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The effects of nitroglycerin on exercise-induced regional myocardial contractile dysfunction are not diminished by pretreatment with dihydroergotamine

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1 Because controversy exists regarding the effects of dihydroergotamine (DHE) on the performance of underperfused myocardium, the effects of DHE were investigated in a model of exercise-induced regional myocardial dysfunction in conscious dogs.

2 We also investigated a possible functional antagonism between DHE and nitroglycerin that might reduce the latter drug's antianginal efficacy.

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

4 DHE (5 $\mu g\,kg^{-1}$, i.v.) induced a decrease in left ventricular dp/dt_{max} at rest and during exercise. DHE did not cause a deterioration in contractile function in the ischaemic myocardium, but led to a slight although not significant improvement in regional myocardial function.

5 After pretreatment with DHE, infusion of nitroglycerin (15 $\mu g\,kg^{-1}$, i.v.) induced an improvement in the underperfused myocardial area during treadmill exercise, accompanied by a decrease in diastolic arterial pressure and left ventricular end-diastolic pressure and an increase in left ventricular dp/dt_{max}.

6 These results suggest that DHE will not worsen exercise-induced angina pectoris, and that the antianginal efficacy of nitroglycerin will not be neutralized by pretreatment with DHE.

Introduction

The vasoactive potency of ergot alkaloids via stimulation and inhibition of receptors in the peripheral sympathetic nervous system has been known for a long time (Dale, 1906). Concerning the vasoactive effects of dihydroergotamine, both stimulation and blockade of α-adrenoceptors (Gatzek *et al.*, 1949) and influences on prostaglandin- or 5-hydroxytryptamine-induced mechanisms have been implicated (Berde & Stürmer, 1978; Müller-Schweinitzer, 1974; 1983; 1984a; Müller-Schweinitzer & Brundell, 1975). Indeed, the therapeutic use of DHE in orthostatic syndrome, postural hypotension, venous insufficiency (Nordenfelt & Mellander, 1972; Krüger & Neff, 1973; Stürmer, 1976), in prevention of migraine attacks (Neumann *et al.*, 1986), and as a vasopressor during epidural anaesthesia (Stanek *et al.*, 1980; Zimpfer *et al.*, 1981) is based on this vasoconstrictor potency. Hence it is commonly assumed that ergot compounds are contraindicated in coronary artery disease patients. We have previously shown in our laboratory that DHE reduced myocardial oxygen consumption in normally perfused myocardium (Raberger *et al.*, 1981), improves myocardial metabolism, i.e. markedly reduces lactate release in underperfused myocardium (Seitelberger *et al.*, 1984b), and shows a beneficial effect on regional function in underperfused myocardial areas during isoprenaline-induced cardiac stimulation in anaesthetized dogs (Seitelberger *et al.*, 1984a). Since these data contradict clinical opinion (Sievert & Bussmann, 1986), it was one objective of the present study to assess the effects of DHE on haemodynamics and regional myocardial function in a model of exercise-induced regional myocardial dysfunction in chronically instrumented conscious dogs (Raberger *et al.*, 1986).

Since a functional antagonism to coronary vasodilatation by intravenous administration of DHE was shown in a previous study (Raberger *et al.*, 1976),

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the second objective of this investigation was to assess a possible functional antagonism between DHE and nitroglycerin-induced vasodilatation, which might reduce the antianginal effect of nitroglycerin.

