Br. J. Pharmacol. (1992), **107**, 710–714

Chronic antihypertensive treatment with captopril plus hydrochlorothiazide improves aortic distensibility in the spontaneously hypertensive rat

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1 Adult male spontaneously hypertensive rats (SHR) were given captopril plus hydrochlorothiazide mixed in the diet for 10 weeks. Calculated daily doses were 44 mg kg^{-1} per day for captopril, and 22 mg kg^{-1} per day for hydrochlorothiazide. Separate groups received captopril or hydrochlorothiazide alone, at similar doses, or no treatment. A final group of WKY normotensive rats received no drug.

2 Systolic arterial blood pressure, measured at regular intervals throughout the 10 weeks' period was lowered but not normalized, in groups receiving either captopril plus hydrochlorothiazide, or captopril alone, but not in the group receiving hydrochlorothiazide alone.

3 Following pentobarbitone anaesthesia, systolic arterial blood pressure, measured in the femoral artery, was found to be lower in all treated groups, but the greatest effect was observed in SHR previously treated with captopril plus hydrochlorothiazide. Aortic pulse wave velocity was also lower in treated SHR, and once again the greatest decrease was observed in the group previously treated with captopril plus hydrochlorothiazide.

4 Following pithing, systolic arterial blood pressures were similar in all SHR groups. Aortic pulse wave velocity was lower in pithed rats previously treated with captopril and hydrochlorothiazide.

5 In conclusion, antihypertensive treatment of SHR produces falls in blood pressure and pulse wave velocity, an indicator of aortic distensibility. Results in pithed rats suggest that treatment with the combination of captopril plus hydrochlorothiazide may increase aortic distensibility independently of blood pressure.

Keywords: Rat blood pressure; pulse wave velocity; captopril; hydrochlorothiazide

Introduction

Hypertension is associated not only with structural and functional changes in small arteries and arterioles (leading to an increase in peripheral resistance), but also with changes in large arteries (leading to an increase in rigidity; Milnor, 1989; Nichols & O'Rourke, 1990). This decrease in large artery distensibility is an important factor in target organ damage such as cardiac hypertrophy (Safar *et al.*, 1987; Pannier *et al.*, 1989). Improvement in arterial compliance may require a specific type of antihypertensive therapy (Safar, 1989). Amongst the drugs available, angiotensin I converting enzyme inhibitors may possess a crucial mechanism of action at the level of the large arteries, possibly through inhibition of the local renin-angiotensin system (Dzau & Safar, 1988). Chronic treatment with angiotensin I converting enzyme inhibitors has been shown to increase arterial compliance in both man (Simon *et al.*, 1985), and animals (Levy *et al.*, 1988).

A therapeutic combination of an angiotensin I converting enzyme inhibitor with a diuretic appears to offer potent antihypertensive efficacy and good tolerability (Hansson, 1987). As the possible impact of chronic treatment with such combinations on large artery distensibility has not to our knowledge been investigated, we studied the effect of chronic treatment with the combination of the angiotensin I converting enzyme inhibitor, captopril, and the diuretic, hydrochlorothiazide, on blood pressure and aortic distensibility, in the adult spontaneously hypertensive rat (SHR). Changes in aortic distensibility were estimated from changes in aortic pulse wave velocity (Messerli *et al.*, 1985; Pannier *et al.*, 1989; Nichols & O'Rourke, 1990). Aortic pulse wave velocity was measured in anaesthetized and pithed rats. In the latter preparation, measurement of pulse wave velocity, in the absence of an intact autonomic nervous system, and at a low arterial blood pressure, was taken as an indication of changes in distensibility arising from structural changes of the aortic wall.

Some of these results were presented at the Seventh Scientific Meeting of the American Society of Hypertension, New York, May 1992 (Chillon *et al.*, 1992).

Methods

Animals and chronic drug treatment

Forty-four male SHR and ten male WKY rats were purchased from Iffa-Credo, L'Arbresle, France. On arrival they were 3 months old and weighed 250–270 g. Following measurement of systolic arterial blood pressure (see below), SHR were randomly assigned to groups receiving the following treatments: standard rat chow (UAR, Villemoisson sur Orge, France), chow plus captopril and/or hydrochlorothiazide (Table 1). WKY rats were given standard rat chow. Treatment was continued for 10 weeks during which time food intake and body weight were measured weekly. Food and water were available *ad libitum*.

