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HEART RATE CONTROL IN HYPERTENSIVE PATIENTS TREATED BY CAPTOPRIL

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1 The effect of captopril on autonomic reflex functions has been investigated in fifteen patients with essential hypertension by examining their responses to tests of baroreceptor function (Valsalva's manoeuvre and upright posture), sympathetic nervous system reactivity (cold pressor and mental stress tests) and parasympathetic reactivity (diving test) before and after 3 weeks' treatment with captopril.

2 Captopril significantly reduced arterial blood pressure and resting heart rate but did not affect cardiovascular responses to Valsalva's manoeuvre, upright posture, cold pressor and mental stress tests.

3 The bradycardia associated with the diving reflex test was significantly enhanced by captopril ($P < 0.01$).

4 These results indicate that treatment with captopril is associated with increased parasympathetic tone but without inhibition of baroreceptor or sympathetic reflexes.

Introduction

The antihypertensive efficacy of captopril has been well documented in man and experimental animals in both renovascular and essential hypertension (Case *et al.*, 1978; Gavras *et al.*, 1978; Muirhead *et al.*, 1978; Bravo & Tarazi, 1979). Acute and long-term studies have reported that the reduction in blood pressure is related to decrease in total peripheral resistance with minimal changes in cardiac output (Tarazi *et al.*, 1980; deBruyn *et al.*, 1981). This pattern of haemodynamic effects has also resulted in the successful use of captopril in the treatment of patients with congestive cardiac failure (Awan *et al.*, 1981; Maslowski *et al.*, 1981). As a result of both its vasodilator action and its hypotensive effect captopril might be expected to produce a reflex tachycardia but many reports have specifically noted an absence of an increase in heart rate (Cody *et al.*, 1978; Tarazi *et al.*, 1980) or even a reduction in heart rate (Friedlander, 1979; MacGregor *et al.*, 1979) despite a significant decrease in arterial pressure and in total peripheral resistance. The association of vasodilation, hypotension and absence of an increase in heart rate are features of many agents that interfere with the renin-angiotensin system at different levels (Mookherjee *et al.*, 1978; Fouad *et al.*, 1980) but the mechanism has not yet been completely elucidated.

This study investigates the possible mechanisms by which captopril might affect heart rate control, particularly by interference with the autonomic nervous system or by impairment of baroreceptor-mediated reflexes. There is some evidence of impaired baroreceptor function in studies of experimental animals (Clough *et al.*, 1979; Adigun *et al.*, 1980) but this has not been confirmed (Petty & Reid, 1981). However, we can find no reports of comparable studies in human subjects.

Methods

Fifteen patients (ten males and five females) aged between 25–58 years (mean 44 years) with mild to moderate essential hypertension (WHO state I–II) and 15 healthy volunteer subjects (nine males and six females) aged between 28 and 54 years (mean 38 years) were studied. All subjects gave their informed consent in writing. Ten patients had not previously been treated with antihypertensive drugs and the remainder were untreated for 1 month before the study. Both patients and volunteer subjects were taking a free dietary intake of sodium and potassium. All subjects were asked to fast overnight and avoid coffee, chocolate, tea, alcohol and smoking for at least 12 h prior to, and during the studies. Hyper-

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tensive patients took part in a trial consisting of four treatment periods, each of 1 week. After an initial placebo period lasting 1 week, captopril (Squibb) was started at a dose of 25 mg thrice daily. The dose was increased weekly by 75 mg/day until the diastolic blood pressure fell below 95 mm Hg or a maximum daily dose of 450 mg was reached. All the patients were seen weekly at the end of each treatment period. At each visit, they arrived at the hospital between 07.30 h and 08.00 h and were given the morning dose of captopril or placebo. After at least 1 h of supine rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Arteriosonde Roche) and heart rate (HR) (Electrocardiography) were recorded. A non-invasive study of the autonomic nervous system, using the tests detailed below, was carried out at the end of the placebo treatment period and at the end of the third week of treatment. All tests were executed between 09.00 h and 12.00 h at a laboratory temperature maintained at 24°C. A calm and relaxed environment was ensured for the tests, which were always performed in the same order at 15 min intervals. Responses in the 15 healthy volunteer subjects were obtained for each test under identical circumstances to the patients. In nine of the 15 normal subjects the diving test was repeated after an interval of 3 weeks. Both patients and volunteer subjects had no previous experience of the tests employed and were studied as outpatients.

