DRUGS EXPTL. CLIN. RES. 6(3) 177-186 (1980)

LONG-TERM EFFECTS OF THE CALCIUM-ANTAGONIST FENDILINE ON EXERCISE PERFORMANCE IN CORONARY HEART DISEASE

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Summary: *In patients with coronary heart disease (N = 7; mean age 53,4 years) the effect of the calcium antagonist, fendiline, was studied after a treatment period of four weeks. Control data (C) were compared with measurements taken at the end of the treatment period two hours after ingestion of 50 mg fendiline (daily dose 200 mg). Non-steady-state exercise was used to assess physical performance by means of graded maximal bicycle ergometry (two minutes increment test; ergospirometry). Central haemodynamics were determined in recumbent position after volume-loading and at maximally tolerable steady-state exercise (mean load 41 Watt). In symptom-limited stress testing work output (+ 7,7%, n. sig) and the highest tolerable work load (C = 85,7 ± 7,4 Watt; F = 92,9 ± 4,6 Watt; + 9,0%, n. sig.) increased slightly, but maximal heart rate (C = 130,7 ± 4,3 b/min) and systolic blood pressure (C = 176,4 ± 6,2 mm Hg) were not affected. The range of endurance performance (C = 1,18 ± 0,07 l/min STPD oxygen uptake) and the degree of metabolic acidosis (base excess) related to work output were invariable. Fendiline produced no significant influence on exercise induced ST-segment depression and on time elapsed for normalization. Haemodynamic investigation revealed an increase in central-venous capacitante to volume-loading (mean pulmonary arterial pressure; − 9,1%; 2P≤0.05). At work the left ventricular filling pressure (PAEDP) fell from 22,3 ± 2,9 mm Hg to 14,5 ± 1,0 mm Hg (2P≤0,05). Fendiline caused no effect on the mean arterial blood pressure (C = 121,5 ± 2,9 mm Hg) and on the exercise heart rate (− 3,3%; n. sig), but reduced the stroke work index significantly (− 17,8%; 2P≤0,10). The results reveal no major increase of the exercise tolerance in coronary patients with low physical capacity by fendiline, as primary determinants of myocardial oxygen consumption (heart rate and after-load) are not affected. Nevertheless, the mechanism of increasing central venous capacitance (decrease of preload) may be of advantage during long-term treatment with the calcium-antagonist, fendiline.*

Introduction

Therapeutical considerations to improve the exercise tolerance of a coronary patient by means of anti-anginal compounds should preferably be based on detailed information about any abnormal behaviour of determinants of myocardial oxygen consumptions in order to select a drug with proper action (2, 7). Besides nitrates and beta-receptor blocking agents calcium-antagonists, such as verapamil, nifedipine, perhexiline, prenylamine

and fendiline proved some anti-anginal activity (11, 28, 20, 29, 9). Favourable effects of these agents on myocardial oxygen consumption may be attributed to the ability of inhibiting the inward displacement of calcium ions across cardiac cell membrane and from the binding sites at the sarcoplasmatic reticulum into the cell plasma, consequently affecting the excitation-contraction coupling with resulting negative inotropic actions. These inhibitory effects of the Ca^{++}-antagonists are responsible for relaxation of smooth muscles, which means vasodilatation in the coronary and peripheral circulation (6). Concerning the onset of anti-anginal activity, the influence on exercise heart rate and arrhythmias as well as the divergent effects on pre and afterload the specific Ca^{++}-antagonists constitute a non-homogenous group.

Clinical studies have demonstrated the efficacy of fendiline in decreasing the frequency and intensity of angina pectoris attacks and the consumption of nitroglyzerine (11, 30, 15). Regarding the overall cardiovascular actions of fendiline in man there is a paucity of data (26, 28). The present study was undertaken to assess effects of long-term treatment with fendiline on ergospirometric data in maximal non-steady-state exercise and on central haemodynamics in steady-state exercise.

Patients and methods of examination

The study included seven male patients, aged 40 to 62 years, who participated voluntarily after proper information.