Methods

The study was carried out in 6 mongrel dogs of either sex, weighing between 17 and 32 kg. The animals were vaccinated with Candivac DHL (distemper, hepatitis, leptospirosis, rabies) and Candur P (parvovirosis). The dogs received 'Loyal' dry food (Tagger, Graz) as standard diet. Prior to instrumentation the dogs were trained to run on a treadmill (Quinton model 1854). In order to accustom the animals to the specific exercise performance, identical time protocols and work load changes (see experimental procedure) were used for the training and 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 one hour 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. A sterile thoracotomy was performed 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 in order to place a hydraulic occluder around the vessel. A Konigsberg microtip manometer was inserted into the left ventricle via the apex. Subsequently two pairs of piezoelectric crystals were implanted subendocardially for ultrasonic distance measurements (Gilly *et al.*, 1983), one pair in the perfusion area of the left circumflex branch (LCX), the other in the area supplied by the left anterior descending coronary artery (LAD). Measurements of the arterial blood pressure were carried out by means of a catheter (Tygon) advanced into the descending aorta via the left carotid artery. A catheter advanced from the left jugular vein into the right atrium served for drug infusions. All catheters and wires were exteriorized between the scapulae, and the pericardium and thorax were closed. The animals were monitored postoperatively and propranolol, lidocaine, flunitrazepam and methadone were administered as required overnight. Ampicillin 0.5 g was given for four days twice a day beginning on the day before surgery. The dogs recovered completely within a couple of days, but the investigations were started only one week after surgery. Subendocardial placement of ultrasonic transducers was confirmed post mortem.

Heart rate (derived from left ventricular pressure), systolic and diastolic arterial pressure (Statham pressure transducer), left ventricular positive and negative dp/dt_{max}, (Konigsberg-microtip, HSE physio differentiator) and the LCX and LAD segment shortening signals were recorded on a Watanabe 6-channel recorder. For assessmentof myocardial function in the LCX- and LAD area, end-diastolic segment length (LED) was determined when left ventricular pressure started to rise. Endsystolic segment length (LES) was determined at the point of maximal shortening during the ejection phase. Systolic shortening (SST = LED − LES) provides an accurate assessment of changes in regional contractile performance (Battler *et al.*, 1980; Brugge-Asperheim *et al.*, 1969; Gallagher *et al.*, 1982; Tomoike *et al.*, 1978). The segment length was normalized according to Theroux *et al.* (1976).

Pre-exercise values were taken 0.5 min before starting the treadmill (C-TE). 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%, then for 1.2 min at 8 km h^{-1} and 8% and another 1.2 min at 10 km h^{-1} and 10%. 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 an 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 the exercise. Exercise runs of 4 min were followed by recovery periods of 11 min, giving exercise cycles of 15 min duration (Figure 1, upper diagram). LCX narrowing was performed by external filling of the hydraulic occluder 2–3 min after a warm up exercise. Prior to this study all dogs were subjected to the above mentioned protocol for 7 consecutive exercise cycles using a constant degree of transient LCX stenosis and showed regional contractile dysfunction of comparable magnitude in the LCX area during all 7 exercise cycles with complete recovery in the intervening periods. Hence stenosis was considered adequate when two subsequent runs following the narrowing exhibited exercise induced dysfunctional episodes of comparable intensity in the LCX area, thus indicating that spontaneous improvement of function was not taking place; stenosis was then maintained at this degree throughout the experimental period.

Previous studies conducted in this laboratory have shown that DHE in a dose of 2 μg kg^{-1}, i.v. did not affect microsphere-assessed regional blood flow in myocardial areas with severe underperfusion (Seitelberger *et al.*, 1984b), whereas DHE given in a dose of 10 μg kg^{-1} i.v. exhibited intense haemodynamic effects (Raberger *et al.*, 1981). For that reason DHE was administered intravenously at a dose of 5 μg kg^{-1} i.v. which corresponds to a clinical dose of ¼ to ½ ampoule in man. The infusion (5 ml per 5 min) was started 5 min after the end of the second run. After two further runs

