± 0.47	9.37 ± 0.41	9.40 ± 0.52
LES_{LAD} (mm)	7.99 ± 1.10	6.67 ± 0.92†	6.41 ± 0.86††	6.30 ± 0.78†††	8.03 ± 0.88	6.60 ± 0.86	6.32 ± 0.68	6.16 ± 0.68*
SST_{LAD} (mm)	2.10 ± 0.92	2.69 ± 0.59	3.08 ± 0.53	3.27 ± 0.53	1.92 ± 0.74	2.54 ± 0.80	3.04 ± 0.59	3.24 ± 0.59

HR = heart rate; PAS, PAD, PAM = systolic, diastolic and mean arterial pressure; dp/dt_{max} = first derivative of left ventricular pressure; PLVED = left ventricular end-diastolic pressure; MVO_2 = myocardial oxygen demand; DP = rate-pressure product; $LED_{LCX,LAD}$ = end-diastolic segment length in the area supplied by the left circumflex branch or left anterior descending branch respectively; LES = end-systolic segment length; SST = systolic shortening.

As the two pre-drug and the two post-drug stimulations did not differ significantly, they are expressed as one stimulation in each case. Means ± s.d.; $n = 12$. Daggers indicate significant differences from respective values during treadmill exercise; t test for unpaired data; †$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$. Asterisks indicate significant differences from respective pre-drug values; t test for paired data; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

et al., 1984) was chosen as a reference parameter since myocardial oxygen demand calculated by this means correlates closely ($r = 0.99$) with actual measured oxygen consumption (Baller et al., 1979). There was no statistical difference in calculated myocardial oxygen demand between treadmill exercise and isoprenaline at any level of stimulation. Resting values of haemodynamic and regional functional parameters also showed no statistical significant difference between the two groups.

Haemodynamic and functional differences due to different modes of stimulation

Whereas the reaction of blood pressure to treadmill exercise consisted of an increase in mean arterial pressure due to an increase in systolic pressure, isoprenaline induced a decrease in mean arterial pressure due to a decrease in diastolic pressure. Left ventricular end-diastolic pressure increased during treadmill exercise, but decreased with isoprenaline. Corresponding to this finding, end-diastolic segment lengths in both the anterior and the posterior wall which also are a rough measure of overall left ventricular volume, increased during treadmill exercise and decreased during isoprenaline infusion. The increase in negative dp/dt_{max} occurred only during treadmill exercise. The posterior wall that showed normal myocardial function at rest, developed severe contractile dysfunction during exercise or isoprenaline infusion, due to an increase in heart rate and left ventricular contractility. In the dogs subjected to treadmill exercise, an increase in arterial blood pressure and left ventricular end-diastolic pressure during exercise (McLaurin et al., 1973; Barry et al., 1974; Rentrop et al., 1976) may contribute to the regional contractile dysfunction in the critically perfused area. In the dogs subjected to isoprenaline infusion, the development of myocardial dysfunction may be facilitated by a decrease in coronary perfusion pressure due to a decrease in diastolic arterial pressure and coronary steal phenomenon (Cohen et al., 1976a; McClenathan et al., 1977).

These differences in haemodynamic and regional functional parameters during treadmill exercise or pharmacological challenge are due to stimulation of different adrenoceptor subtypes. The infusion of isoprenaline leads to stimulation of β-adrenoceptors only, whereas treadmill exercise leads to a stimulation of both α- and β-adrenoceptors via an enhanced sympathetic tone and adrenal catecholamine release (Kirlin et al., 1987).

Different responses to nitroglycerin

After nitroglycerin infusion ($15\,\mu g\,kg^{-1}\,15\,min^{-1}$, i.v.), contractile dysfunction during exercise in the critically perfused posterior wall was completely abolished and this area showed a near normal reaction, i.e. an increase in systolic shortening during exercise. This may be associated with improved subendocardial perfusion consequent to a decrease in preload and left ventricular end diastolic pressure (Smith et al., 1984). A coronary vasodilator effect leading to this functional improvement via an increase in collateral flow to an ischaemic area (Cohen et al, 1976b) could not be quantified under our experimental conditions.

This impressive improvement in regional contractile function during treadmill exercise following nitroglycerin contrasts with the much less pronounced effect of this drug on regional function in the underperfused myocardial area when isoprenaline is employed for stimulation. A reduction in arterial blood pressure through arterial vasodilatation, as well as a reduction in preload and left ventricular end-diastolic pressure by venous dilatation induced by isoprenaline may explain the inability of nitroglycerin to abolish isoprenaline-induced myocardial dysfunction through its vasodilator potency, since these mechanisms are already maximally activated by stimulation of vascular β-adrenoceptors.

Clinical implications

Since the haemodynamic effects of stress testing and the therapeutic effect of nitroglycerin differed in the present study according to the experimental set up, it must be concluded that clinical antianginal drug testing is likely to be similarly highly dependent on the test method chosen. In view of the multifactorial nature of angina pectoris in man, it is most important to use methods mimicking the complex physiological and pathophysiological reactions of human disease as closely as possible. Furthermore, a relevant evaluation of the course of disease in patients with coronary artery disease can only be guaranteed if the pathophysiological principles used in diagnostic stress testing are comparable to those which induce angina pectoris spontaneously, i.e. physical or psychological stress.

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