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Table 1 Chronic treatment of spontaneously hypertensive rats (SHR) for 10 weeks with captopril and hydrochlorothiazide (Cap + HCZ): experimental groups

Group	n	*Rat*	*Treatment*
SHR	12	SHR	Standard rat chow
Cap + HCZ	12	SHR	Captopril (44) + hydrochlorothiazide (22)
Cap	11	SHR	Captopril (41)
HCZ	9	SHR	Hydrochlorothiazide (21)
WKY	10	WKY	Standard rat chow

The average daily doses (mg kg^{-1}) are given in parentheses and were calculated from the quantity of drug in the rat chow and the food intake (determined weekly).

Systolic arterial blood pressure and heart rate measurements in awake rats

Rats were placed in restraining cages in a specially constructed incubator (40°C) for 15 min. A cuff was put around the base of the tail and a microphone was placed over the ventral tail artery, distal to the cuff. The cuff was inflated and systolic arterial blood pressure (mmHg) was taken as being equivalent to the cuff pressure at which the pulse of the tail artery could no longer be detected. Heart rate (beats min^{-1}) was obtained from a fast speed chart recording. Measurements were repeated at least 3 times and an average taken. Systolic arterial blood pressure and heart rate were recorded before the start of treatment, and at 28, 42 and 70 days after the start of treatment.

Arterial blood pressure and pulse wave velocity recording in anaesthetized and pithed rats

Twenty-four h following the final measurement of systolic arterial blood pressure, rats were anaesthetized with sodium pentobarbitone (50 mg kg^{-1}, i.p.), then given atropine (1 mg kg^{-1}, i.p.). Nylon cannulae (1.02 mm external, 0.58 mm internal diameter; Portex-LSA, Fontenay-sous-Bois, France) were introduced into the right common carotid and left femoral arteries up to their aortic ostia. Cannulae were connected to low volume pressure transducers that were in turn connected to a MacLab/MacBridge system (AD Instruments Ltd., Hampstead, UK) for on-line recording of the two arterial blood pressure signals. The frequency response of the cannula plus pressure transducer, filled with 0.15 M NaCl, was flat within ± 5% up to 25 Hz. At 25 Hz, the phase lag was −7°. From 25 to 50 Hz the cannula plus pressure transducer system was underdamped.

Aortic pulse wave velocity (cm s^{-1}) was determined by first calculating the foot of each systolic arterial blood pressure wave, following digital conversion of the original analogue pulse signals. The foot was defined as the point obtained by extrapolating the wave front downward to the point of intersection with the exponential decay of the diastolic arterial blood pressure. The distance (cm) between the 2 cannulae tips was determined by direct measurement following *post mortem* dissection of the aorta.

Carotid arterial blood pressure dP/dt was estimated by electronic differentiation of the blood pressure signal in the carotid artery, before data storage in the computer. As any frequency distortion up to the 20th harmonic of the input signal could affect a rapid phenomenon such as dP/dt, our values are not absolute. Our underdamped system presumably overestimates values for dP/dt. As heart rates were similar in all SHR groups, it can be argued that overestimation of dP/dt would be similar in all groups.

Pulse wave amplification was calculated by dividing the femoral pulse arterial blood pressure by the carotid pulse arterial blood pressure. Pulse wave velocity and amplification, carotid arterial dP/dt, systolic, diastolic, mean and pulse arterial blood pressures, and heart rate were determined over a respiratory cycle and the values of 5 respiratory cycles averaged.

Pressure and heart rate were measured 45 min following induction of anaesthesia. Rats were then pithed and artificially ventilated (50 strokes min^{-1}, 10 ml kg^{-1}) with air. Forty-five min following pithing, a blood sample was taken to check blood gas values (PCO_2, PO_2, and pH) and pressure and heart rate were again recorded.

A final blood sample (5 ml) was taken from the carotid artery cannula for the determination of calcium, phosphate, creatinine, urea, cholesterol, triglycerides, glucose, protein, albumin, and bilirubin levels, and alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase activities. This analysis was performed by use of standard clinical chemistry techniques modified for rat plasma by J.P. Nicolas (INSERM U308, CHRU Brabois, Nancy, France). The first 0.5 ml of blood removed was used for the determination of plasma renin activity (Peters-Haefeli, 1971) and plasma angiotensin I converting enzyme activity (Ryan *et al.*, 1977). The heart was removed, the ventricles dissected out and weighed.