Tests of autonomic nervous system function

Valsalva's manoeuvre The subject was studied supine and trained to maintain an expiratory pressure of 40 mm Hg for 13 s, by blowing through a mouthpiece attached to an anaeroid manometer. HR was recorded continuously throughout the manoeuvre and for 30 s after release of the strain. The result was expressed as the ratio between the shortest R-R interval in phase III to the longest R-R interval in phase IV (Valsalva ratio). The manoeuvre was repeated three times and the highest ratio accepted.

Upright posture After 1 h of supine rest the subject's arterial blood pressure (ABP) and HR were recorded ten times at 1 min intervals (resting values). Each patient was then asked to stand up quietly, for 7 min, without making any other movement. During standing ABP and HR were recorded at 1 min intervals. Changes of SBP and DBP and HR were expressed as the variation with respect to the mean values recorded during the control period.

After assuming the sitting position the patient performed the following tests:

Cold pressor test After a control period of 10 min, the patients performed a cold pressor test by placing their right hand in a basin containing equal parts of water and ice for 2 min. In the control period and during the test ABP and HR were measured at 1 min intervals. The results were expressed as the difference between the mean resting values of SBP, DBP and HR and the highest value obtained during the manoeuvre.

Mental stress test The patients underwent three measurements of ABP and HR (resting values) at 5 min intervals. A mental arithmetic test was done by continuously subtracting 17 from a four-digit number as quickly as possible for 5 min. The patient was asked to subtract the number mentally and to write down the answers. ABP and HR were recorded at 1 min intervals during and immediately after the test. The results were expressed as the difference between the mean resting values of SBP, DBP and HR and the mean of the five values found under stress.

Diving test The subjects sat for 5 min and breathed quietly. They then bent forward so that their faces were 3–4 cm over a basin with water at 18°C, and on a signal, lowered the face until it was covered with water to the level of the ears. No maximal inspiration before or Valsalva manoeuvre during the procedure was permitted. Facial immersion was continued as long as tolerated with a minimum period of 13 s. Before and during the test HR was monitored. The results were expressed as the difference between resting HR (the average of the five R-R intervals immediately preceding the test) and the maximal bradycardia during the manoeuvre. The test was performed three times at 5 min intervals, and the manoeuvre in which the maximum bradycardia was achieved was used in data analysis.

Statistical procedures

Statistical analysis of the results were peformed by the Wilcoxon pairs signed-ranks test. Results are presented as mean values ± s.e. mean. All values identified as significant have a P value of at least < 0.05.

Results

Effect on supine ABP and HR

Long-term administration of captopril produced a significant reduction of SBP (170.5 ± 3.8 *v* 159.8 ± 6.1 mm Hg, $P < 0.05$) and DBP (110 ± 2.3 *v* 99.4 ± 2.8 mm Hg, $P < 0.01$). Six patients achieved normotensive levels (DBP ≤ 95 mm Hg), at a maintenance dose of 150 mg/day. The mean HR decreased from 75.6 ± 2.5 to 70.9 ± 2.2 beats/min, $P < 0.05$ (Figure 1).

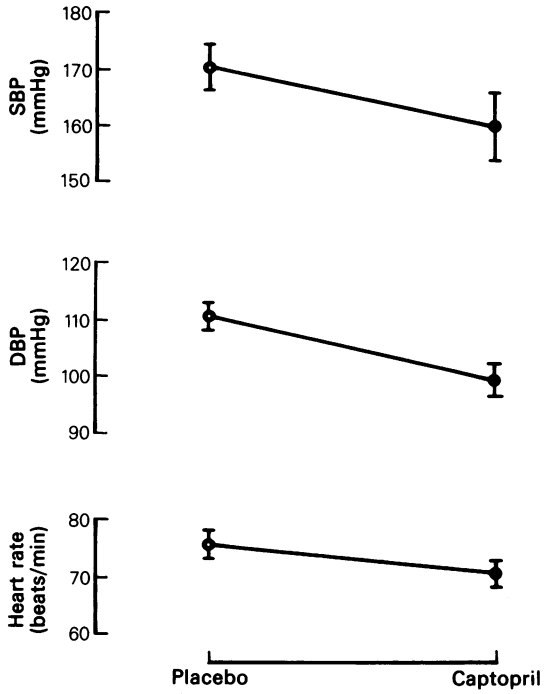

Figure 1 Effect of treatment with captopril on supine blood pressure and heart rate. Reduction in both systolic blood pressure (SBP) and heart rate was significant at $P < 0.05$. The decrease in diastolic blood pressure (DBP) was significant at $P < 0.01$. Data are shown as mean ± s.e. mean.

