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Antihypertensive treatment with felodipine but not with a diuretic reduces episodes of myocardial ischaemia in elderly patients with hypertension

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Episodes of transient myocardial ischaemia can frequently be observed in hypertensive patients. To assess the effects of antihypertensive treatment with the calcium antagonist felodipine or the diuretic combination hydrochlorothiazide/triamterene on episodes of ischaemic-type ST-segment depression (ST-D), simultaneous ambulatory electrocardiographic and blood pressure (BP) monitoring was performed in 42 elderly hypertensives without manifest coronary artery disease. All patients (mean age 79 ± 6 years, office BP ≥ 160/95 mmHg) were evaluated off any antihypertensive or anti-ischaemic therapy and after 3 months treatment with either felodipine or the diuretic (randomized, double-blind study) for episodes of significant ST-D (≥0·1 mV, duration ≥1 min, interval ≥1 min). The reduction in office BP and daytime ambulatory BP was similar for both agents, as was a significant reduction in the heart rate × systolic BP product (DP) over 24 h (felodipine: 12 441 ± 2076 vs 11 643 ± 1953 mmHg . min^{-1}; P=0·048; diuretic: 12 366 ± 2782 vs 11 062 ± 2012 mmHg . min^{-1}; P=0·003). While felodipine significantly decreased the total number of ST-D (from 40 to six episodes; P=0·03), the total number of ST-D remained unchanged with the diuretic (non-significant increase from 31 to 45 episodes; P=0·24). The same trend was observed for the number of patients with ST-D. The ischaemic threshold, defined as DP at the onset of the episodes of ST-D, increased with felodipine (12 171 ± 340 vs 13 770 ± 138 mmHg . min^{-1}) and decreased with the diuretic (16 210 ± 312 vs 14 092 ± 319 mmHg . min^{-1}). In conclusion, antihypertensive treatment with felodipine reduces blood pressure and episodes of transient myocardial ischaemia in elderly hypertensive patients, while hydrochlorothiazide/triamterene increases these episodes despite a similar BP reduction. Felodipine may influence structural and functional factors at the coronary microcirculation level. These mechanisms improve coronary blood flow and increase the ischaemic threshold.

Introduction

Episodes of transient myocardial ischaemia can frequently be observed in hypertensive heart disease, even in the absence of left ventricular hypertrophy or epicardial coronary artery disease (macroangiopathy)[1–4]. This phenomenon also holds true for elderly patients with hypertension[5]. Myocardial ischaemia is a risk factor for sudden cardiac death in hypertension, together with arrhythmias and changes in autonomic tone[6–8]. Effective treatment of hypertension and hypertensive heart disease should thus aim to improve myocardial ischaemia.

In congestive heart failure due to coronary artery disease and in systemic hypertension, the effects of diuretic-based treatment on myocardial ischaemia have not been investigated[9]; most facts about calcium antagonists and myocardial ischaemia come from studies in patients with coronary artery disease and angina pectoris[10,11]. Our study evaluates the effect of antihypertensive treatment with felodipine, a new second generation calcium antagonist, or the diuretic combination hydrochlorothiazide/triamterene on episodes of transient myocardial ischaemia in elderly patients with hypertension. Simultaneous ambulatory electrocardiographic and blood pressure monitoring should reveal possible mechanisms of myocardial ischaemia and the influence of treatment.

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Methods

PATIENTS

Patients ≥70 years of age with systemic hypertension, office blood pressure (BP) ≥160/95 mmHg who were not taking any antihypertensive or anti-ischaemic treatment (14- to 21-day single-blind placebo wash-out period) and without manifest coronary artery disease (no history of myocardial infarction, electrocardiogram at rest without Q waves or ST-segment changes) were included. Forty-three patients (29 women, 14 men) entered the study; the mean age was 79 ± 6 years (age range 70–94 years). Patients with pacemakers, atrial fibrillation, bundle branch block, Wolff–Parkinson–White syndrome, stroke within the last 6 months,

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electrolyte disturbances, valvular heart disease, renal failure, severe congestive heart failure (NYHA III and IV) and office BP>250/130 mmHg were excluded.

