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Comparison of the haemodynamic effects of the selective bradycardic agent UL-FS 49, with those of propranolol during treadmill exercise in dogs

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1 To clarify whether the bradycardic agent UL-FS 49 exhibits a positive inotropic effect even in the absence of improvement in regional myocardial function of an underperfused myocardial area, this study was undertaken in dogs with unimpaired coronary flow.

2 We also investigated the haemodynamic and functional effects of the negative chronotropic and inotropic β-adrenoceptor blocker propranolol.

3 UL-FS 49 did not depress total or regional myocardial performance. Moreover, an increase in positive left ventricular *dp/dt max* at rest suggests a positive inotropic effect of UL-FS 49.

4 Propranolol, in contrast to UL-FS 49, led to a marked reduction in positive *dp/dt max*, stroke volume and systolic wall thickening at rest and during exercise. Additionally, propranolol decreased the exercise values of cardiac output, left ventricular work and left ventricular power to a far greater extent than UL-FS 49.

5 In contrast to propranolol, the selective bradycardic agent UL-FS 49 did not decrease total or regional ventricular performance and caused less reduction in cardiodynamic parameters during exercise.

6 These results suggest that patients with moderate coronary insufficiency or patients with coronary vessel disease and mild left ventricular failure may attain a higher exercise limit under selective bradycardia with UL-FS 49 in comparison to that possible with a β-adrenoceptor antagonist, such as propranolol.

Introduction

The so-called selective bradycardic agents alinidine and UL-FS 49 (1,3,4,5-tetra-hydro-7,8-dimethoxy-3-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-methylimino]-propyl]-2H-3-benzazepin-2-on-hydro-chloride) lower heart rate by mechanisms other than cardiac β-adrenoceptor blockade (Kobinger *et al.*, 1979; Kobinger & Lillie, 1984; Lillie & Kobinger, 1986) or calcium channel blockade (Lillie & Kobinger, 1987). As a mode of action for alinidine and possibly also for UL-FS 49, effects on anionic channels (Millar & Vaughan Williams, 1981) or on the I_f channel have been proposed (Bouman *et al.*, 1985; Snyders & Van Bogaert, 1985). In recent experiments with a canine model of exercise-induced angina pectoris (Raberger *et al.*, 1986), we found that both bradycardic agents and the β-adrenoceptor antagonist propranolol can abolish regional exercise-induced contractile dysfunction in an underperfused myocardial area (Krumpl *et al.*, 1986a; Mayer *et al.*, 1986; Raberger *et al.*, 1987). This observation was recently confirmed for UL-FS 49 in exercising dogs with collateral-dependent perfusion of the posterior myocardial wall (Guth *et al.*, 1987). It is noteworthy that the purely negative chronotropic agent UL-FS 49 improved regional myocardial function in a comparable manner to that of the β-adrenoceptor blocker propranolol and alinidine (Krumpl *et al.*, 1986b). This has been attributed to the marked reduction in exercise-induced increase in heart rate observed with UL-FS 49. The bradycardic effect could be expected to reduce myocardial oxygen consumption (Laurent *et al.*, 1956; Berglund *et al.*, 1958; Sonnenblick *et al.*, 1968; Boerth *et al.*, 1969) and to increase diastolic coronary perfusion time (Boudoulas *et al.*, 1979). Since regional function can also influence positive left ventricular *dp/dt max* (Theroux *et al.*, 1976;

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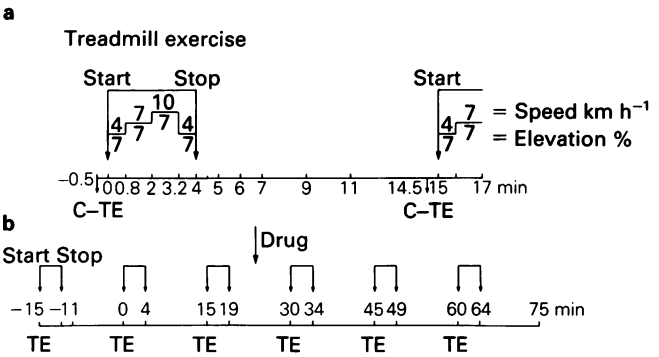

Figure 1 Time protocol of a single experiment. (a) Single exercise cycle, (b) time protocol of a complete experiment. Abbreviations: TE = treadmill exercise, C-TE = pre-exercise control.