Table I *Clinical data.*

N.N.	a	kg	BI	RT-X	RP-X	FAI	WOP	MI	X-abnor.	Angio
A.A.	54	79	109,7	75	40	43.6	215	0	CI, AP	3-vessel d.
R.H.	57	80	108,1	75	50	43,1	290	0	CI, AP	3-vessel d.
H.F.	62	69	98,6	75	30	52,4	290	0	CI, AP	no angio
N.K.	62	77	110	75	50	48,7	290	0	CI	3-vessel d.
F.K.	45	68	94,4	75	20	43.1	215	0	CI, AP	LAD, by-pass occl.
F.J.	54	68	97,1	100	50	60,7	390	inf.	CI	no angio
H.J.	40	80	105,3	125	50	62,5	615	0	CI, AP	2-vessel d.
N = 7	53,4	73,6	103,3	87,7	41,4	50,6	329,3		mean	
	3,1	2,7	2,4	7,4	4,6	3,1	52,6		S.E. of mean	
				Watt	Watt	%	W · min			

BI = Broca-Index (body-length – 100)/kg b.w.
RT-X = non-steady-state maximal exercise, rectangular bicycle ergometry;
RP-X = steady-state exercise, rectangular progressive bicycle ergometry;
FAI = functional impairement (work load tolerated/work load predicted · 100);
WOP = work output during RT-X;
MI inf. = inferior myocardial infarction;
X-abnor. = abnormal response to physical stress: ST-segment depression (CI), angina pectoris (AP).

Symptoms of exercise-induced angina pectoris and electrocardiographic signs of myocardial ischemia limiting physical performance have been stated as criteria for acceptance. Pertinent data of the individuals are given in Table I. All patients had a typical history of stable angina pectoris and had participated previously in several bicycle ergometer tests before they entered the study.

Design of investigation

During a wash-out period of 14 days only nitroglycerin preparation were permitted (no digitalis, antihypertensives and diuretics). Subsequently the patients were given fendiline (Sensit® 200 mg daily; dragées, each containing 50 mg) over a period of at least four weeks. Control data were obtained at the end of the wash-out period. Additionally in three patients the effect of 0.8 mg nitroglycerin on exercise haemodynamics has been studied. The measurements were repeated at the end of the treatment period two hours after intake of one dragée fendiline.

Technics and measurement

The exercise performance of the patients was assessed quantitatively by computer assisted ergospirometry. The patients were familiar with the procedure of exercising in a sitting position on an electrically braked bicycle ergometer (Ergotest, Jäger, Fed. Rep. of Germany). The test protocol was based on the rectangular-triangular test procedure (two-minute increment test (19), following the principle of symptom-limited maximal stress-testing. The work load was incremented every two minutes by 25 Watts, unless the patient was physically exhausted or alarming signs of physical intolerance gave reason for prompt break-off.

The electrocardiogram was taken from precordial leads and monitored continually. The blood pressure was measured by cuff every second minute. Primary ergospirometric parameters (oxygen uptake, carbon dioxide release, minute ventilation volume, tidal volume, respiratory quotient and others) were evaluated by means of an open-air circuit system, applying on-line computer techniques for rating of data and calculation of derived parameters (Ergopneumotest mit EDV, Jäger, Fed. Rep. of Germany). A print-out and a graphical display of the data was available every 30 seconds. The anaerobic threshold (defined in l/min STPD oxygen uptake) was assessed during non-steady-state exercise by plotting the paired data of oxygen uptake and minute ventilation in a rectangular co-ordinate system. The threshold was indicated by the changing of the linear relationship of delta $\dot{V}O2/\dot{V}E$ caused by the onset of hyperventilation due to acidaemia (23). During the recovery period (two-minute) blood samples were taken from the ear lobe to calculate the base excess. The method of computer assisted ergospirometric stress-testing has been fully described elsewhere (21, 23).