Statistics

One- or two-way analysis of variance followed by the Scheffé test was used. Linear and multiple regression analyses were performed by use of standard parametric methods (a = intercept, b = slope, r = correlation coefficient). Results are given as means ± s.e.mean.

Drugs

Captopril, hydrochlorothiazide and atropine were purchased from Sigma Chemical Co., St Louis, MO, U.S.A. and sodium pentobarbitone from Sanofi SA Paris, France.

Results

Body weight, food intake and clinical chemistry

Body weight increased progressively throughout the 10 weeks' treatment period, but this progression was slower in SHR receiving diets containing hydrochlorothiazide (Table 2). The slower growth rate in these groups was not due to a decrease in foot intake (due to adverse taste, for example) as food intake was significantly higher in the group receiving captopril and hydrochlorothiazide (Table 2).

Furthermore, clinical chemistry analysis revealed that drug treatment had no effect apart from a fall in blood glucose in groups treated with diets containing captopril (Table 3).

Plasma renin activity (SHR: 25 ± 3 g AI ml^{-1} h^{-1}), and angiotensin I converting enzyme activity (SHR: 28 ± 4 nmol ml^{-1} min^{-1}) were similar in all groups. Although these values do not represent basal values because both pithing and pentobarbitone anaesthesia stimulate renin release, they suggest that drug treatment did not chronically stimulate renin release.

The heart weight was reduced in groups treated with captopril and captopril plus hydrochlorothiazide (Table 2). Regression analysis revealed significant correlations between heart weight and pulse wave velocity ($r = 0.485$, $P < 0.05$, d.f. 51), and mean arterial blood pressure ($r = 0.486$, $P < 0.05$, d.f. 51), determined in anaesthetized rats. Multiple regression analysis revealed no significant independent correlation between either arterial blood pressure, or pulse wave velocity, and heart weight (results not shown).

Table 2 Body weight, heart weight and food consumption in rats used in these experiments

	SHR	*Cap + HCZ*	*Cap*	*HCZ*	*WKY*
Body weight (g)					
Day 1	261 ± 5	259 ± 5	257 ± 6	251 ± 3	256 ± 5
Day 70	363 ± 8	311 ± 5*	352 ± 8	325 ± 6*	360 ± 6
Food comsumption (g kg^{-1} per day)					
Day 1	71 ± 1	75 ± 1	71 ± 2	69 ± 2	75 ± 3
Day 70	54 ± 2	69 ± 2*	60 ± 1	62 ± 1	61 ± 2
Heart weight (mg kg^{-1} body weight)	377 ± 11	344 ± 7*	347 ± 9*	381 ± 11	288 ± 8*

*$P < 0.05$ compared to group SHR.
SHR = untreated spontaneously hypertensive rats.
Cap + HCZ = spontaneously hypertensive rats treated with captopril and hydrochlorothiazide.
Cap = spontaneously hypertensive rats treated with captopril.
HCZ = spontaneously hypertensive rats treated with hydrochlorothiazide.
WKY = untreated Wistar-Kyoto normotensive rats.

Table 3 Clinical chemistry of plasma samples from groups of rats used in this study

	SHR	*Cap + HCZ*	*Cap*	*HCZ*	*WKY*
Calcium (mM)	2.54 ± 0.12	2.62 ± 0.06	2.71 ± 0.05	2.68 ± 0.04	2.62 ± 0.08
Phosphate (mM)	2.20 ± 0.34	2.67 ± 0.35	2.59 ± 0.35	2.15 ± 0.23	2.97 ± 0.26
Creatinine (μM)	112 ± 10	107 ± 3	94 ± 13	98 ± 10	94 ± 10
Urea (mM)	8.1 ± 0.6	10.4 ± 0.9	6.0 ± 1.6	7.8 ± 1.2	8.0 ± 0.9
Cholesterol (mM)	0.8 ± 0.1	0.7 ± 0.03	0.9 ± 0.1	0.8 ± 0.1	1.2 ± 0.1*
Triglycerides (mM)	0.43 ± 0.07	0.51 ± 0.08	0.42 ± 0.09	0.48 ± 0.12	0.61 ± 0.09
Glucose (mM)	8.9 ± 1.8	5.3 ± 0.5*	5.5 ± 1.0*	7.2 ± 0.7	4.5 ± 0.9*
Protein (g l^{-1})	47 ± 1	46 ± 1	44 ± 5	46 ± 1	46 ± 2
Albumin (g l^{-1})	26 ± 1	28 ± 1	26 ± 3	26 ± 1	27 ± 1
Bilirubin (μM)	1.08 ± 0.22	1.86 ± 0.91	0.90 ± 0.25	1.33 ± 0.31	1.29 ± 0.40
Alkaline phosphatase (iu l^{-1})	77 ± 6	97 ± 8	92 ± 3	75 ± 11	103 ± 9
Aspartate amino-transferase (iu l^{-1})	282 ± 109	256 ± 82	246 ± 38	204 ± 14	202 ± 20
Alanine amino-transferase (iu l^{-1})	149 ± 86	148 ± 89	97 ± 29	71 ± 8	61 ± 10