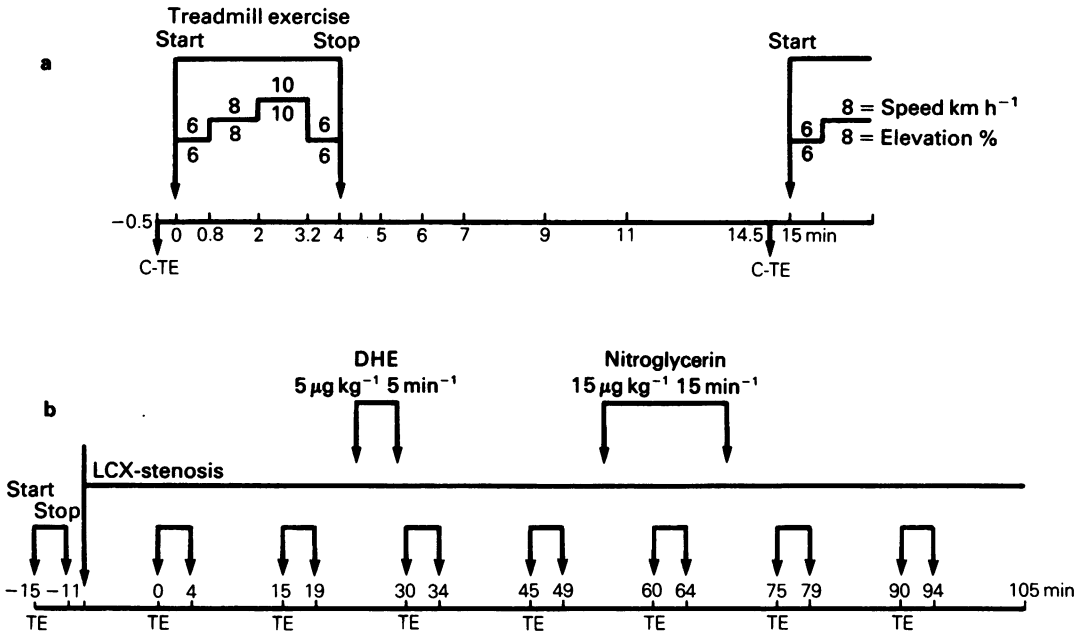

Figure 1 Time protocol for a single experiment: (a) single exercise cycle; (b) time protocol of a complete experiment. TE = treadmill exercise.

nitroglycerin was administered intravenously at a dosage of 15 $\mu g\,kg^{-1}$. This dose has been shown to improve function in underperfused myocardial areas in a similarly designed investigation (Schneider *et al.*, 1987). The infusion (15 ml per 15 min) began 5 min after the end of the fourth run and finished 5 min after the end of the fifth run. Subsequently two further runs were performed (Figure 1, lower diagram). The occluder was completely evacuated after each experiment.

Student's *t* test for paired data was used for statistical analysis.

Results

Control treadmill exercise

After a warm up exercise and critical stenosis of the LCX by filling the hydraulic occluder, two control runs were performed on the treadmill. Exercise led to an increase in heart rate, systolic arterial pressure, positive and negative left ventricular dp/dt_{max} and left ventricular end-diastolic pressure, all 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 2 min after the start of the treadmill. All changes returned to pre-exercise control values by 3 min indicating a rapid recovery after the end of each exercise cycle (Figures 2, 3).

End-diastolic segment length increased slightly in both the LCX and LAD supplied area with rising treadmill work load. Endsystolic segment length decreased during exercise in the LAD supplied area, indicating an increase in systolic shortening and a normal myocardial response to work load. In contrast, endsystolic segment length in the critically perfused LCX area increased with treadmill exercise, leading to a reduction of systolic shortening which indicates myocardial dysfunction in the area perfused by the stenosed LCX (Figures 3, 4, 5). Changes in these parameters returned to pre-exercise values within 3 min after the end of each exercise cycle.