Haemodynamic investigations were performed in a semi-recumbent position at rest, after lifting the legs to the pedals of the ergometer (Volume-leading; 18) and at maximally tolerable steady-state conditions of ergometer work. Besides ergospirometric data the pressure in the pulmonary artery was assessed by means of floating catheters (Pulmoflex ® F-4; systolic, endiastolic and mean pressure data were averaged electronically), peripheral arterial blood pressure was measured by auscultation. Blood was withdrawn

from the pulmonary artery to calculate the mixed venous oxygen content. The arterial oxygen content was calulated from data of blood gas analysis obtained from blood samples taken from the hyperemic ear lobe. Fick's principle was used to calculate cardiac output and derived parameters of central haemodynamics on-line (22).

Calculations used to evaluate the cardiocirculatory changes included the following:

– cardiac index (CI) = cardiac output ($\dot{Q}$)/body surface area (l/min/m²);

– peripheral vascular resistance (PVR) = BPpm · 1332 · 10^{-3} · Q^{-1} · 60 (dyn. sec. cm^{-5});

– mean arterial blood pressure (BPpm) = diastolic pressure + 1/3 (systolic diastolic pressure) (mm Hg);

– stroke work index (SWI) = BPpm · SV (stroke volume) · 1,36 · 1,055 · 10^{-3}/m² b.s.a. (g · m/m²);

– pulmonary vascular resistance (PulmVR) = mean pulmonary artery pressure (APpm) · 1332 · $10^{-3}Q^{-1}$ · 60 (dyn. sec. cm^{-5}).

Statistical analysis was performed using Student's t-test with paired comparisons. All the results in the text and in the tables are expressed as the mean + S.E. of the mean.

Results

Ergospirometric stress testing (non-steady-state exercise sitting position)

The ergospirometric data are given in Table II. At the end of a four-week treatment period with fendiline (50 mg, four times daily) the work output increased slightly (+7,7%; n. sig.) and the patients were able to tolerate a higher work load (+8,4%; n. sig.).

Concerning maximal heart rate and systolic blood pressure we found no difference compared to the control. As the patients achieved a slightly higher work load the maximal oxygen uptake increased by 7,1% (n. sig.). Fendiline caused no change of the level of endurance performance (anaerobic threshold) and the degree of metabolic acidosis (s. base excess) related to work output.

At comparable work rates (50 Watt) the heart rate was unchanged. The oxygen uptake at the first minute per load exceeded the control state insignificantly (at the mean: C = 0,87 l/min STPD $\dot{V}O2$; F = 0,95 l/min; reference: 0,83 ± 0,11) and the oxygen pulse increased from 8,20 (C) to 8,97 (F) ml/beat at the mean (2P ⩽ 0.10).

The onset of ST-segment changes (ST-depression of more than 0,10 mV) referred to work load (C = 67,8 ± 7,1 Watt) and time elapsed for normalization after the test (C = 4,42 ± 8,87 min) were invariable. Under treatment with fendiline, four patients (4/7) had to break off the test primarily due to chest pain (C = 5/7).

Table II *Ergospirometric data in non-steady-state maximal bicycle ergometry. Before and after long-term treatment with fendiline. (N = 7).*

Parameter	Control	Fendiline	
Maximal performance			
Work output (Watt × min)	329,3 ±52,6	354,3 ±32,2	n. sig.
Maximal load (Watt)	85,7 ± 7,4	92,9 ± 4,6	n. sig.
Work period (min)	6,3 ± 0,5	6,8 ± 0,3	n. sig.
Heart rate (beats/min)	130,7 ± 4,3	133,7 ± 5,0	n. sig.
Systolic blood pressure (mm Hg)	176,4 ± 6,2	177,9 ±11,5	n. sig.
fh × BPsyst (mm Hg × sec^{-1} × 10^{-2})	230,3 ± 9,9	239,8 ±21,1	n. sig.
Oxygen uptake (l/min STPD), $\dot{V}02$	1,41 ± 0,13	1,51 ± 0,07	n. sig.
Anaerobic threshold (l/min $\dot{V}02$)	1,18 ± 0,07	1,24 ± 0,08	n. sig.
Base excess (BE, mmol/l)	−3,94 ± 1,1	−4,41 ± 0,8	n. sig.
Work period without pain (min)	5,5 ± 0 96 (5/7)	5,0 ± 0,41 (4/7)	n. sig.
Maximal ST-depression (mV)	0,21 ± 0,04	0,23 ± 0,06	n. sig.
Onset of ST-depression (more than 0,10 mV; work load)	67,8 ± 7,1	65,0 ±10,0	n. sig.
Normalization of ST-depression after work (min)	4,42 ± 0,87	4,42 ± 1,52	n. sig.
Submaximal work load (50 Watt; 1. and 2. min)			
Heart rate (2. min)	107,7 ± 5,1	109,1 ± 4,0	n. sig.
Oxygen uptake (1. min = adaptation)	0,87 ± 0,07	0,95 ± 0,03	n. sig.
Oxygen pulse (2. min; ml/beat)	8,20 ± 0,53	8,97 ± 0,39	2P = 0,10