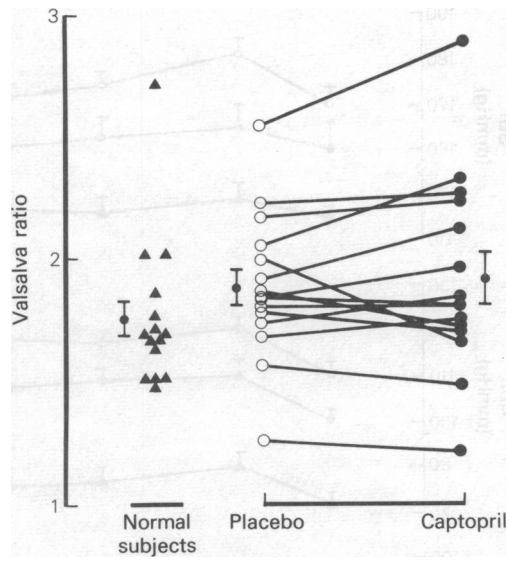

Figure 2 Individual values of Valsalva ratio in normal subjects (▲) and in hypertensive patients during placebo and after treatment with captopril (○–●).

Effects on responses to autonomic tests

Valsalva's manoeuvre The individual values of the Valsalva ratios for hypertensive patients during placebo and after captopril therapy are shown in Figure 2. Treatment with captopril produced a slight increase in Valsalva ratio from 1.88 ± 0.07 to 1.91 ± 0.1, but the difference was not statistically significant. One patient showed a Valsalva ratio below the lowest level within the normal range both during placebo period and during treatment.

Upright posture Mean values of HR and ABP changes in response to upright posture during placebo and after therapy are shown in Figure 3. In both periods tested SBP and DBP peaked at 2 min and declined slightly thereafter. There was no difference between the mean increase in SBP and DBP before and after therapy. HR increase due to postural changes was not significantly altered by the administration of captopril. Only one patient had a significant orthostatic hypotension (SBP fall > 20 mm Hg) during placebo. The haemodynamic response to upright posture slightly improved after therapy.

Cold pressor test The average changes of ABP and HR from basal values in response to the cold pressor test performed in the two periods tested are shown in Table 1. There were no significant differences between the average increments found during placebo and after therapy of SBP, DBP and HR.

Mental stress test The average changes in ABP and in HR from basal values induced by mental stress test are shown in Table 1. In all patients HR and ABP (both systolic and diastolic) markedly increased when under mental stress both during placebo period and after treatment. There was no significant difference between the actual rises found before and after therapy, in SBP, DBP and HR.

Diving test Fourteen patients responded to apnoeic face immersion with a rapid fall in resting HR both during the placebo period and after therapy. Individual decrements in HR from basal values are shown in Figure 4. The mean fall in HR was significantly greater after treatment with captopril (from −25.2 ± 3.2 to −31.9 ± 2.7, $P < 0.01$). One patient had an increase in HR in response to the diving test in both periods tested and was omitted in data analysis. Treatment with captopril, however, slightly improved the response to diving test in this patient. The mean drop in HR during diving test was similar in the two periods tested in volunteer subjects (24.4 ± 2.6 *v* 24.2 ± 2.9).

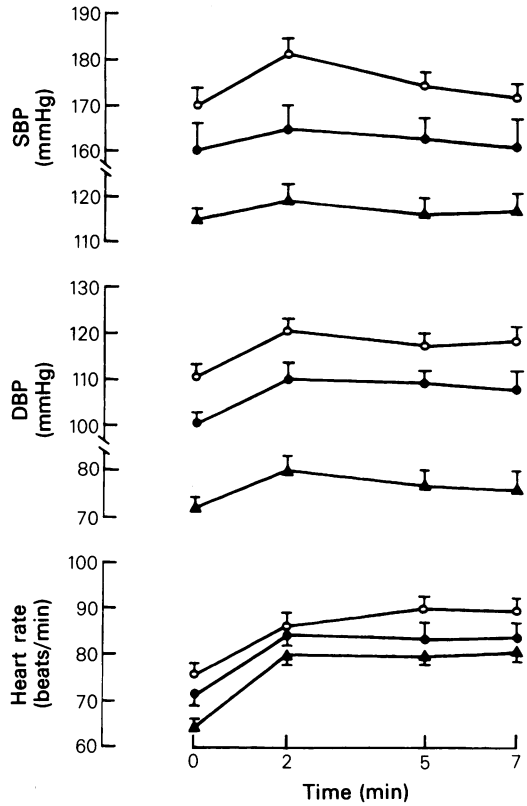

Figure 3 Systolic (SBP) and diastolic (DBP) arterial blood pressure and heart rate during 7 min upright posture in normal subjects (▲) and hypertensive patients during placebo and after treatment with captopril (O–●). Data are shown as mean ± s.e. mean.