Treadmill exercise after dihydroergotamine

After infusion of DHE, pre-exercise resting values showed no alterations except for a decrease in systolic blood pressure and in positive and negative dp/dt_{max}. The basic pattern of haemodynamic changes induced by treadmill exercise was similar to that before drug

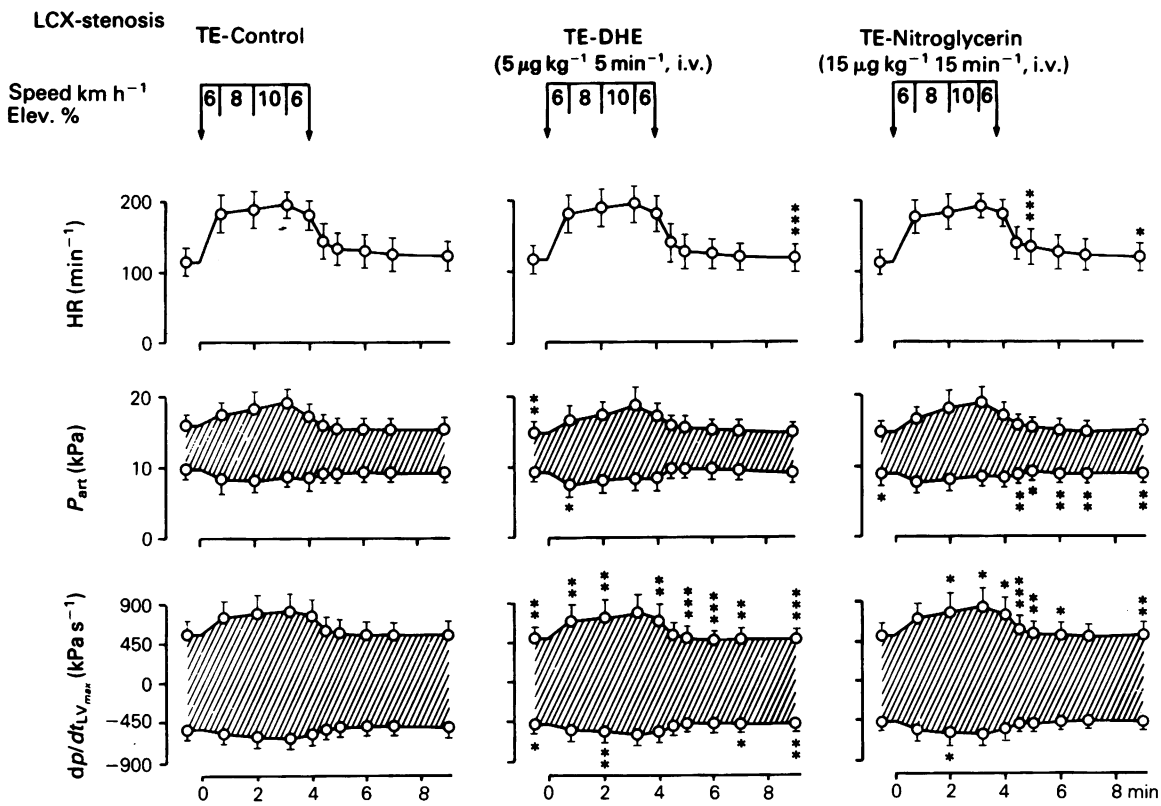

Figure 2 Haemodynamic parameters in dogs at rest and during exercise. Since the two exercise cycles before drug infusion were not significantly different from each other, they are expressed as one cycle (TE-Control). For the same reason the two exercise cycles after infusion of dihydroergotamine (DHE) and nitroglycerin are expressed as single exercise cycles respectively (TE-DHE, TE-Nitroglycerin). The asterisks indicate significant differences from the corresponding moment in the preceding exercise cycle. Values are mean ± s.d.; $n = 12$; t test for paired data; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

infusion. In contrast to pre-drug values, the decrease in diastolic blood pressure was more pronounced. With the exception of the unaltered peak value at maximum work load, positive dp/dt_{max} was reduced throughout the whole run compared to pre-drug control runs. Also negative dp/dt_{max} showed a decrease during and after the treadmill exercise compared to values before DHE infusion (Figure 2). The exercise-induced increase in left ventricular end-diastolic pressure was reduced 0.8 min after initiation of the run, but the normalization of end-diastolic pressure lasted significantly longer (Figure 3). While DHE did not induce significant changes in the critically perfused LCX area, systolic shortening showed a decrease in the LAD area (Figures 3, 4, 5).