Central haemodynamics (steady-state exercise, semi-recumbent position)

At rest. These data are listed in Table III. The control values of cardiac output were equal to a hypercirculatory state with an adequately lower peripheral vascular resistance. After treatment with fendiline the cardiac output at rest lay within normal ranges. There was no significant change of haemodynamic data except for a decrease of the PAEDP (C = 10,5 ± 1,4 mm Hg; F = 7,1 ± 1,29 mm Hg; 2P = 0,01) and an increase of the pulmonary vascular resistance.

Volume loading by postural changes (lifting the legs to the pedals of the ergometer). A volume displacement of about 200-300 ml blood from the lower extremities centralwards caused no specific changes of haemodynamics compared to data at rest after treatment with fendiline. Compared to the control fendiline reduced the pulmonary artery pressure significantly, indicating an increase in central-venous capacitance (s. Fig. 1 and Table III). The arterio-venous oxygen concentration difference was not affected (C = 48,8 ± 1,5 ml/l), but due to a decline in oxygen uptake (C = 0,36 l/min STPD on the mean; F = 0,28 l/min) a lower cardiac index was calculated (−28%; n. sig). Fendiline did not influence heart rate and mean arterial pressure.

Central haemodynamics at work (steady-state bicycle ergometer work). Fendiline improved steady-state exercise tolerance in three patients (3/7) by 25 Watt. Comparable

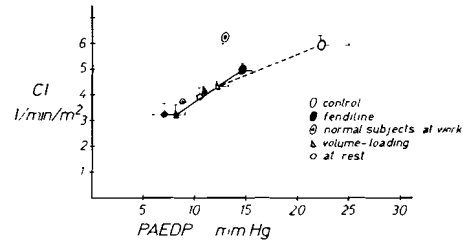

Fig. 1 Left ventricular function graph comparing cardiac index and left ventricular filling from rest and during volume-loading to exercise. Note the shift to the left and downwards. (Before and after long-term treatment with fendiline, N = 7; normal subjects, N = 14).

Table III *Haemodynamic responses to fendiline treatment at rest, during volume loading and at work (N = 7; mean work load 41,1 Watt; normal subjects N = 14; haemodynamics data at work have been extrapolated to 40 Watt, as measurements have been taken at 20, 50 and 100 Watt).*

Parameter		At rest			
		Control	Fendiline		Normal subjects
fh	(beats/min)	74,2 ± 5,6	69,0 ± 3,4		76,0 ± 3,8
CI	(l/min/m² b.s.a.)	3,90 ± 0,44	3,23 ± 0,48		3,76 ± 0,26
SV	(ml)	97,8 ± 7,3	86,4 ± 12,7		97,8 ± 5,1
avD02	(ml/l)	45,7 ± 4,4	48,8 ± 1,5		4,65 ± 0,32
V̇02	(l/min STPD)	0,32 ± 0,03	0,28 ± 0,03		0,32 ± 0,02
PASP	(mm Hg)	23,6 ± 2,3	21,3 ± 2,2		22,9 ± 1,2
PApm	(mm Hg)	15,8 ± 1,7	14,0 ± 1,4		15,2 ± 0,8
PAEDP	(mm Hg)	10,5 ± 1,4	7,1 ± 1,2	***	8,9 ± 0,6
BPpm	(mm Hg)	104,1 ± 3,5	105,6 ± 1,3		103,0 ± 3,5
PVR	(dyn × sec × cm⁻⁵)	1188 ± 185	1594 ± 185		1179 ± 73
PulmVR	(dyn × sec × cm⁻⁵)	164,6 ± 30,3	213,7 ± 37,6	*	174,9 ± 17,2
SWI	(g × m/m²)	78,4 ± 8,2	70,4 ± 12,0		74,7 ± 5,2

