The Influence of Long-Term ACE Inhibitor Treatment on Circulatory Responses to Stress in Human Hypertension
Thomas Kahan and Keith Eliasson

The objective of the study was to examine the influence of angiotensin converting enzyme (ACE) inhibition on circulatory responses to standardized stress tests in primary mild to moderate hypertension. Patients (n = 28) received 5 mg ramipril daily or placebo for 6 weeks in a double-blind crossover design, followed by 6 months of open ramipril treatment. Mental stress (a 20-min Stroop’s color word conflict test) and a cold pressor test were performed at the end of each of the three study periods. Noninvasive blood pressure and heart rate were recorded.

Ramipril reduced systolic and diastolic blood pressure levels at rest (from 146 ± 3/99 ± 3 with placebo to 135 ± 4/94 ± 3 at 6 weeks, and 136 ± 4/91 ± 3 mm Hg at 6 months, in the laboratory) and during mental stress. Resting heart rates were unchanged by ramipril. Ramipril reduced systolic blood pressure and heart rate responses during mental stress; diastolic blood pressure responses were unchanged. Ramipril reduced cardiac workload (systolic blood pressure × heart rate) levels and responses. Treatment effects at 6 months were generally greater than at 6 weeks. During the cold pressor test systolic and diastolic blood pressure levels were lowered by ramipril, but responses were unchanged. Heart rate responses, however, were reduced. Thus, ramipril reduced cardiac workload levels and responses also during the cold pressor test.

These findings show that ACE inhibitors can reduce cardiac workload during stressful situations. If confirmed, this would seem to offer an advantage in the treatment of hypertension.

Key Words: Hypertension, human, stress, angiotensin converting enzyme inhibitors, ramipril.
pressure levels may be particularly beneficial. One way to evaluate antihypertensive drugs in this respect would be to study the effects of drugs on 24-h ambulatory blood pressure monitoring. Another approach is to examine the effects of antihypertensive therapy on circulatory responses evoked by stress tests in the laboratory. This would allow for a greater standardization of the conditions under which the patient is studied.

Mental stress elicits a response similar to that evoked by the hypothalamic defense reaction, with an increased cardiac output, vasoconstriction in splanchic organs and the kidneys, skeletal muscle vasodilatation, and reduced systemic vascular resistance. This response is similar to the circulatory pattern observed in early hypertension. The resemblance has led us and others to examine the possible relationship between hypertension and responses to behavioral stress. The cold pressor test evokes a generalized sympathetic neurogenic activation in peripheral vascular beds, and a quite different circulatory response to that of mental stress. Our previous findings suggest larger reductions in cardiac workload during stress by β-adrenoceptor antagonist treatment than by therapy with a thiazide or by a calcium antagonist. These differences in the circulatory responses between antihypertensive drugs suggest that the reduction in cardiac workload during stress is not only an effect of the reduction in blood pressure.

The influence of long-term angiotensin converting enzyme (ACE) inhibitors on cardiovascular responses to stress has not been well studied in randomized controlled studies. The present investigation aimed to examine this issue. We studied the effects of ramipril on mental stress induced by Stroop’s color word conflict test in a double-blind placebo controlled crossover design. For comparison, a cold pressor test was included. To evaluate possible long-term effects, the tests were repeated after an additional 6 months’ period of active ramipril treatment in all subjects. The stress provocations were studied under similar experimental conditions as we have used in previous studies with other drug classes.

MATERIALS AND METHODS

Subjects Patients attending the outpatient hypertension clinics at Danderyd Hospital and Karolinska Hospital were offered to take part in the study, provided their casual supine diastolic blood pressure was 95 to 115 mm Hg (inclusive) with no antihypertensive drug therapy for the previous 4 weeks. The study population consisted of 18 men and 10 women. Their mean age was 49 ± 2 (range, 22 to 69) years, weight 77 ± 3 (range, 55 to 111) kg, height 174 ± 2 (range, 156 to 193) cm, and body mass index 25 ± 1 (range, 19 to 35) kg/m². Clinical investigation and routine laboratory examinations revealed no signs of secondary hypertension or organ damage and the patients were classified to have mild to moderate primary hypertension, corresponding to WHO stages I and II (24 and four subjects, respectively). The estimated mean duration of hypertension was 7 ± 1 (range, 0 to 25) years; five subjects were previously untreated. The study was performed according to institutional guidelines and was approved by the Ethics Committee of the Karolinska Hospital. Informed consent was obtained from all subjects.