Treadmill exercise after nitroglycerin

After nitroglycerin infusion resting values of diastolic blood pressure and endsystolic segment length in the LAD area were reduced. Positive and negative dp/dt_{max} showed an increase compared to the exercise cycles after DHE and nearly reached control values obtained before DHE infusion (Figure 2). After nitroglycerin, left ventricular end-diastolic pressure was reduced at exercise and during the following resting period (Figure 3). In the normally perfused LAD area, both end-diastolic and endsystolic segment length were reduced after nitroglycerin. In the area perfused by the stenosed LCX branch the endsystolic length showed a highly significant reduction at work load and after

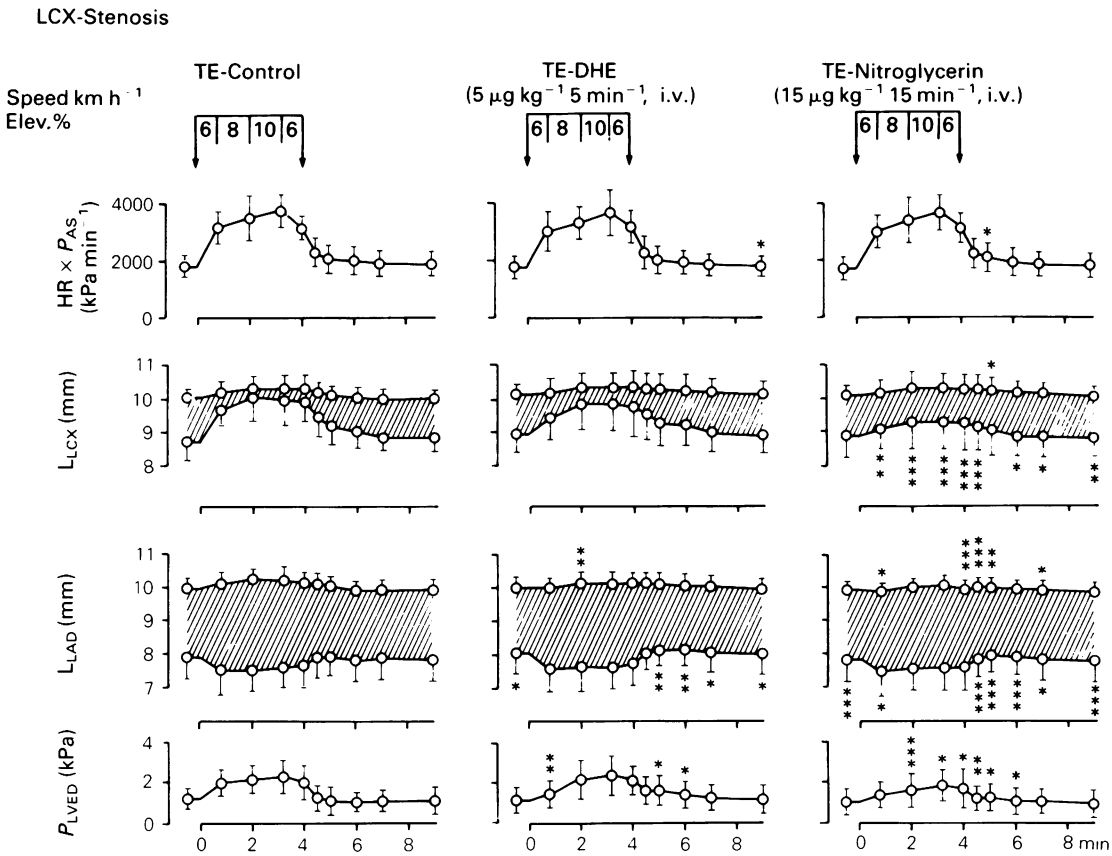

Figure 3 Haemodynamic and functional parameters in dogs at rest and during exercise. Since the two exercise cycles before drug infusion were not significantly different from each other, they are expressed as one cycle (TE-Control). For the same reason the two exercise cycles after infusion of dihydroergotamine (DHE) and nitroglycerin are expressed as single exercise cycles respectively (TE-DHE, TE-Nitroglycerin). The asterisks indicate significant differences from the corresponding moment in the preceding exercise cycle. In functional parameters (L_{LCX}, L_{LAD}) the upper points represent the end-diastolic segment length and the lower points the endsystolic segment length; the height of the hatched area corresponds to systolic shortening.