ST-SEGMENT ANALYSIS AND AMBULATORY BLOOD PRESSURE MONITORING

At the end of the placebo period and after 3 months treatment, simultaneously 24 h Holter monitoring and 24 h ambulatory BP monitoring were performed. A detailed description of the method has recently been published[5]. For Holter monitoring we used the Mortara PR 3 recorder (double channel, bipolar, amplitude-modulated, frequency: 0·05 to 100 Hz; Mortara Inc., Milwaukee, Wisconsin, U.S.A.) with analysis of precordial leads CM_2 and CM_5 (corresponding to V_2 and V_5). The monitor was calibrated before each recording; with use of monitor control, any modification in the ST-segment due to changes of position or hyperventilation (15 s) were excluded. During the recording, patients were encouraged to pursue their normal activities and to keep a diary. ST-segment analysis was performed with the Mortara Prodigy system semi-automatically under visual control; the observer was unaware of patient data and the nature of treatment. The isoelectric point in the PR segment and the J point were determined individually, and the L point was determined automatically 60 to 80 ms after the J point according to heart rate. Significant ischaemic-type ST-segment depression (ST-D), as a marker of transient myocardial ischaemia, was defined as a horizontal or descending shift of the ST-segment ≥ 1 mm (0·1 mV) with a duration of at least 1 min and an interval between two episodes of at least 1 min.

Ambulatory BP monitoring was performed with the oscillometric recorder 90 207 (Spacelabs Inc., Redmond, Washington, U.S.A.), a device of proven accuracy and validation[12]. Application of the device and first measurement were performed in the presence of a physician and controlled by simultaneous BP measurement with a standard sphygmomanometer. Measurements were taken every 20 min between 0600h and 2200h, (daytime period) and every 30 min between 2200h and 0600h (night-time period). Mean heart rate over 24 h, number of ventricular premature complexes, ventricular runs (>3 ventricular premature complexes, but duration <30 s) and ventricular tachycardias (duration $\geq$ 30 s), ambulatory BP over 24 h, during daytime and night-time were recorded.

PARAMETERS OF THE EPISODES OF ST-SEGMENT DEPRESSION

For each episode of ST-D the following parameters were determined: duration (in min), maximal degree (in mm), and heart rate (derived from Holter monitoring) 30 min before the episode, at the onset, at maximum ST-D and 30 min after the episode. For analysis of the relationship between ST-D and BP for each episode, the BP value 20–40 min (night-time: 15–45 min) before, the value at the onset (during the interval 10 to 1 min before ST-D), the value(s) during ST-D and the value 20–40 min (night-time: 15–45 min) after ST-D were assessed. Due to the limited interval for BP recording at onset and the variable duration of the episodes, all four BP values could only be determined in 90 (74%) of the total of 122 episodes of ST-D (which were observed before and during treatment in both treatment groups). Heart rate × systolic BP product (double product; DP) was calculated from the corresponding data before, at onset, during and after ST-D.

Episodes of ST-D were considered (1) as being preceded by an increase in HR, if increases >15% between the time before and the onset were recorded, (2) as being preceded by an increase (respectively decrease) in BP, if increases (decreases) >20/10 mmHg were measured, and (3) as being preceded by an increase in DP, if increases >10% were observed.

ECHOCARDIOGRAPHY

All measurements were obtained according to the Penn convention[13] with a Toshiba SSH 65 A with an electronic 2·5 MHz transducer (Toshiba Medical Systems, Shimoishigami, Otawara, Japan).

Left ventricular mass (in g) was calculated using the Devereux and Reichek formula[13], and left ventricular muscle mass index after correction for body surface area (in $g \cdot m^{-2}$). For systolic and diastolic function of the left ventricle, the shortening fraction (in %), and the E/A ratio (ratio between peak velocity during early and late diastolic filling) were determined (according to[5]).

TREATMENT

After the baseline visit (at the end of the placebo period) the patients were randomized to treatment with either felodipine (5 mg o.i.d.) — 21 patients — or hydrochlorothiazide (25 mg)/triamterene (50 mg) o.i.d. — 22 patients — in a double-blind, parallel-group design. After 2 weeks (10–18 days) the dosage could be doubled if diastolic (office) BP was still $\geq$95 mmHg. After 3 months the patients were reinvestigated with the same methods as at baseline.