*$P < 0.05$ compared to group SHR.
SHR = untreated spontaneously hypertensive rats.
Cap + HCZ = spontaneously hypertensive rats treated with captopril and hydrochlorothiazide.
Cap = spontaneously hypertensive rats treated with captopril.
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WKY = untreated Wistar-Kyoto normotensive rats.

Systolic arterial blood pressure and heart rate in awake rats

Systolic arterial blood pressure in control SHR increased up to the 42nd day. Diets containing captopril produced an initial fall in systolic arterial blood pressure up to the 28th day (Figure 1).

In SHR given captopril alone, the antihypertensive response flattened out, whereas if captopril was given in combination with hydrochlorothiazide, systolic arterial blood pressure continued to fall. The latter treatment did not, however, completely normalize systolic arterial blood pressure (comparison with WKY rats). Hydrochlorothiazide alone had no effect on systolic arterial blood pressure. Systolic arterial blood pressure in WKY rats was stable throughout the study (day 70: 143 ± 2 mmHg).

There was no significant effect of drug or time on heart rate; values on day 70 were 431 ± 16 beats min^{-1} for SHR and 360 ± 9 beats min^{-1} for WKY.

Arterial blood pressure and pulse wave velocity in anaesthetized and pithed rats

Arterial blood pressure measured under pentobarbitone anaesthesia revealed that all drug treatments lowered mean and diastolic arterial blood pressures but did not normalize these pressures (Table 4). Only diets containing hydrochlorothiazide lowered systolic and pulse arterial blood pressures. Pulse wave velocity was diminished by all treatments, the greatest fall being observed in the group of SHR previously treated with captopril and hydrochlorothiazide. In WKY rats, pulse wave velocity (Y) was significantly correlated to arterial blood pressure (X). Values for mean arterial blood pressure were $a = -21$, $b = 5.6$, $r = 0.77$, $P < 0.05$, $n = 10$. Values for systolic arterial blood pressure were $a = -32$, $b = 4.8$, $r = 0.76$, $P < 0.05$, $n = 10$. In the different SHR groups there were no significant correlations between pulse wave velocity and arterial blood pressure.

Pulse wave amplification was not significantly different from 1 in SHR. In SHR treated with captopril plus hydrochlorothiazide, pulse wave amplification was 1.23 ± 0.06 and was similar to the value for WKY (1.32 ± 0.05).

In pithed rats, there was no significant correlation between pulse wave velocity and arterial blood pressure in any group. Drug treatment did not lower arterial blood pressure. The combination of captopril and hydrochlorothiazide produced a significant fall in pulse wave velocity. Drug treatment had no effect on heart rate (Table 4) or carotid arterial dP/dt (anaesthetized SHR 1750 ± 231 mmHg s^{-1}, and pithed SHR 1174 ± 111 mmHg s^{-1}, $n = 12$), in either anaesthetized or pithed rats.

Discussion

The main result of this experiment is that antihypertensive treatment of adult SHR with a combination of captopril and

hydrochlorothiazide improves aortic distensibility as shown by an increase in pulse wave amplification in anaesthetized SHR, and a decrease in pulse wave velocity, in the absence of any significant effect on arterial blood pressure, in pithed SHR. The latter result suggests that the combination of captopril and hydrochlorothiazide may have a specific effect on aortic rigidity.