Study Procedures The patients were randomized to receive placebo or 5 mg ramipril once daily for 6 weeks in a double-blind crossover design. All subjects then continued into a 6-month period of open treatment with ramipril. During this part of the study, dose titration was allowed (2.5, 5, or 10 mg once daily) to achieve a supine diastolic blood pressure less than 95 mm Hg. No other medication that could possibly interfere with blood pressure control was allowed during the study. The visits at the outpatient clinic were made at randomization, at the end of the two double-blind treatment periods at 6 and 12 weeks, respectively, and after 3 and 6 months of open ramipril treatment. Blood pressures and heart rate were recorded at each outpatient clinic visit 24 h after the preceding dose, ie, at estimated trough drug plasma concentrations. General wellbeing was assessed by two sets of scales that the patient was asked to fill in at home a few days before each outpatient clinic visit, except the visit at 3 months of open ramipril treatment. Laboratory stress testing was done at the end of the two double-blind treatment periods at 6 and 12 weeks, respectively, and after 6 months of open ramipril treatment. The patients took the study medication with a light meal 3 to 4 h before the arrival in the laboratory at noon, ie, stress testing was made at estimated peak drug plasma concentrations. They were asked to refrain from caffeine-containing beverages and from smoking during the morning. After application of a blood pressure cuff, the patients rested in a quiet room for 30 min in the seated position. They were then subjected to a mental stress test, a 20-min modified video version of Stroop’s color word conflict test. Color words written in incongruent colors are shown rapidly, and simultaneously a third incongruent color word is presented by a voice. The subject is asked to mark the color he sees on a protocol where the color words are randomly listed and to disregard the other two conflicting pieces of information. The hemodynamic responses reach steady state within 8 to 10 min and are reproducible. Test performance improves somewhat with repeat testing. The mental stress test was followed by a 25-min period of seated rest, after which the patients were subjected to a cold pressor
test. This was done by immersing the dominant hand in ice cold water for 3 min.

**Measurements and Calculations** Systolic and diastolic blood pressures (Korotkoff phase V) and heart rate at the outpatient clinic were measured in the supine position after 5 min of rest. Blood pressures were recorded by standard procedures as the mean of two recordings with a mercury sphygmomanometer. In the laboratory, blood pressures and heart rate were measured noninvasively on the nondominant arm by a Dinamap Exercise Monitor (Critikon Inc., Tampa, FL). The microphone of the blood pressure cuff was placed over the brachial artery with the aid of a Doppler instrument to obtain Korotkoff sounds of highest intensity. Peak responses to the provocations are expressed as percentage change in blood pressures, whereas heart rate peak responses are given in absolute terms, for physiologic reasons discussed previously.8

General wellbeing was assessed by two sets of scales. The psychologic general wellbeing index consists of 22 questions divided into six subscales: anxiety, depression, general health, positive wellbeing, self control, and vitality.14 Also, adjective scales including 39 different adjectives representing seven mood variables were used.15 For both scales, a global score was constructed and the subscales were only explored if there appeared to be differences in the global score.

**Statistical Analysis** Data are presented as mean values and SEM. Regression lines were constructed according to the least-squares’ method. Statistical evaluation was made by Student’s t test, by one-way repeated measures analysis of variance with Scheffe’s procedure for post hoc comparisons, or by two-way repeated measures analysis of variance, where appropriate. The potentially confounding effects of the order of blinded treatment was included as factor in the model. Two-tailed tests were used throughout and a probability (P) of < .05 was considered statistically significant.

Part of these results have been presented in preliminary form.16

**RESULTS**

**General** Supine systolic and diastolic blood pressures in the outpatient clinic at randomization (155 ± 2/101 ± 1 mm Hg) were reduced by 6 weeks of active treatment with 5 mg of ramipril, whereas placebo had no effects (to 145 ± 3/94 ± 1 vs 153 ± 2/102 ± 2 mm Hg measured 24 h after taking the last dose of study medication, P < .05). There was no influence on heart rate (72 ± 2, 71 ± 2, and 71 ± 1 beats/min at randomization with ramipril, and placebo, respectively). These effects of ramipril on systolic and diastolic blood pressures and on heart rate were also maintained during 3 and 6 months of open ramipril treatment (146 ± 2/94 ± 1 mm Hg and 70 ± 2 beats/min, and 149 ± 3/97 ± 2 mm Hg and 70 ± 2 beats/min, respectively). At 6 months 19 patients received 5 mg ramipril once daily and the remaining nine patients 10 mg once daily; the mean daily ramipril dose was 6.6 ± 0.4 mg. For comparison, seated resting blood pressures in the laboratory (see Figure 1), measured at expected peak plasma concentrations 3 to 4 h after tablet intake, were reduced from 146 ± 3/99 ± 3 mm Hg with placebo to 135 ± 4/94 ± 3 mm Hg at 6 weeks with ramipril, and maintained at 6 months (136 ± 4/91 ± 3 mm Hg; P < .05).