Parameter		Volume-loading			
		Control	Fendiline		Normal subjects
fh	(beats/min)	72,4 ± 6,0	69,4 ± 2,5		77,4 ± 3,3
CI	(l/min/m² b.s.a.)	4,36 ± 0,56	3,21 ± 0,38		4,15 ± 0,32
SV	(ml)	109,0 ± 9,1	85,2 ± 10,3		103,2 ± 5,3
avD02	(ml/l)	48,0 ± 5,0	48,7 ± 1,4		4,51 ± 0,27
V̇02	(l/min STPD)	0,36 ± 0,03	0,28 ± 0,02		0,34 ± 0,02
PASP	(mm Hg)	28,4 ± 2,3	23,7 ± 1,9		28,7 ± 1,6
PApm	(mm Hg)	19,6 ± 1,8	16,4 ± 1,4	**	18,9 ± 1,0
PAEDP	(mm Hg)	12,1 ± 1,2	8,1 ± 1,0	***	10,9 ± 0,6
BPpm	(mm Hg)	107,9 ± 3,5	109,5 ± 3,7		104,1 ± 3,0
PVR	(dyn × sec × cm⁻⁵)	1171 ± 191	1568 ± 199		1104 ± 71
PulmVR	(dyn × sec × cm⁻⁵)	192,1 ± 33,1	228,1 ± 44,1		201,5 ± 17,6
SWI	(g × m/m²)	91,1 ± 9,6	71,2 ± 9.5		80,7 ± 5,9

Parameter		At work			
		Control	Fendiline		Normal subjects
fh	(beats/min)	107,5 ± 2,5	103,9 ± 2,2		97,5
CI	(l/min/m² b.s.a.)	5,96 ± 0,43	4,93 ± 0,31	**	6,25
SV	(ml)	102,1 ± 2,5	87,5 ± 6,0	**	119,3
avD02	(ml/l)	90,0 ± 5,0	95,0 ± 6,0		79,2
V̇02	(l/min STPD)	0,99 ± 0,07	0,85 ± 0,06	**	0,94
PASP	(mm Hg)	47,2 ± 4,8	42,9 ± 4,7		35,0
PApm	(mm Hg)	33,4 ± 3,8	29,7 ± 3,0		23,4
PAEDP	(mm Hg)	22,3 ± 2,9	14,5 ± 1,0	**	12,9
BPpm	(mm Hg)	121,5 ± 2,9	120,1 ± 6,1		113,7
PVR	(dyn × sec × cm⁻⁵)	896 ± 43	1094 ± 107	*	765
PulmVR	(dyn × sec × cm⁻⁵)	252,0 ± 33,4	289,3 ± 39,3		165,9
SWI	(g × m/m²)	96,7 ± 5,2	82,1 ± 7,7	*	99,4

fh = heart rate; CI = cardiac index; SV = stroke volume; avD02 = arterio-venous oxygen difference; V̇02 = oxygen uptake; PASP = pulmonary artery systolic pressure; PApm = pulmonary artery mean pressure; PAEDP = pulmonary artery endiastolic pressure; BPpm = mean arterial pressure; PVR = peripheral vascular resistance; PulmVR = pulmonary vascular resistance; SWI = stroke work index; (means ± S.E. of the means; * = 2P < 0,10; ** = 2P < 0,05; *** = 2P < 0,01, before and after fendiline).

steady-state work levels were taken for statistical analysis (mean load: 41,4 Watt; range 20-50 Watt). Fendiline reduced the exercise heart rate only slightly (−3,3%; n. sig.). We observed a significant fall in oxygen uptake (C = 0,99 ± 0,07 l/min STPD; F = 0,85 ± 0,06 l/min) and an increase of arterial-venous oxygen extraction (avDO2); +5,6%; n. sig.).