Sasayama *et al.*, 1981; Akaishi *et al.*, 1985), the question remained whether the lack of a negative inotropic effect or even a positive inotropic effect of UL-FS 49 (Raberger *et al.*, 1987) was, at least to some extent, due to the UL-FS 49-induced improvement of regional contractile function.

Thus, the aim of the study was to investigate the effects of UL-FS 49 on total and regional ventricular performance in dogs with unimpaired coronary flow at rest and during exericse. These results were compared with the haemodynamic and functional changes obtained with propranolol, a β-adrenoceptor blocker, at a dose causing a comparable reduction in heart rate.

Methods

The study was carried out in 6 mongrel dogs of either sex, weighing between 17 and 35 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 opened. A Konigsberg microtip manometer was inserted into the left ventricle via the apex. A pair of piezoelectric crystals was implanted for measurement of wall thickening of the anterior left ventricular wall (Gallagher *et al.*, 1983; Gilly *et al.*, 1983). Subsequently an electromagnetic flow probe was placed around the pulmonary artery. A Tygon-catheter was inserted into the left atrium to calibrate end diastolic pressure which was derived from left ventricular pressure. Measurements of arterial blood pressure were carried out by means of a Tygon-catheter advanced into the descending aorta via the left carotid artery. Another catheter advanced from the left jugular vein into the right atrium served for drug infusion. All catheters and wires were exteriorized between the scapulae and the thorax was closed. The animals were monitored postoperatively and propranolol, lignocaine, 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 commenced only one week after surgery. Proper placement of the ultrasonic transducers was confirmed *post-mortem*.

Heart rate (derived from the left ventricular pressure signal), systolic and diastolic arterial pressure (Statham pressure transducer), left ventricular positive and negative *dp/dt max* (Konigsberg microtip manometer, HSE physio differentiator) and wall thickening (piezoelectric crystals, ultrasonic gauge) were recorded on a Watanabe 6-channel recorder. The end diastolic wall thickness was normalized according to Theroux *et al.* (1974).

Experimental protocol (Figure 1)

Pre-exercise values were taken 0.5 min before starting the treadmill (C-TE). The load was changed stepwise during the runs. At a constant treadmill

Table 1 Haemodynamic and functional parameters at rest (Rest) and during maximal exercise (Run)

	Rest			*Run*		
	Control	*Propranolol*	*UL-FS 49*	*Control*	*Propranolol*	*UL-FS 49*
HR (beats min^{-1})	119 ± 4	121 ± 5	100 ± 5††† **	176 ± 5	154 ± 4 ***	143 ± 5† ***
BP_{AS} (kPa)	14.7 ± 0.3	14.8 ± 0.4	14.9 ± 0.5†††	19.3 ± 0.4	16.8 ± 0.6 **	18.3 ± 0.8†
BP_{AD} (kPa)	9.0 ± 0.3	10.2 ± 0.5	8.33 ± 0.3†††	8.7 ± 0.4	8.8 ± 0.4	8.2 ± 0.6
HR × BP_{AS} (:100)	17.5 ± 0.7	18.0 ± 1.0	14.9 ± 0.9 *	34.3 ± 0.4	25.9 ± 1.1 **	26.2 ± 1.6 **
P_{LVED} (kPa)	0.59 ± 0.10	0.90 ± 0.11 **	0.72 ± 0.11	0.83 ± 0.04	1.50 ± 0.15 **	1.25 ± 0.12 **
dp/dt max + (kPa s^{-1})	527 ± 23	442 ± 32 **	628 ± 44††† **	959 ± 47	523 ± 37 ***	977 ± 69†††
dp/dt max − (kPa s^{-1})	497 ± 16	470 ± 17	523 ± 32†	650 ± 43	503 ± 28 ***	640 ± 56††
CO (l min^{-1})	2.41 ± 0.13	2.09 ± 0.20 ***	2.16 ± 0.09	4.39 ± 0.24	2.94 ± 0.25 ***	3.74 ± 0.15†† *
SV (ml)	20.9 ± 1.5	18.3 ± 2.7 **	21.2 ± 1.4	25.6 ± 1.8	19.4 ± 2.1 **	26.4 ± 0.1††
Work (mJ)	233 ± 17	206 ± 28 **	230 ± 16	333 ± 22	225 ± 32 ***	315 ± 14††
Power (mW)	450 ± 26	394 ± 33 **	374 ± 19 **	958 ± 53	564 ± 65 ***	745 ± 45† ***
TPR (m units)	5.19 ± 0.27	6.60 ± 0.68 **	5.81 ± 0.38	3.42 ± 0.20	4.64 ± 0.34 ***	3.60 ± 0.20††
WT (mm)	1.45 ± 0.08	1.14 ± 0.08 **	1.57 ± 0.25†††	1.95 ± 0.10	1.11 ± 0.09 ***	2.07 ± 0.35†††