Discussion

Our results show that the reduction in systemic arterial pressure in patients with essential hypertension treated with captopril was associated with a decrease in supine heart rate. Most investigators have found that in hypertensive patients the reduction of blood pressure induced by both acute and chronic treatment with captopril (MacGregor *et al.*, 1979; Fagard *et al.*, 1980; deBruyn *et al.*, 1981) was not associated with an increase in heart rate and more recently Millar *et al.* (1981) have described the absence of reflex tachycardia in response to an acute fall in blood pressure after a single oral dose of captopril in salt-depleted normal subjects.

A decrease or a lack of change in heart rate despite a significant blood pressure reduction could have several explanations, including (1) restoration to normal of previously impaired left ventricular function when the blood pressure is normalised, (2)

Table 1 Blood pressure and heart rate responses to cold pressor and mental stress tests

		Cold pressor test					*Mental stress test*				
	n	*ΔSBP (mm Hg)*	P	*ΔDBP (mm Hg)*	P	*ΔHR (beats/min)*	*ΔSBP (mm Hg)*	P	*ΔDBP (mm Hg)*	P	*ΔHR (beats/min)*
Normal subjects	15	18.9 ± 2.2		16.4 ± 2.1		5.9 ± 2.3	16.7 ± 1.8		12.4 ± 1.0		11.0 ± 2.4
Hypertensive patients											
During placebo	15	27.4 ± 3.0	NS	17.4 ± 1.9	NS	9.1 ± 0.7	33.5 ± 3.2	NS	16.0 ± 1.4	NS	13.5 ± 2.2
During captopril	15	32.7 ± 3.3		19.3 ± 2.3		9.5 ± 1.1	33.4 ± 3.1		13.6 ± 1.3		12.6 ± 2.2

Mean values ± s.e. mean
NS: no statistically significant difference
ΔSBP: changes in systolic blood pressure from basal values
ΔDBP: changes in diastolic blood pressure from basal values
ΔHR: changes in heart rate from basal values

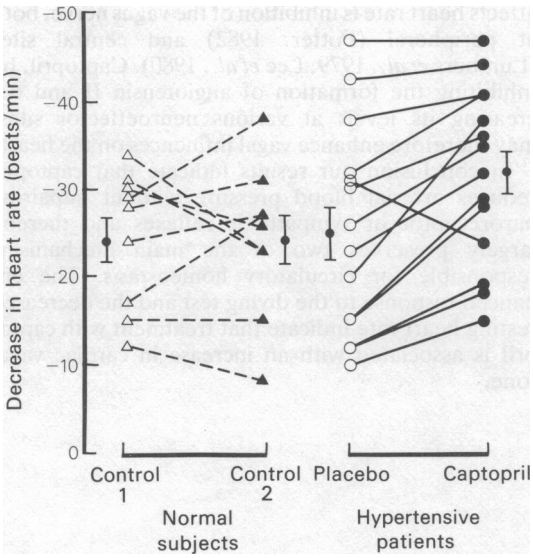

Figure 4 Individual decrements in heart rate in response to diving test in normal subjects tested on two occasions separated by 3 weeks (△---▲) and in 14 hypertensive patients during placebo and after captopril (○–●). The response to diving test was significantly ($P < 0.01$) accentuated by therapy in hypertensive patients.

alteration in the baroreceptor reflexes, for example increased baroreceptor threshold leading to decreased sensitivity to blood pressure reduction, (3) reduction in sympathetic nervous system activity, (4) enhanced parasympathetic activity.

Our patients showed no evidence of left ventricular failure or left ventricular dysfunction in the pretreatment period. This was confirmed by their responses to Valsalva's manoeuvre, which is known to be a sensitive test for detecting left ventricular dysfunction (Levin, 1966; Zema *et al.*, 1980). This result indicates that improvement in cardiac function is not the factor responsible for the changes in heart rate.