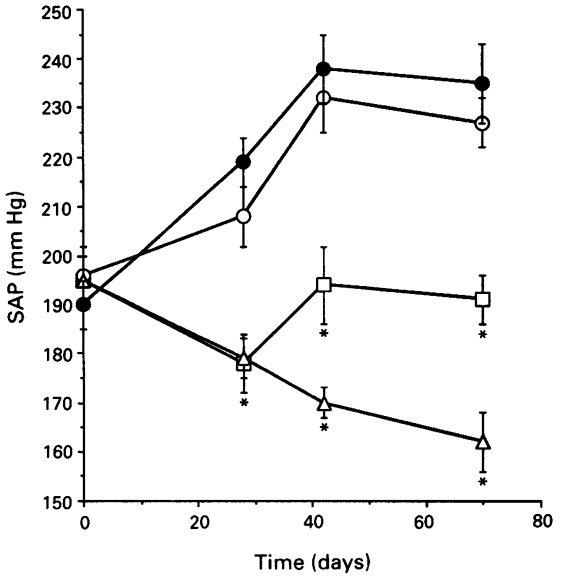

Figure 1 Change in systolic arterial pressure (SAP) (mmHg) in spontaneously hypertensive rats (SHR) treated (open symbols) with captopril plus hydrochlorothiazide (triangles), captopril (squares) or hydrochlorothiazide (circles). A control group of SHR (solid circles) received standard rat chow. *$P<0.05$ compared to SHR group.

Our observation that in the group treated with captopril plus hydrochlorothiazide, the antihypertensive effects of the representatives of two separate classes of drugs are additive is interesting but not original (Rubin *et al.*, 1978; Oster & Epstein, 1987). The explanation generally given for this synergistic effect is stimulation by the diuretic of the renin-angiotensin-aldosterone axis, possibly following diuretic-induced salt and water loss (Miyamoto *et al.*, 1983). Other factors such as direct vascular effects may be involved. Hydrochlorothiazide and captopril are synergistic in SHR in which urinary loss is prevented by bilateral ureteral ligation (Chiu *et al.*, 1985), although this has been contested (Chan *et al.*, 1982). One argument in favour of an effect on vascular function and structure in our experiment can be based on the fact that the synergism between the two drugs was seen after 1 month of treatment only. The authors cited previously reported an immediate synergistic effect using protocols in which the drugs were given by gavage, and arterial blood pressure was measured shortly afterwards. Our protocol in which the drugs were mixed into the diet and arterial blood pressure was measured during the day, presumably a long time after the drug was ingested during the night, probably investigates longer term effects of the antihypertensive treatment on vascular structure.

It should be noted that the evidence for the synergism between captopril and hydrochlorothiazide comes from the recordings of systolic arterial blood pressure in awake SHR. Systolic arterial blood arterial recordings obtained in pentobarbitone anaesthetized SHR were similar to those obtained in awake SHR except in the case of SHR previously treated with hydrochlorothiazide.

An effect of antihypertensive treatment with captopril plus

Table 4 Arterial blood pressure (mmHg), heart rate (beats min^{-1}) and pulse wave velocity (PWV, cm s^{-1}) in SHR chronically treated with captopril (Cap) and/or hydrochlorothiazide (HCZ) and in WKY, measured in the anaesthetized and pithed states

	SHR	*Cap + HCZ*	*Cap*	*HCZ*	*WKY*
Pentobarbitone anaesthesia					
Arterial blood pressure (carotid)					
systolic	209 ± 11	149 ± 7*	188 ± 7	179 ± 13*	112 ± 5*
diastolic	158 ± 10	107 ± 7*	135 ± 7*	136 ± 9*	84 ± 4*
mean	175 ± 10	121 ± 7*	153 ± 7*	149 ± 10*	94 ± 4*
pulse	51 ± 3	42 ± 3*	53 ± 4	43 ± 5*	28 ± 1*
Arterial blood pressure (femoral)					
systolic	215 ± 9	155 ± 8*	184 ± 8	177 ± 11*	118 ± 5*
diastolic	155 ± 9	102 ± 8*	127 ± 7*	130 ± 9*	81 ± 4*
mean	175 ± 10	120 ± 7*	149 ± 7*	146 ± 9*	93 ± 4*
pulse	60 ± 3	53 ± 4	67 ± 5	47 ± 2*	37 ± 1*
PWV	1005 ± 43	587 ± 47*	708 ± 35*	674 ± 72*	490 ± 25*
Heart rate	336 ± 9	343 ± 7	352 ± 12	332 ± 7	276 ± 7*
Pithed					
Arterial blood pressure (carotid)					
systolic	67 ± 2	64 ± 3	64 ± 4	71 ± 4	60 ± 2
diastolic	38 ± 2	34 ± 2	38 ± 3	42 ± 2	31 ± 2*
mean	46 ± 2	44 ± 2	47 ± 3	52 ± 3	40 ± 2
pulse	29 ± 2	30 ± 1	27 ± 2	29 ± 3	29 ± 2
Arterial blood pressure (femoral)					
systolic	61 ± 3	53 ± 3	55 ± 3	64 ± 3	49 ± 2*
diastolic	35 ± 2	33 ± 2	31 ± 2	41 ± 2	28 ± 1*
mean	44 ± 2	40 ± 2	39 ± 2	49 ± 2	35 ± 2*
pulse	25 ± 2	20 ± 1	24 ± 1	23 ± 2	21 ± 2
PWV	434 ± 12	368 ± 22*	392 ± 20	379 ± 29	368 ± 19*
Heart rate	247 ± 9	253 ± 5	251 ± 5	268 ± 12	242 ± 8