Control: combination of all respective control runs before drug administration (see also Figures 2–5). Values are mean ± s.e. mean ($n = 12$); t test for paired data; significance symbols: †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ for comparison of propranolol with UL-FS 49; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for comparison of propranolol or UL-FS 49 with the corresponding control exercise cycle.
Abbreviations: HR = heart rate, BP_{AS} = arterial systolic blood pressure, BP_{AD} = arterial diastolic blood pressure, HR × BP_{AS} = double product, P_{LVED} = left ventricular end diastolic pressure, *dp/dt max*+ = rate of increase in left ventricular pressure, *dp/dt max*− = rate of decrease in left ventricular pressure, CO = cardiac output, SV = left ventricular stroke volume, Work = left ventricular stroke work, Power = left ventricular minute work, TPR = total peripheral resistance, WT = systolic wall thickening.

elevation of 7% the dogs were exercised for 0.8 min at a speed of 4 km h^{-1}, then for 1.2 min at 7 km h^{-1} and for another 1.2 min at 10 km h^{-1}. 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 4 km h^{-1}. Consequently, exercise parameters were recorded 0.8, 2, 3.2, and 4 min after the start. Haemodynamic data for the recovery period were registered 4.5, 5, 6, 7, and 9 min after initiation of the exercise. Thus, exercise runs of 4 min were followed by recovery periods of 11 min, giving exercise cycles of 15 min duration (Figure 1a). The dogs were subjected to the above mentioned protocol for 6 consecutive exercise cycles (Figure 1b). The first exercise cycle was a warm-up run. The second and third cycles served as controls within the experiment. Propranolol (1 mg kg^{-1}) or UL-FS 49 (0.5 mg kg^{-1}) was infused intravenously over 5 min, after termination of the second run. The following third exercise cycle, which started when drug distribution had not achieved equilibrium, was not evaluated. Thus, drug effects were analysed during the fifth and sixth exercise cycle which were started 21 and 36 min after commencement of infusion. The drugs were randomly assigned to the individual dogs. A period of three days was left between the experiments to allow complete elimination of the drugs. Student's t test for paired data was used for statistical analysis.

Results

Haemodynamic and functional data at rest and during exercise before drug administration are presented in Figures 2a and 3a (propranolol), 4a and 5a (UL-FS 49).

The values of the control runs before propranolol and UL-FS 49 administration exhibited no statistical difference; thus, they were pooled and expressed as one pre-drug control run in Table 1 (Control). The resting values (Rest) and the values during exercise at