Values are mean ± s.d.; $n = 12$; t test for paired data; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

the treadmill run, indicative of an increase in systolic shortening, so that myocardial contractile dysfunction in the critically perfused area was markedly reduced by nitroglycerin infusion (Figure 3, 4, 5).

Discussion

In our experiments episodes of myocardial dysfunction were provoked in chronically instrumented conscious dogs by transient stenosis of the LCX branch of the left coronary artery and treadmill exercise. After infusion of DHE (5 μg kg^{-1}, i.v.), a dosage that is similar to an application of ¼ to ½ ampoule of DHE in man, no effects were observed on myocardial function in the ischaemic LCX area, although highly significant alterations occurred in myocardial overall performance, i.e. a decrease in positive and negative left ventricular dp/dt_{max}. This decrease of contractility after DHE could be attributed to a presynaptic inhibition of noradrenaline release from cardiac sympathetic nerves as shown by Saxena & Cairo-Rawlins (1979) in the case of ergotamine, but the failure to decrease heart rate makes a presynaptic effect of DHE difficult to explain. An alternative explanation for the decreased left ventricular dp/dt_{max} may be a direct negative

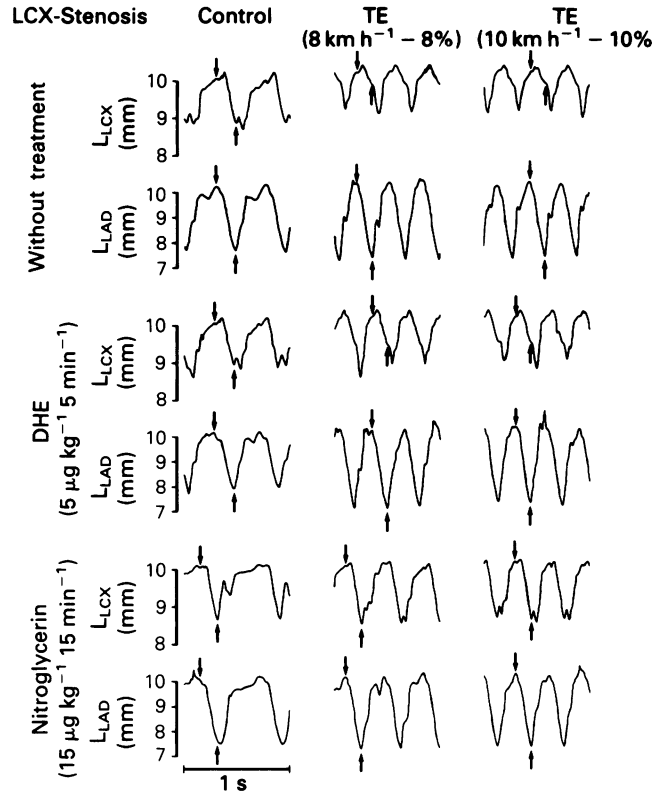

Figure 4 Original recordings of regional segmental shortening. Regional systolic shortening of the LCX area (SS_T-LCX) or LAD area (SS_T – LAD) corresponds to the distance between end-diastolic length (LED: ↓) and end-systolic length (LES: ↑)