ETHICAL APPROVAL

The study protocol and the methods used were approved by the ethical committee of the Ludwig Maximilian University of Munich.

STATISTICAL METHODS

All data were analysed using the NCSS 5 system (Kaysville, Utah, U.S.A.) and are shown as number (of patients or episodes), or as mean ± SD. For direct comparisons between two different groups the unpaired t-test was used, and for a comparison within one group the paired t-test. Non-parametric data were analysed using the Wilcoxon, Mann–Whitney (independent samples) and Kruskal Wallis (for non-parametric ANOVA) tests. To reject the overall null hypothesis (of

Table 1 Characteristics of the felodipine and the diuretic groups at randomization. Indicated are means ± SD. No differences are significant, P>0·05, with the exception of systolic ambulatory BP at night

Characteristics	Felodipine group	Diuretic group
Number of patients	21	21
Men/Women	7m/14w	6m/15w
Office BP (mmHg)	194 ± 22/102 ± 6	195 ± 22/101 ± 9
Heart rate 24 h (min^{-1})	75 ± 10	75 ± 714
Ambulatory BP 24 h (mmHg)	161 ± 18/88 ± 11	164 ± 15/87 ± 8
Ambulatory BP daytime (mmHg)	164 ± 18/91 ± 11	165 ± 17/89 ± 9
Ambulatory BP night-time (mmHg)	154 ± 19*/80 ± 12	161 ± 15*/81 ± 10
Fractional shortening (%)	35 ± 4	33 ± 3
Left ventricular muscle mass index ($g . m^{-2}$)	138 ± 25	134 ± 21
Creatinine ($mg . dl^{-1}$)	0·85 ± 0·22	0·86 ± 0·25
Total cholesterol ($mg . dl^{-1}$)	229 ± 44	222 ± 44
LDL cholesterol ($mg . dl^{-1}$)	139 ± 44	136 ± 46
HDL cholesterol ($mg . dl^{-1}$)	57 ± 19	54 ± 10
Previous antihypertensive treatment (n)	18	20
Diabetes mellitus (n)	3	5
Cigarette smokers (n)	4	1
Transient ischaemic attack/stroke (n)	2	1

no differences between treatments and between times of observation within each treatment) multiple ANOVA for repeated measurements was used with two treatments, two periods of observation and four periods of measurements within each time of observation). For all tests $P<0·05$ was considered significant.

Results

FREQUENCY OF ST-SEGMENT DEPRESSION

Simultaneous recordings of Holter and ambulatory BP monitoring at baseline and after 3 months treatment could be obtained from 42 patients (one patient in the diuretic group himself stopped treatment after 3 weeks and died 2 weeks later due to pneumonia); 21 patients belonged to the felodipine group and the same number to the diuretic group. The two groups were adequately matched for age, gender, BP and heart rate at randomization, renal function, lipid status, previous treatment, and concomitant diseases (Table 1). Table 2 summarizes the results on ST-D: The total number of episodes decreased significantly in the felodipine group and tended to increase in the diuretic group. While before treatment the number of patients with ST-D and the total number of episodes in the felodipine and diuretic group were comparable ($P=0·8$ and $0·7$), during treatment significantly ($P=0·02$) fewer patients had ST-D in the felodipine group, and there were significantly ($P=0·001$) fewer episodes. The mean duration (felodipine: 15 ± 17 vs 17 ± 16 min; diuretic: 16 ± 18 vs 18 ± 22 min) and the maximum degree (felodipine: 1·6 ± 0·5 vs 1·9 ± 0·8 mm; diuretic 2·4 ± 1·2 vs 2·4 ± 1·4 mm) of each episode did not change in either group; the mean total duration per patient decreased in the felodipine group (155 ± 66 vs 43 ± 45 min; $P<0·05$) and tended to increase in the diuretic group (56 ± 49 vs 74 ± 71 min). Most episodes of ST-D were 'silent', both at baseline (94%) and during treatment (92%).