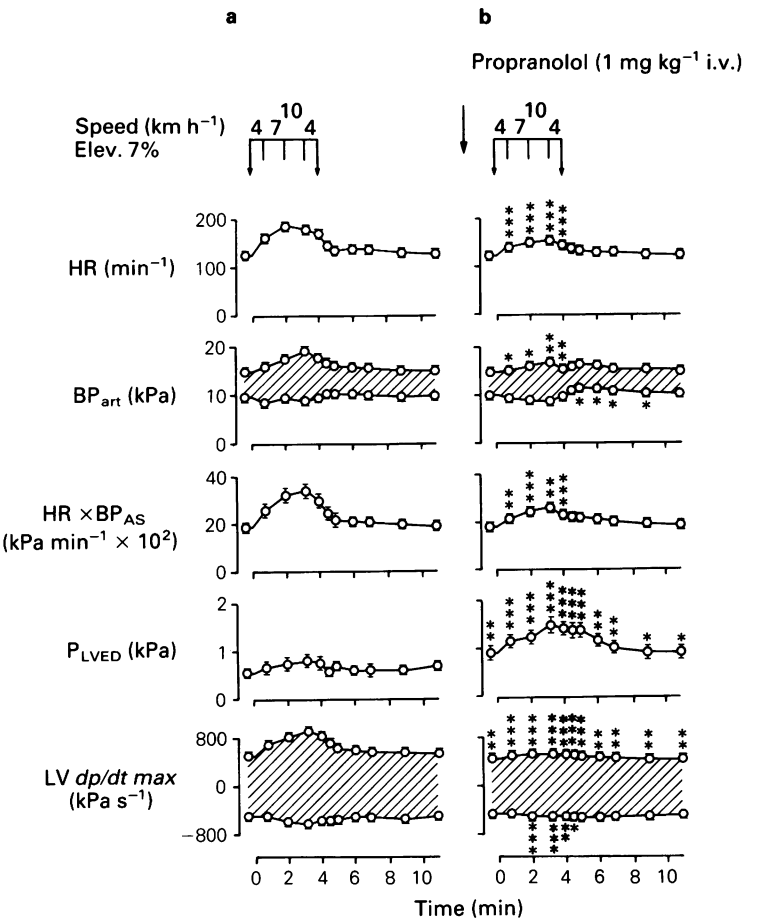

Figure 2 Haemodynamic parameters at rest and during exercise (values are mean and vertical lines s.e. mean, $n = 12$). The two exercise cycles before administration of propranolol did not differ statistically and were expressed as one exercise cycle (a). For the same reason the second and third exercise cycle after propranolol administration were expressed as one post drug exercise cycle (b). The asterisks indicate significant differences from the corresponding moment of the control exercise cycle (t test for paired data; significance symbols: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). Abbreviation: BP_{art} = arterial blood pressure. For further abbreviations see Table 1.

maximal work load (Exercise) are also given in Table 1.

During exercise, all haemodynamic variables were changed in a load-dependent manner. Heart rate, systolic blood pressure, left ventricular end diastolic pressure, positive and negative *dp/dt max*, cardiac output, stroke volume, left ventricular work, left ventricular power and systolic wall thickening were increased while total peripheral resistance was decreased. Diastolic blood pressure remained almost unchanged.

The effects of propranolol ($1\,mg\,kg^{-1}$, i.v.) are demonstrated in Figures 2b and 3b. Values at rest and during maximal exercise are also presented, numerically, in Table 1.

At rest, propranolol decreased positive *dp/dt max*, cardiac output, stroke volume, left ventricular work, left ventricular power and systolic wall thickening and increased left ventricular end diastolic pressure and total peripheral resistance.

During exercise, propranolol decreased heart rate, systolic blood pressure, double product, positive and negative *dp/dt max*, cardiac output, stroke volume, left ventricular work, left ventricular power and systolic wall thickening and increased left ventricular end diastolic pressure and total peripheral resistance.