Applying direct Fick's principle a decrease of cardiac output (C = 5,96 ± 0,43 l/min/m²; F = 4,93 ± 0,31; 2P = 0,05) and of stroke volume (C = 102,1 ± 6,0 ml; 2P = 0,05) have been ascertained. Mean arterial blood pressure was not affected. Consequently the increase in peripheral vascular resistance was attributable to the decrease in cardiac output. The stroke work index (SWI) declined by 17,8% (2P = 0,10).

In contrast to the influence on peripheral arterial pressure fendiline caused a significant fall in the pulmonary arterial pressure. In particular the index of the left ventricular filling pressure (PAEDP) declined by 34,9% (C = 22,3 ± 2,9 mmHg; F = 14,5 ± 1.0 mm Hg; s. Fig. 1).

In three patients the response to fendiline was compared with the acute effect of nitroglycerine, which was given after control data had been obtained (Table IV). In contrast to the long-term treatment with fendiline, nitroglycerin improved the cardiac index (+4%) slightly and decreased the index of left ventricular filling pressure (PAEDP) by 32,7% (F = 23,6%) in these patients.

Discussion

The impairment of physical performance in patients with coronary heart disease is caused by a disparity between myocardial oxygen demand and myocardial oxygen supply. To improve this energetic imbalance measures should be taken to reduce heart rate, left ventricular wall tension during systole (arterial blood pressure; ventricular afterload), endiastolic volume (preload) and contractility, consequently increasing blood flow to areas of ischemic myocardium during diastole (redistribution of flow).

Analyzing our haemodynamic data with respect to the influence of fendiline on determinants of myocardial oxygen demand we may conclude as follows: At comparable work rates the *exercise heart rate* was not changed effectively (−3,3%; n. sing.). Concerning the

Table IV *Haemodynamic response to fendiline in comparison to nitroglycerine at volume-loading and at work (N = 3; means ± S.E. of the means).*

Parameter		Volume-loading		
		Control	Nitroglycerine	Fendiline
CI	(l/min/m²)	3,67 ± 0,51	3,0 ± 0,61	2,82 ± 0,43
PAEDP	(mm Hg)	10,9 ± 2,5	9,0 ± 2,0	7,8 ± 1,6

Parameter		At work		
		Control	Nitroglycerine	Fendiline
CI	(l/min/m²)	5,38 ± 0,43	5,60 ± 0,67	4,24 ± 0,31
PAEDP	(mm Hg)	22,0 ± 1,15	14,8 ± 3,8	16,8 ± 1,04

effect on exercise heart rate the Ca^{++}-antagonists constitute a non-homogenous group: fendiline does not reduce exercise heart rate, whereas verapamil (27) and perhexiline (20) lower heart rate at work by −22,1% and −5,6% respectively. Nifedipine increases exercise heart rate (+9,7%) (5) due to baroreceptor stimulation by the fall of blood pressure. Compared to the efficacy of beta-receptor-blocking agents (e.g. pindolol: −19,3%) (8) the fall in heart rate induced by the Ca^{++}-antagonist fendiline (−3%) is a negligible factor in lowering myocardial oxygen demand.

The dose regime of fendiline applied in this study did not lower *arterial blood pressure*. Ca^{++}-antagonists such as verapamil and nifedipine have some potent antihypertensive activity (11, 13, 29, 25). This influence on afterload may contribute to the prompt anti-anginal activity of these drugs, which is missing in fendiline (9) and perhexiline as well (3).

In our study the reduction of cardiac index (=19,9%; $2P \leq 0{,}05$) at bicycle work in a semi-recumbent position is primarily due to a lower oxygen uptake, as the assessment of cardiac output was based on direct Fick's principle. This effect under treatment with fendiline is remarkable as oxygen uptake at steady-state work loads is very constant. Studying the influence of sublinqual nitroglycerine on exercise performance in patients with coronary heart disease we have observed no alteration of oxygen uptake (mean load 40,9 Watt; control VO2: 0,95±0,41 l/min STPD; nitroglycerine: 0,96±0,07 l/min; Reiterer et al., 1978).