Our findings also suggest that blood pressure reduction by captopril does not interfere with baroreceptor reflexes. The cardiovascular responses to the Valsalva's manoeuvre and to the postural test, which are widely used to assess the integrity of the baroreflex arc, were unmodified by the drug. The absence of postural hypotension in patients receiving captopril, either alone (Bravo & Tarazi, 1979; Gavras *et al.*, 1980; Rockel *et al.*, 1980; deBruyn *et al.*, 1981) or in combination with diuretics or with a low sodium diet (Cody *et al.*, 1978; Cody *et al.*, 1979; Johns *et al.*, 1980) is also consistent with intact baroreflex function. Furthermore, Mancia *et al.* (1981) have recently suggested that reducing blood pressure with captopril may be accompanied by increased baroreflex sensitivity during administration of trinitroglycerine. Two other orally active converting enzyme inhibitors, MK421 and MK521, are also without effect on responses to Valsalva's manoeuvre or head-up tilt (Millar *et al.*, 1982).

Although a possible effect of captopril on sympathetic nervous system activity has been proposed (Cody *et al.*, 1978; Antonaccio & Kerwin, 1981; Muiesan, 1981) the cardiovascular responses to upright posture and Valsalva's manoeuvre in our patients do not support this hypothesis. The blood pressure and heart rate responses to the cold pressor test and to the mental stress test, which are used to assess efferent sympathetic fibres (Ibrahim *et al.*, 1974) were similar before and during captopril therapy in our patients. This also suggests that there was no interference with sympathetic nervous system activity. The same conclusion has been reached by other authors who have tested sympathetic activity by determination of supine and standing plasma catecholamines (Morganti *et al.*, 1980; deBruyn *et al.*, 1981).

There is evidence that the parasympathetic system is involved in the reflex compensatory cardiostimulation which occurs during vasodilator treatment (Man in't Veld *et al.*, 1980). In our study, two results indicate that captopril is associated with an increase in parasympathetic tone. Firstly, resting heart rate was significantly lower during captopril treatment than during placebo in our hypertensive patients. It is known that the relative contributions to heart rate of vagal and sympathetic activity vary according to the levels of mental and physical activity (Nyberg, 1981). However, parasympathetic tone is the major factor determining heart rate in the resting supine position (Kent & Cooper, 1974; Hager *et al.*, 1981). Secondly, a significant effect of captopril on the response to the diving test was found in our hypertensive patients. Diving-induced bradycardia was significantly enhanced during treatment with captopril, compared to placebo, despite the decrease in resting heart rate. The diving reflex is an oxygen-conserving reflex which has been extensively studied in man (Kawakami *et al.*, 1967; Heistad *et al.*, 1968; Bergman *et al.*, 1972; Finley *et al.*, 1979). Apnoea combined with facial immersion in water, leads to a number of physiological responses including a marked decrease in heart rate (Brick, 1966). Since this reflex does not involve baroreceptor pathways (Bennett *et al.*, 1976) and the immediate reflex bradycardia is mediated only by vagal efferent pathways (Heistad *et al.*, 1968; Finley *et al.*, 1979) this test offers a simple and safe method of assessing the parasympathetic system. It is likely that intra-subject variability and adaptive mechanisms will affect the performance of the diving test and consequently the interpretation of the results. In an attempt to assess the relevance of these factors and to overcome this problem, we deliberately selected normal subjects who had not previously par-

ticipated in research studies and we repeated the diving test in both normals and patients after 3 weeks with the test being performed several times on each study day. It was noted that there was no significant change in the normal group, although individual results varied when the diving test was repeated three weeks later, with three subjects showing an increased response and six a decreased or unchanged response. In contrast, thirteen of the fifteen hypertensive patients showed an increased response after treatment with captopril for 3 weeks, suggesting that the enhanced diving-induced bradycardia was an effect of the therapy.

It has been demonstrated in animal studies that the most important mechanism by which angiotensin II affects heart rate is inhibition of the vagus nerve, both at peripheral (Potter, 1982) and central sites (Lumbers *et al.*, 1979; Lee *et al.*, 1980). Captopril, by inhibiting the formation of angiotensin II and decreasing its levels at various neuroeffector sites, may therefore enhance vagal influences on the heart.

In conclusion our results indicate that captopril reduces arterial blood pressure without impairing baroreceptor or sympathetic reflexes and thereby largely preserves two of the main mechanisms responsible for circulatory homeostasis. The enhanced response to the diving test and the decreased resting heart rate indicate that treatment with captopril is associated with an increase in cardiac vagal tone.

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