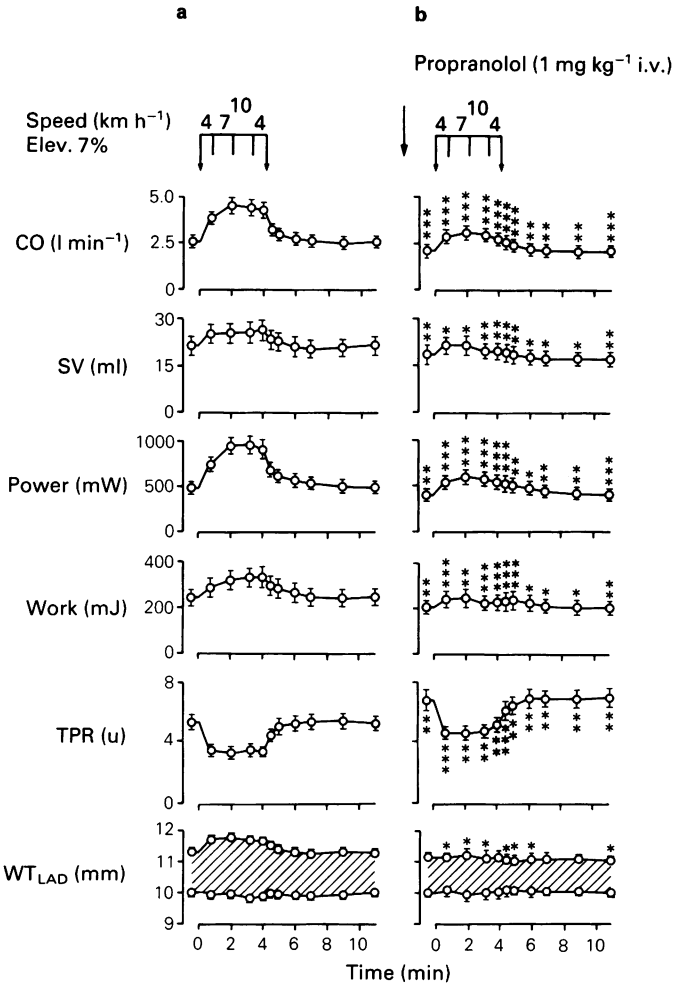

Figure 3 Haemodynamic and functional parameters at rest and during exercise (values are mean and vertical lines s.e. mean, $n = 12$). The two exercise cycles before administration of propranolol did not differ statistically and were expressed as one exercise cycle (a). For the same reason the second and third exercise cycle after propranolol administration were expressed as one post drug exercise cycle (b). The asterisks indicate significant differences from the corresponding moment of the control exercise cycle (t test for paired data; significance symbols: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). For abbreviations see Table 1 and Figure 2.

The effects of UL-FS 49 (0.5 mg kg^{-1}, i.v.) are demonstrated in Figures 4b and 5b. Values at rest and during maximal exercise are also presented, numerically, in Table 1.

At rest, UL-FS 49 decreased heart rate, double product and left ventricular power and increased positive *dp/dt max*.

During exercise, UL-FS 49 decreased heart rate, double product, cardiac output and left ventricular power and increased left ventricular end diastolic pressure.

A direct comparison between the propranolol- and UL-FS 49-induced changes is presented in Figure 6. During exercise at maximal work load, the values after drug administration are expressed as percentage changes of the corresponding values at maximal work load during control exercise (100%).

Propranolol and UL-FS 49 reduced heart rate to the same extent. However a marked difference in their effects on positive *dp/dt max*, cardiac output, stroke volume, left ventricular work, left ventricular power and systolic wall thickening was evident. The

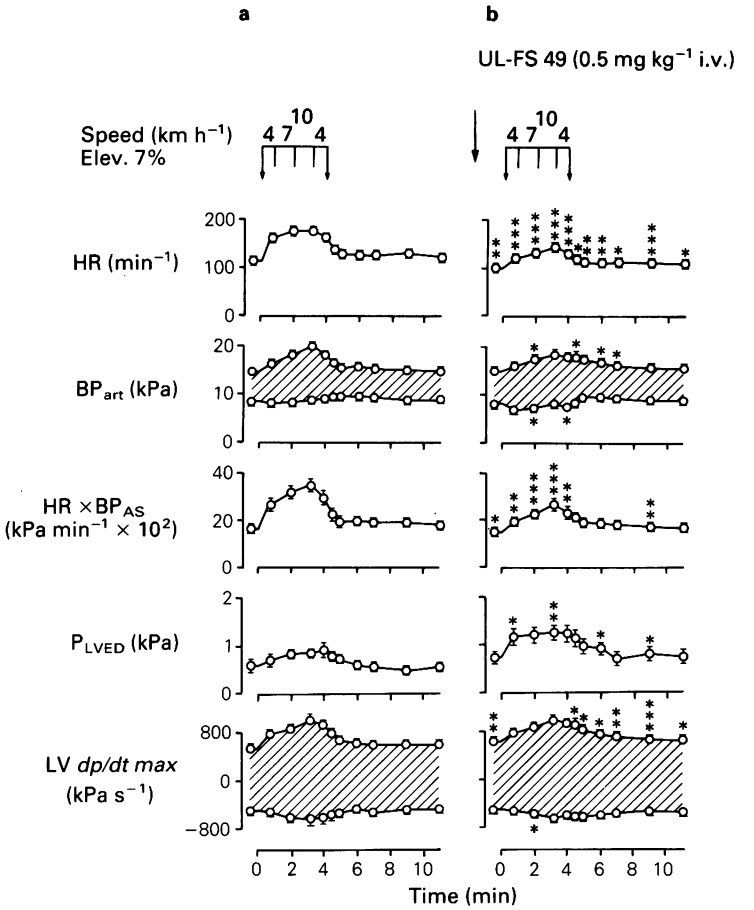

Figure 4 Haemodynamic parameters at rest and during exercise (values are mean and vertical lines s.e. mean, $n = 12$). The two exercise cycles before administration of UL-FS 49 did not differ statistically and were expressed as one exercise cycle (a). For the same reason the second and third exercise cycle after UL-FS 49 administration were expressed as one post drug exercise cycle (b). The asterisks indicate significant differences from the corresponding moment of the control exercise cycle (*t* test for paired data; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). For abbreviations see Table 1 and Figure 2.

influence of propranolol and UL-FS 49 on arterial systolic blood pressure differed only to a minor extent.