The reason for the decline in oxygen uptake under treatment with fendiline (−14,1%; $2P \leq 0{,}05$) may be due to the reduction of luxury perfusion, as is seen after beta-receptor blockade (12). In addition, it should be pointed out that the onset of subjective complaints, anxiety and the stress of the invasive investigation may contribute to a greater variability of oxygen uptake and consequently of cardiac output at low work rates in diseased people. The decrease of volume work of the heart (stroke work index: −17,8%; $2P = 0{,}10$) was attributable to a fall of the stroke volume in particular (−14,3%; $2P = 0.05$). Concerning the underlying mechanism a reduction of myocardial contractility by the calcium antagonist can be suspected. But as cardiac output depends on preload as well, it should be taken into account that fendiline caused a distinct fall in ventricular filling pressure (PAEDP) and pulmonary artery pressure. This effect on the low pressure system is to be interpreted as an increase in capacitance (venous pooling), as after volume loading by postural changes the pulmonary artery pressure remains invariable.

The fall in pulmonary artery pressure at work after long-term treatment with fendiline is comparable to the prompt effect of nitroglycerine in coronary patients with low exercise performance, we have studied previously (PAEDP: −39,4%) (24). In contrast to nitroglycerine (0,8 mg s.l.), which caused a small increase in cardiac output, fendiline lowered the cardiac index considerably. Compared to slow release nitrates fendiline has been shown to be of equipotent effect on the PAEDP, but in this study control data were not available (26).

At the end of the wash-out period three patients were given 0,8 mg nitroglycerine after control data had been obtained. The exercise test was repeated 15 minutes. afterwards. Compared to the long-term effect of fendiline nitroglycerine improved the cardiac index (+4%) slightly and decreased the index of the left ventricular filling pressure (PAEDP) by 32,7% (fendiline: −23,6%) in these patients.

The calcium antagonist perhexiline does not lower the cardiac output despite a decline of the heart rate (−10%) at work, but the reduction of the left ventricular filling pressure is similar to that observed with nitroglycerine (17).

The haemodynamic effect of verapamil in subjects with coronary insufficiency has been reported by Carlens (4). The heart rate, stroke volume and cardiac output were unchanged at rest and during exercise. But the systolic and enddiastolic pressures in the left ventricle were both significantly lower at comparable load. Nifedipine reduced the systemic (11-18%) and the diastolic pressure in the pulmonary artery (15-39%), the cardiac output is unchanged during exercise (10). Some authors have observed a somewhat more marked increase in cardiac output (14, 16). Both verapamil and nifedipine consistently show about the same central haemodynamic effects provided they are given in equipotent doses.

In comparison to the haemodynamic effects of other calcium antagonists, which refer to acute intervention studies, it should be kept in mind, that we have studied the long-term effect of a standard dose regimen of fendiline to reveal the efficacy of the compound from a more practical standpoint.

With regard to the physical performance in graded maximal stress testing (rectangular-triangular bicycle ergometry) (20, 21, 22) the improvement of work output by fendiline is rather small (+7,6%; n. sig.) and the ST-depression at the maximal work load was not ameliorated. The computer assisted analysis of ergospirometric parameter during non-steady-state exercise, such as oxygen uptake, minute-ventilation, endurance performance (anaerobic threshold) and metabolic acidosis revealed no changes by fendiline. In particular the oxygen uptake at the first minute per load (50 Watt) increased fast, indicating the adequate cardio-circulatory adjustment to graded exercise (1).

In our study electrocardiographic signs of myocardial ischemia have not been improved, whereas König et al. (11) and Streicher et al. (28) have found a reduction of the ST-depression at rest and at work. A decrease of nitroglycerine consumption has been reported by König et al. (11) and by Weikl et al. (30).

In conclusion the long-term treatment with the calcium antagonist fendiline caused a small and insignificant improvement of maximal exercise tolerance in patients with very low physical capacity. Haemodynamic investigations revealed a decline in pulmonary artery pressure and a reduction of cardiac index and stroke work index. Exercise heart rate and mean arterial blood pressure as the major determinants of myocardial oxygen consumption were not affected.

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