ST-SEGMENT DEPRESSION AND TIME OF THE DAY

Table 3 shows the number of episodes and the proportion of ST-D during the daytime period (0800h–2200h), the night-time period (2200h–0600h) and the 'early morning' period (0600h–0800h). Both at baseline and during treatment, significantly more episodes (in absolute terms) occurred in daytime than during the other time periods.

The largest number of episodes per hour was observed between 0700h and 0800h (ANOVA for the different rates per hour was, however, not significant).

EFFECT OF TREATMENT ON BLOOD PRESSURE, HEART RATE, LEFT VENTRICULAR MASS, PARAMETERS OF LEFT FUNCTION, AND ARRHYTHMIAS

Figure 1 shows that the reduction in office BP and daytime ambulatory BP was comparable for both treatment groups. Diastolic ambulatory BP over 24 h (see Fig. 1) and night-time systolic (−20 ± 12 vs −7 ± 12 mmHg) and diastolic (−11 ± 7 vs −4 ± 7 mmHg) ambulatory BP were significantly more reduced by the diuretic than by felodipine. Eight patients in the diuretic group were treated with the higher dose after 2 weeks compared to three patients in the felodipine group. An analysis of patients with (felodipine: n=4; diuretic: n=12) and without (felodipine: n=17; diuretic: n=9) ST-D during treatment revealed no differences in BP reduction (office BP and ambulatory BP), in either group.

Table 2 Number of patients with ST-D and total number of episodes of ST-D both in the felodipine group and in the diuretic group at baseline and during treatment. Number of episodes, preceded by an increase in heart rate, BP or heart rate × systolic BP product, or a decrease in BP

	Felodipine group			Diuretic group		
	Baseline	Treatment	*P*	Baseline	Treatment	*P*
Patients with ST-D (%)	7 (33%)*	4 (19%)	ns	10 (48%)	12 (57%)	ns
Total number of episodes	40*	6*	0·03	31*	45*	ns (0·24)
Increase in heart rate (%)	6 (15%)	3 (50%)	0·048	22 (71%)	18 (40%)	0·009
Increase in BP (%)**	8 (20%)	1 (17%)	ns	8 (26%)	12 (27%)	ns
Decrease in BP (%)**	7 (18%)	1 (17%)	ns	8 (26%)	12 (27%)	ns
Increase heart rate × systolic BP product (%)	16 (40%)	4 (67%)	ns	27 (87%)	27 (60%)	0·01

For definitions see text. Indicated are absolute numbers and %.
ns=not significant ($P>0·05$). *multiple ANOVA performed to reject the null hypothesis.
**BP measurements performed in 90 of 122 episodes: felodipine baseline· 31 of 40; treatment: 5 of 6; diuretic baseline: 23 of 31; treatment: 31 of 45.

Table 3 Distribution of the episodes of ST-D during the 24 h period

	Felodipine group			Diuretic group		
	Baseline	Treatment	*P*	Baseline	Treatment	*P*
Episodes between 0800h–2200h	28 (70%)	4 (66%)	ns	18 (58%)	34 (76%)	ns
Episodes between 2200h–0600h	8 (20%)	1 (17%)	ns	5 (16%)	6 (13%)	ns
Episodes between 0600h–0800h	4 (10%)	1 (17%)	ns	8 (26%)	5 (11%)	ns
	*			*	*	

Daytime period: 0800h–2200h. Night-time period: 2200h–0600h. Early morning period: 0600–0800h. Indicated are absolute numbers and %.
ns=differences between baseline and treatment are not significant.
*=significant differences between the different daytimes (by non-parametric ANOVA).