Discussion

UL-FS 49, a specific bradycardic agent, has been shown to abolish regional exercise-induced myocardial contracile dysfunction in dogs with coronary stenosis (Raberger *et al.*, 1987). In addition, UL-FS 49 increased left ventricular positive *dp/dt max* at comparable heart rates, confirming the absence of a negative inotropic effect and indicating an improvement of total left ventricular performance or even a positive inotropic effect. Hence, it was of interest to investigate the specific bradycardic action and the influence of UL-FS 49 on positive *dp/dt max* in dogs with unimpaired coronary flow and intact regional function at rest and during exercise. In addition, haemodynamic and functional changes obtained with propranolol, at a dose causing a comparable heart rate reduction, were analysed.

At rest and during exercise, UL-FS 49 reduced heart rate without decreasing positive *dp/dt max*, stroke volume and systolic wall thickening. This further substantiates the absence of a negative inotropic effect of UL-FS 49 and confirms the selective bradycardic action of this agent. Moreover, positive inotropic effects of UL-FS 49 could be anticipated

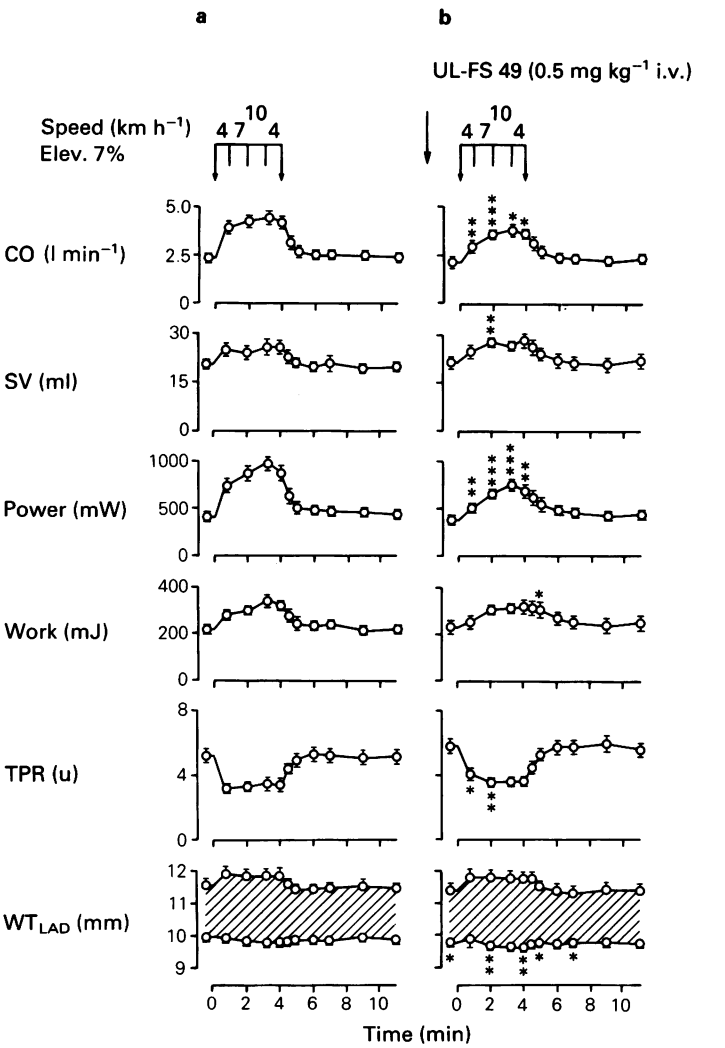

Figure 5 Haemodynamic and functional parameters at rest and during exercise (values are mean and vertical lines s.e. mean, $n = 12$). The two exercise cycles before administration of UL-FS 49 did not differ statistically and were expressed as one exercise cycle (a). For the same reason the second and third exercise cycle after UL-FS 49 administration were expressed as one post drug exercise cycle (b). The asterisks indicate significant differences from the corresponding moment of the control exercise cycle (*t* test for paired data; significance symbols: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). For abbreviations see Table 1 and Figure 2.