The order in which the active study drug or placebo was given did not significantly influence the ramipril-induced reductions in resting blood pressure. Thus, the reductions in supine systolic and diastolic blood pressures in the outpatient clinic by ramipril for 6 weeks and for 6 months were 9 ± 2/7 ± 2 and 5 ± 4/6 ± 2 mm Hg in patients randomized to start treatment with placebo followed by ramipril, and 6 ± 4/6 ± 2 and 3 ± 5/1 ± 3 mm Hg in the group randomized to start with ramipril followed by placebo. Similarly, there were no significant differences in the ramipril-induced reductions in seated resting blood pressures in the laboratory. Corresponding val-
ues were 16 ± 3/10 ± 3 and 15 ± 4/8 ± 2 mm Hg, and 6 ± 5/8 ± 3 and 6 ± 5/8 ± 3 mm Hg, respectively.

The general wellbeing of the patients was assessed by means of two scoring systems. The scorings were done at randomization, after 6 weeks of placebo, after 6 weeks of blind ramipril treatment, and after 6 months of open ramipril treatment. The total score of the psychologic general wellbeing index was not influenced during any of the study periods (ie, 105.2 ± 3.0, 103.2 ± 2.7, 105.1 ± 2.7, and 105.0 ± 2.3, respectively). Hence no further analyses of the subscales were performed. Also the adjective scales for the mood variables remained unchanged throughout the study (data not shown).

The Effects of Ramipril on Mental Stress  The effects of mental stress are presented in Figures 1 and 2. Mental stress induced rapid and pronounced increases in systolic and diastolic blood pressures and in heart rate within 1 min of the stress test ($P < .001$). The early peak response was followed by persistent elevations of systolic and diastolic blood pressures and heart rate for the remainder of the mental stress test.

Compared with placebo treatment, 6 weeks of ramipril treatment reduced systolic and diastolic blood pressure levels at rest and during mental stress, whereas heart rate levels tended to decrease. Systolic blood pressure and heart rate responses to mental stress were reduced, whereas diastolic blood pressure response remained unchanged. Consequently, ramipril treatment for 6 weeks reduced the rate pressure product level and response. The peak responses in blood pressures and heart rate during mental stress were, however, not influenced by 6 weeks of ramipril treatment.

After 6 months of ramipril treatment systolic and diastolic blood pressure levels at rest and during mental stress were further reduced, when compared with 6 weeks of active treatment. Heart rate and rate pressure product levels remained unchanged; when all three test occasions were compared, however, ramipril significantly ($P < .05$) decreased heart rate levels. The responses in systolic blood pressure, heart rate, and rate pressure product to mental stress were
The present results confirm an antihypertensive effect of ramipril on resting blood pressure in primary hypertension with little influence on general wellbeing. Furthermore, blood pressure levels were reduced during mental stress and a cold pressor test, in general agreement with findings during stressful provocations in hypertensive patients treated with, eg, ACE inhibitors, α- or β-adrenoceptor blockers, calcium antagonists, or thiazide diuretics.11,17–20

The new and major finding of this study is that circulatory responses to mental stress (ie, the relative increases in blood pressure and the increase in heart rate) were attenuated by ramipril. A reduced systolic blood pressure response largely explains the attenuated rate pressure product response, but a reduced heart rate response apparently contributes as well. Others have not been able to show a reduced blood pressure response to mental stress by ACE inhibitor treatment in randomized studies.17–19,21 However, the study by Dimsdale et al used mental stress models with short (3-min) duration eliciting small circulatory effects, and the patients were given active treatment for only 4 days.17 Also Cardillo et al18 and two small German studies19,21 used short-lasting (3-min) mental stress exposure. It is likely that more stressful tasks with longer duration, such as the mental stress used in the present study, are better suited to show drug-induced changes in stress reactivity.