After 3 months treatment there was no significant change in heart rate (felodipine: 75 ± 10 vs 76 ± 8 beats . min^{-1}; diuretic: 75 ± 14 vs 75 ± 12 beats . min^{-1}), left ventricular muscle mass index (felodipine: 138 ± 25 vs 136 ± 30 g . m^{-2}; diuretic: 134 ± 21 vs 134 ± 23 g . m^{-2}), fractional shortening (felodipine: 35 ± 4% vs 36 ± 5%; diuretic: 33 ± 3% vs 33 ± 3%) or E/A ratio (felodipine: 0·76 ± 0·27 vs 0·72 ± 0·20; diuretic: 0·63 ± 0·12 vs 0·60 ± 0·12 vs 0·60 ± 0·16). The DP over 24 h was significantly reduced in both groups: felodipine: 12 441 ± 2076 vs 11 643 ± 1953 mmHg . min^{-1} (P= 0·048); diuretic: 12 366 ± 2782 vs 11 062 ± 2012 mmHg . min^{-1} (P=0·003). The (average) number of ventricular premature complexes did not change significantly in either group (felodipine: 237 ± 464 vs 178 ± 232; diuretic: 712 ± 2487 vs 597 ± 1811), nor did the number of ventricular runs (felodipine: 1 ± 4 vs 0·2 ± 0·7 episodes per patient; diuretic: 0·1 ± 0·2 vs 0·1 ± 0·4 episodes per patient); ventricular tachycardias were not observed. No correlation between ventricular arrhythmias and episodes of ST-D could be revealed.

INFLUENCE OF CHANGES IN HEART RATE, BLOOD PRESSURE AND HEART RATEXSYSTOLIC BLOOD PRESSURE PRODUCT ON ST-SEGMENT DEPRESSION

While at baseline only a few episodes of ST-D in the felodipine group were preceded by an increase in heart rate or DP; this was the case during treatment in the majority of the remaining episodes. In the diuretic group the opposite trend could be observed. In both groups the number of episodes preceded by an increase or decrease in BP did not change (see table 2).

Table 4 shows the time course of the DP during the episodes of ST-D. In the diuretic group, the DP significantly increased at the onset of ST-D both at baseline and during treatment; in the felodipine group, only during treatment. The threshold for ST-D

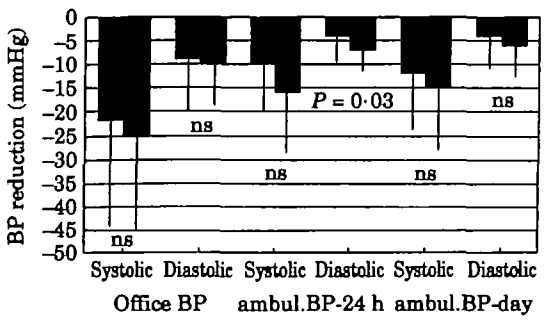

Figure 1 Blood pressure (BP) reduction (in mmHg) after 3 months treatment with felodipine (dark columns) or the diuretic hydrochlorothiazide/triamterene (hatched columns). Indicated are means ± SD and the results of the comparison between the two forms of treatments. ambul=ambulatory; h=hours; ns=not significant.

Table 4 Time course of the heart rate × systolic BP product before, at onset, at maximum and after the episodes of ST-D

		Felodipine group		Diuretic group	
		Baseline	Treatment	Baseline	Treatment
Heart rate × systolic BP product	Before ST-D	11 765 ± 393*	11 017 ± 274*	10 981 ± 267*	12 513 ± 318*
	At onset of ST-D	12 171 ± 340*	13 770 ± 138*	16 210 ± 312*	14 092 ± 319*
	At maximum ST-D	12 015 ± 325	12 306 ± 231	18 870 ± 412	15 653 ± 308
	After ST-D	12 515 ± 423	10 149 ± 189	13 173 ± 280	12 173 ± 297
		*P0·40	*P0·05	*P0·0001	*P0·01

Indicated are means ± SD. For definitions see text.
Comparison between the values before and at onset by paired t-test (data with *).
Multiple ANOVA was performed for all data to reject the null hypothesis (of no difference between treatments and between times of observation).

('ischaemic threshold'), defined as DP at the onset of ST-D, increased during treatment in the felodipine group ($P=0·05$) and decreased in the diuretic group ($P=0·01$).