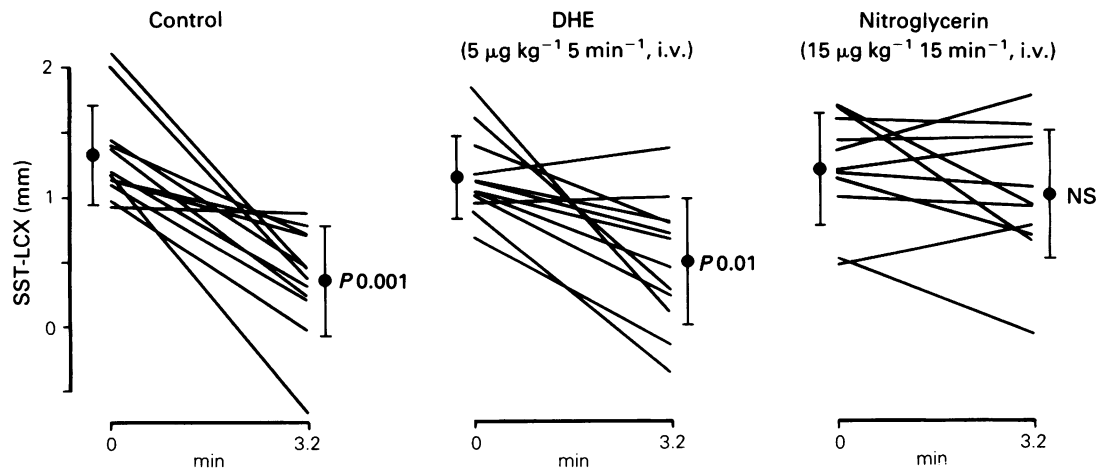

Figure 5 Systolic segmental shortening in the LCX area (SS_T – LCX) before and during treadmill exercise (LCX-stenosis, 10 km h^{-1} – 10%). Since the two exercise cycles before drug infusion were not significantly different from each other, they are expressed as one cycle (Control). For the same reason the two exercise cycles after infusion of dihydroergotamine (DHE) and nitroglycerin are expressed as single exercise cycles respectively (DHE, Nitroglycerin). Values are mean ± s.d.; $n = 12$; t test for paired data.

Table 1 Haemodynamic and functional parameters at rest and exercise-induced changes in the dog: effects of dihydroergotamine (DHE) and nitroglycerin (Nitro).