The reduction in the rate pressure product response, ie, cardiac workload, to mental stress in this study (38% at 6 months) is somewhat larger than what we have previously shown11 after 6 months treatment with β-adrenoceptor blockade (27–30% reduction), and twice as large as the reduction observed with hydrochlorothiazide (19%). The present and our previous11 study were conducted under similar experimental conditions. These differentiated rate pressure product responses would argue against the notion that the reduced circulatory response to mental stress by ramipril can be explained just by a reduction in blood pressure itself.

Different classes of drugs seem to affect circulatory responses differently. Lee et al demonstrated that the α-adrenoceptor antagonist doxazosin reduced the blood pressure response elicited by mental stress by 30–40%.20 Thus, ramipril (and doxazosin) reduces the rate pressure product to mental stress mainly by a reduction in systolic blood pressure response. β-adrenoceptor blockade affects rate pressure product responses by reducing the heart rate response with no effect on the blood pressure response.10 Finally, hydrochlorothiazide has small effects on both blood pressure and heart rate responses. Blood pressure variability, and the integrated blood pressure load over time, has a closer relationship than casual blood pressure to hypertensive target organ damage and long-term prognosis in hypertension.1–4 Furthermore, there is animal experimental evidence to suggest that repeat transient pressor episodes may influence left ventricular geometry unfavorably without permanent elevation of resting blood pressure.22 If ACE inhibitors could reduce blood pressure increases during everyday stress more effectively than other antihyperten-
sive drug classes, this may have clinical implications for the long-term treatment of hypertension.

Heart rate levels and heart rate responses were reduced by ramipril, suggesting an altered autonomic influence on the heart. Angiotensin II is generally considered to facilitate the release of noradrenaline, and a reduced formation of angiotensin II by ramipril could attenuate sympathetic neurogenic stimulation of the heart. However, we have previously not been able to show that the ACE inhibitors ramipril or benazepril reduced noradrenaline release in skeletal muscle circulation in vivo. This was suggested to be related to additional effects of ACE inhibition on sympathetic neurotransmission mediated by bradkinin and prostaglandins. Alternatively, ramipril may reduce heart rate by an increased vagal influence on the heart. Circumstantial evidence is provided by the findings that angiotensin II inhibits cardiac vagal activity in the dog and in humans, and that lisinopril and enalapril enhance cardiac parasympathetic activity in humans. Thus, a reduced formation of angiotensin II by ramipril might lower heart rate by interactions with sympathetic or parasympathetic cardiac nerves.

Under control conditions the observed blood pressure responses evoked by mental stress and by the cold pressor test were of similar magnitude. Mental stress elicits a circulatory response with an increased cardiac output, splanchic and renal vasoconstriction, skeletal muscle vasodilatation, and reduced systemic vascular resistance. The circulatory response to the cold pressor test, on the other hand, is characterized by a more generalized sympathetic nerve activation to peripheral vascular beds. Ramipril attenuated the systolic blood pressure response during mental stress, whereas the heart rate response was reduced more markedly during the cold pressor test. The relative lack of correlations between the responses to the two stressors studied suggests qualitative differences between the mental stress and the cold pressor stress test, in support of earlier observations. The rate pressure product response was, however, reduced by ramipril during both stress provocations. This may be of interest from a clinical standpoint, as it could be assumed that an ideal antihypertensive drug should reduce stress-evoked increases in cardiac workload to a broad variety of stressful situations in everyday life.

When comparing 6 weeks and 6 months of ramipril therapy, prolonged treatment further reduced resting systolic and diastolic blood pressure levels, and also reduced systolic blood pressure and heart rate responses to mental stress. Repeat reactivity testing by the mental stress test used in the present study has been shown to give reproducible results so that adaptation is not likely to be a strong confounding factor. Our results were, however, obtained during 6 months of open drug therapy and should be interpreted with caution. The effects of ramipril on the formation of the various components of the renin-angiotensin-aldosterone system and, subsequently, the possible interaction with autonomic neurotransmission, are acute. Other antihypertensive mechanisms may have a different time course. Indeed, drug-induced regression of left ventricular hypertrophy and vascular hypertrophy of resistance vessels may continue for months or years. Our results would be compatible with the observation that long-term treatment with ACE inhibitors can improve arterial vascular compliance.

In conclusion, ramipril reduces the mental-stress-induced increase in cardiac workload, mainly by a reduced systolic blood pressure response. The cardiac workload during a cold pressor test was also reduced by ramipril. However, the potential advantage by these observations in the treatment of hypertension remains to be confirmed.

REFERENCES