Discussion

INFLUENCE OF ANTIHYPERTENSIVE TREATMENT ON EPISODES OF ISCHAEMIC-TYPE ST-SEGMENT DEPRESSION

In a group of elderly and very elderly hypertensive patients without manifest coronary artery disease, antihypertensive treatment with felodipine significantly reduced the total number of episodes with ST-D; the number of patients with ischaemic-type ST-D did not change (non-significant decrease). In contrast, antihypertensive treatment with the diuretic combination hydrochlorothiazide/triamterene did not significantly change the number of patients with ST-D and the total number of episodes (non-significant increase). The influence of diuretics on myocardial ischaemia in systemic hypertension (or coronary artery disease) have not been previously tested[9]; our results with the calcium antagonist felodipine are similar to those reported with calcium antagonists in younger patient groups with hypertension[14–16]. Most of the ischaemic episodes both at baseline and during treatment were 'silent', occurred during the day and were preceded by an increase in heart rate and DP, corresponding to data of other investigators[4,5,17].

IS THERE A CORRELATION BETWEEN THE DEGREE OF BP REDUCTION AND THE OCCURRENCE OF ISCHAEMIC EPISODES IN HYPERTENSIVE PATIENTS?

Although the J-curve hypothesis[18,19], that lowering diastolic BP below 85 mmHg may increase the risk of coronary events, seems unlikely in our patients without manifest coronary artery disease (and probably severe coronary artery stenoses), we looked for a possible correlation between BP reduction and episodes of ST-D. The two treatment groups were adequately matched for BP at randomization (with the exception of systolic night-time BP), and BP reduction with both treatment regimens was comparable for office and daytime BP; night-time BP reduction was stronger in the diuretic group. (The latter aspect can partially be explained by the lower night-time BP in the felodipine group at baseline, and the larger proportion of patients in the diuretic group who received the higher dose regimen after 2 weeks due to treatment adjustment according to diastolic office BP.) The major changes in the number of ischaemic episodes (i.e. decrease in the felodipine, non-significant increase in diuretic group) occurred during the day where BP reduction was similar with felodipine and the diuretic. At night, the more pronounced BP reduction with the diuretic was not accompanied by an increase in episodes of ST-D. In addition, the proportion of episodes of ST-D, which were preceded by a decrease in BP, did not change during treatment in either group (Table 3). With our method of discontinuous BP measurement and measurement intervals of 20 min (daytime) and 30 min (night-time) we cannot, however, exclude short-term changes in BP preceding episodes of ST-D. We conclude, that moderate BP reduction (change in office BP from 194/102 to 171/92 mmHg) per se is not associated with an increase in ischaemic episodes in elderly hypertensives without manifest coronary artery disease; even a mean night-time diastolic BP of <80 mmHg was well tolerated without an increase in episodes of ST-D.

MECHANISMS OF TRANSIENT MYOCARDIAL ISCHAEMIA AND OF THEIR TREATMENT IN HYPERTENSION

Most episodes of ST-D were preceded by an increase in heart rate and DP, i.e. by an increase in the oxygen demand of the heart. This confirms previous results in younger[17,20] and older[5] patients with hypertension and stable angina pectoris[21]. Both treatment regimens in our study significantly lowered the DP over 24 h as an indicator of oxygen demand. Therefore, afterload reduction alone with reduced systolic wall stress and reduced oxygen demand cannot explain the different effect of felodipine and the diuretic on the number of ischaemic episodes. Since left ventricular mass remained unchanged during the 3 month treatment period, an

improvement in coronary flow reserve due to regression of left ventricular hypertrophy and following a decrease in the extravascular (myocardial) part of coronary resistance can also be excluded.

The ischaemic threshold, defined as the DP at the onset of ST-D, was increased by felodipine, whereas it was decreased by treatment with the diuretic. In parallel, the proportion of episodes of ST-D preceded by an increase in heart rate or DP, i.e. an increase in oxygen demand, increased during treatment in the felodipine group, while the opposite trend could be observed in the diuretic group. Only changes at the coronary microcirculation level (vascular component of coronary flow reserve) with an improvement in coronary blood flow can adequately explain the anti-ischaemic action of felodipine with a higher ischaemic threshold induced by treatment. Possible mechanisms include reversal of structural and functional impairments in the coronary vascular bed. Calcium antagonists may induce regression of smooth muscle hypertrophy in abnormally 'remodelled' coronary resistance vessels[22,23]; data on felodipine obtained in spontaneous hypertensive rats showed a reduction in media hypertrophy[24]; calcium antagonists may further — at least partially — restore the impaired endothelial function (endothelial mediated relaxation) in patients with systemic hypertension[25–27] (Lüscher: personal communication 1993), and improve blood viscosity[28].