*$P<0.05$ compared to group SHR.
SHR = untreated spontaneously hypertensive rats.
Cap + HCZ = spontaneously hypertensive rats treated with captopril and hydrochlorothiazide.
Cap = spontaneously hypertensive rats treated with captopril.
HCZ = spontaneously hypertensive rats treated with hydrochlorothiazide.
WKY = untreated Wistar-Kyoto normotensive rats.

hydrochlorothiazide on vascular structure could explain the decrease in pulse wave velocity seen in pithed rats. The values for pulse wave velocity in normotensive WKY rats are similar to those published for man and the dog (for review see Milnor, 1989). Pulse wave velocity was increased in anaesthetized or pithed SHR, and the increase seen in anaesthetized SHR corresponds to the increase reported to occur in hypertensive patients by Messerli *et al.* (1985). Pulse wave velocity also increases with age in man (Messerli *et al.*, 1985; Milnor, 1989) and we have recently shown that the same phenomenon occurs in rats (Chillon *et al.*, 1992).

Angiotensin I converting enzyme-inhibitors have been previously reported to improve large artery compliance in rats (Levy *et al.*, 1988; 1989), and in man (Simon *et al.*, 1985). To our knowledge this is the first description of the effect of a combination of an angiotensin I converting enzyme inhibitor and a diuretic on arterial distensibility. Levy and coworkers reported that the decrease in arterial distensibility (as reflected by carotid artery compliance) in hypertensive rats, and the increase produced by antihypertensive drugs, were maximal when measured at pressures near the operating blood pressure of the animal. A similar phenomenon is observed in our results. Changes in pulse wave velocity induced by hypertension or antihypertensive treatment are much greater in anaesthetized rats than in pithed rats in which arterial blood pressure is much lower. Measurement of pulse wave velocity at the lower arterial blood pressure of the pithed rat presumably reflects elastic stiffness relatively unaffected by smooth muscle contractility.

Pulse wave velocity and arterial blood pressure were both higher in SHR than in WKY, and in anaesthetized than in pithed rats. The observation that pulse wave velocity is linked to arterial blood pressure is not original (Milnor, 1989). The fact that in pithed rats, captopril plus hydrochlorothiazide significantly lowered pulse wave velocity, but not arterial blood pressure, argues against our observing a lower pulse wave velocity in this group simply because they had a lower arterial blood pressure. A chronic effect of arterial blood pressure cannot be excluded. The more efficient chronic control of blood pressure obtained with the captopril plus hydrochlorothiazide combination may have produced a more pronounced decrease in transmural pressure leading to a greater regression of the structural changes of the vessel wall.

Drug-induced changes in the arterial blood pressure of the anaesthetized rats suggest that treatment with diets containing hydrochlorothiazide has a specific effect on arterial rigidity. In both the hydrochlorothiazide and captopril plus hydrochlorothiazide groups, the decrease of systolic arterial blood pressure was greater than that of diastolic arterial blood pressure, and both treatments decreased pulse arterial blood pressure. Systolic arterial blood pressure depends upon ventricular ejection and aortic rigidity (Safar *et al.*, 1983). Although we have no measurement of possible drug effects on ventricular hypertrophy, simple regression analysis revealed a significant correlation between pulse wave velocity and cardiac hypertrophy. Further experiments with larger groups and longer treatment may permit a definite answer to be given.

In conclusion, antihypertensive treatment with captopril plus hydrochlorothiazide improved aortic distensibility, as judged from the decrease in aortic pulse wave velocity in SHR. We suggest that this effect may be related to an effect of this combination of drugs on the vascular wall.

The authors thank Théraplix SA, Paris, France for financial support.

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(Received April 30, 1992
Revised July 2, 1992
Accepted July 6, 1992)