from the increase in positive *dp/dt max* at rest (Table 1). Positive inotropic effects of UL-FS 49 have also been seen in guinea-pig isolated atria (Kobinger & Lillie, 1984; Lillie & Kobinger, 1986), although elevation of contractility turned out to depend on stimulation frequency, disappearing at higher pacing rates. By analogy, in the present study UL-FS 49 increased positive *dp/dt max* at rest but not during exercise. However, when analysing positive *dp/dt max*, changes in heart rate and left ventricular end diastolic pressure have to be taken into account, since studies have shown that positive *dp/dt max* is decreased by heart rate reduction (Higgins *et al.*, 1973; Mahler *et al.*, 1974) but increased by preload elevation (Quinones *et al.*, 1975). Thus it remains unclear, whether unaltered positive *dp/dt max* values during exercise observed in this study really reflect a rate dependence of the positive inotropic effect of

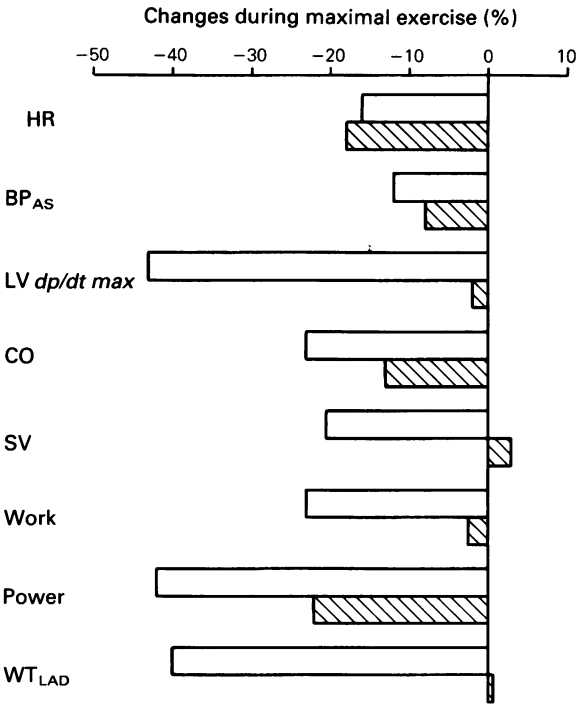

Figure 6 Exercise at maximal work load: mean values of percentage changes after drug administration in comparison to the corresponding moment of control exercise (=100%). Open columns: propranolol; hatched columns: UL-FS 49. For abbreviations see Table 1.

UL-FS 49 in intact animals. The small increase in stroke volume at rest may also result from a direct positive inotropic effect of UL-FS 49, although a slight increase in preload (Table 1) has to be considered. During exercise, however, the significant increase in stroke volume most possibly reflects a preload dependent 'Frank-Starling-like' indirect inotropic effect of UL-FS 49.

The well-known negative inotropic effect of propranolol was confirmed by the marked reductions in positive *dp/dt max*, stroke volume and systolic wall thickening at rest and during exercise. A comparison of Figures 3 and 5 shows that propranolol reduced left ventricular work and power and cardiac output to a markedly greater extent than the bradycardic agent UL-FS 49 (see also Figure 6). Clinically, β-adrenoceptor blocking drugs increase exercise tolerance in patients with coronary insufficiency (Ho *et al.*, 1985). Since β-adrenoceptor blockers also reduce total exercise capacity (Epstein *et al.*, 1965; Sklar *et al.*, 1982; Wilmore *et al.*, 1985), some patients, possibly those with moderate coronary stenosis, may under β-adrenoceptor blockade be limited by skeletal muscle fatigue but not by anginal pain (Ho *et al.*, 1985). The results of this experimental study suggests that patients with mild angina pectoris or patients with coronary insufficiency and moderate left ventricular failure may achieve higher exercise limits with UL-FS 49 than with a β-adrenoceptor blocker. However, this suggestion has to be confirmed in clinical trials.

In conclusion, our results confirm the highly selective negative chronotropic action of UL-FS 49. Evaluation of haemodynamic and functional data during treadmill exercise after UL-FS 49 administration have shown that, in contrast to the effects of β-adrenoceptor blockade, a selective reduction of heart rate does not compromise total or regional ventricular performance and induces a lesser reduction in cardiac output.

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