Whether diuretics have any negative effect on coronary microcirculation, which might explain the increase in ischaemic episodes in our study, has not yet been investigated, and can only be answered by further clinical and experimental studies.

We conclude that the afterload reduction with lower systolic wall stress (i.e. the reduced oxygen demand) can only partially explain the anti-ischaemic action of antihypertensive treatment with felodipine; further mechanisms include effects on coronary blood flow and blood viscosity with improved oxygen supply and increased ischaemic threshold of the heart.

STUDY LIMITATIONS

In our group of elderly and very elderly hypertensive patients, we cannot rule out concomitant coronary artery disease — which might be expected in that age group — since coronary arteriography was not performed in all patients; there was, however, no evidence of clinical or electrocardiographic features of manifest coronary artery disease. The majority of previous studies on transient myocardial ischaemia and ST-D were carried out in patients with coronary artery disease[21,29,30]. Altogether, number, type, duration, extent and daily variability of ST-D seem comparable in patients with hypertensive microangiopathy and coronary macroangiopathy[31].

The major limitation of our method of simultaneous Holter and BP recording was discontinuous BP measurement with intervals of 20 min (daytime) and 30 min (night-time) between the BP readings. Short-term changes in BP preceding or accompanying episodes of ST-D cannot therefore be excluded. In addition the BP measurements used for our analyses were not taken at the precise moment of onset of ST-D and at maximum ST-D. The next generation of recorders with BP measurements triggered by ST-segment changes may resolve the latter problem.

CLINICAL IMPLICATIONS

Patients with hypertensive heart disease carry a considerable risk of congestive heart failure, myocardial infarction and sudden cardiac death. While congestive heart failure can be prevented by most forms of antihypertensive treatment, the optimal treatment for prevention of myocardial infarction and sudden cardiac death is still a matter of debate. Transient myocardial ischaemia can be associated with ventricular arrhythmias[8], although other investigators[4] and our study did not find such a correlation. The ultimate role of transient myocardial ischaemia and/or ventricular arrhythmias in the pathogenesis of sudden cardiac death remains to be determined[32].

In most intervention trials in the elderly, diuretics have been used as first-line antihypertensive agents[33,34], showing a reduction in stroke, cardiovascular and total mortality. The exact mechanisms of these positive effects of diuretics have not been elucidated, since diuretics do not necessarily induce regression of left ventricular hypertrophy[35], can impair glucose and lipid metabolism[36], may trigger cardiac arrhythmias[37], and may aggravate episodes of myocardial ischaemia, as shown in our study.

Calcium antagonists are widely used for treatment of systemic hypertension and angina pectoris. In angina pectoris, besides positive results, pro-ischaemic complications have been observed with dihydropyridine calcium antagonists[38], possibly due to a reduction in coronary perfusion pressure and a parallel increase in heart rate. In hypertensive patients without manifest coronary artery disease, we and other investigators[14,16] found a significant anti-ischaemic effect of calcium antagonists. The relatively small reduction in night-time BP with the long-acting calcium antagonist felodipine contrasts with other results, showing a clear 24-h action[39]. Although our study could not demonstrate a regression of left ventricular mass after 3 months, others observed such an effect after prolonged treatment[40,41]; most of these studies were performed with non-dihydropyridine calcium antagonists, which seem, according to a recent meta-analysis[42], more effective than dihydropyridines in inducing regression of left ventricular hypertrophy. In one of these studies, a parallel reduction in ventricular ectopy was shown[40]. Ongoing intervention trials with calcium antagonists (STOP — Hypertension II with felodipine and isradipine; NORDIL with diltiazem; SYST-EUR with nitrendipine; HOT with felodipine — L. Hansson: personal communication 1993) must demonstrate whether the antihypertensive efficacy and positive haemodynamic

profile of these agents will finally improve cardiovascular morbidity and mortality.

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