	Resting values			*Exercise-induced changes*		
	Control	*DHE*	*Nitro*	*Control*	*DHE*	*Nitro*
HR (min^{-1})	115 ± 5	117 ± 4	114 ± 4	+74 ± 3	+77 ± 3	+79 ± 10
P_{AS} (kPa)	16.0 ± 0.3	15.0 ± 0.3**	15.0 ± 0.3	+3.2 ± 0.4	+3.8 ± 0.5	+4.0 ± 0.4
P_{AD} (kPa)	9.8 ± 0.2	9.4 ± 0.2	8.9 ± 0.4*	−1.1 ± 0.8	−1.0 ± 0.3	−0.3 ± 0.4
dp/dt_{+max} ($kPas^{-1}$)	561 ± 32	501 ± 25**	525 ± 28	+267 ± 24	+292 ± 30	+317 ± 34
dp/dt_{-max} ($kPas^{-1}$)	520 ± 21	476 ± 17*	466 ± 12	+107 ± 17	+122 ± 20	+145 ± 21
P_{LVED} (kPa)	1.20 ± 0.10	1.16 ± 0.14	1.00 ± 0.14	+1.11 ± 0.20	+1.17 ± 0.17	+0.84 ± 0.14
LED_{LCX} (mm)	10.05 ± 0.05	10.13 ± 0.07	10.09 ± 0.06	+0.27 ± 0.12	+0.22 ± 0.06	+0.22 ± 0.07
LES_{LCX} (mm)	8.72 ± 0.13	8.96 ± 0.14	8.88 ± 0.16	+1.24 ± 0.22	+0.90 ± 0.18*	+0.42 ± 0.16**
SST_{LCX} (mm)	1.33 ± 0.11	1.17 ± 0.09**	1.21 ± 0.12	−0.97 ± 0.16	−0.68 ± 0.16*	−0.20 ± 0.13**
LED_{LAD} (mm)	9.99 ± 0.05	10.01 ± 0.07	9.91 ± 0.05	+0.22 ± 0.07	+0.11 ± 0.05	+0.15 ± 0.06
LES_{LAD} (mm)	7.90 ± 0.16	8.05 ± 0.16*	7.81 ± 0.17***	−0.29 ± 0.04	−0.44 ± 0.07*	−0.24 ± 0.06**
SST_{LAD} (mm)	2.09 ± 0.20	1.96 ± 0.19**	2.09 ± 0.20*	+0.51 ± 0.08	+0.55 ± 0.08	+0.40 ± 0.07
DP ($kPa*min^{-1}$)	18.4 ± 0.9	17.6 ± 0.8	17.1 ± 0.8	+18.1 ± 0.9	+19.0 ± 1.3	+19.6 ± 0.8

The asterisks indicate significant differences to the corresponding moment in the preceding exercise cycle.
Values are mean ± s.e.mean; $n = 12$; t test for paired data. For abbreviations, see text.

inotropic effect of DHE through blockade of myocardial α_1-adrenoceptors (Brückner *et al.*, 1985; Mügge, 1985). This is also unlikely, since canine myocardium has relatively few α_1-adrenoceptors compared to other species (Mukherjee *et al.*, 1983). However, with this decrease in contractility one might expect an improvement in myocardial function; in this case the almost unchanged dysfunction may be explained by the counteracting increase in preload after DHE. Surprisingly, systolic and diastolic arterial blood pressure showed a slight but significant decrease after infusion of DHE while in most previous studies DHE induced at least a transient increase in blood pressure. Since Aellig & Berde (1969) showed that the efficacy of ergot compounds is dependent on the pre-existing vascular resistance, the decrease in peripheral blood pressure could be attributed to a preponderance of the α-blocking activity in peripheral arterial vessels. This might be due to a higher sympathetic tone in conscious dogs subjected to a treadmill exercise compared to anaesthetized animals.

The second phase of the experiment was designed to study the efficacy of nitroglycerin under premedication with DHE. In this phase the full vasoactive effect of DHE was guaranteed, as the vasconstrictor response starts about 1 min after injection of DHE and remains stable for more than 90 min (Müller-Schweinitzer, 1984b). After infusion of nitroglycerin, myocardial function showed an improvement in the underperfused LCX-supplied area during exercise, i.e. an increase in systolic shortening, similar to data in a previous study (Schneider *et al*, 1987). This improvement in function was accompanied by a decrease in diastolic arterial pressure and in left ventricular end-diastolic pressure pointing at possible mechanisms involved (Smith *et al.*, 1984; Hermann *et al.*, 1986). The increase in left ventricular dp/dt_{max} seems to be the result of the restored myocardial function in the critically perfused area.

The haemodynamic effects of DHE, namely an increase in pre- and afterload, and reduction in coronary perfusion, led Sievert & Bussmann (1986) to warn against the simultaneous application of DHE and nitroglycerin in the treatment of angina pectoris. Despite this possible functional antagonism of these drugs, we could not show a weakening or neutralization of the efficacy of nitroglycerin in myocardial dysfunction after pretreatment with DHE. In addition to this, DHE alone did not cause a deterioration of contractile function in the ischaemic myocardium, but led to a slight although not significant improvement in regional myocardial function.

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