Effects of acute and chronic angiotensin converting enzyme inhibition by spirapril on cardiovascular regulation in essential hypertensive patients. Assessment by spectral analysis and haemodynamic measurements

DERK P. VEERMAN, CAROLINE E. DOUMA, MARIE-CECILE JACOBS, THEO THIEN & GERT A. VAN MONTFRANS

1 The effects of a first dose and of chronic treatment with spirapril, a novel angiotensin converting enzyme (ACE) inhibitor, on short-term blood pressure and heart rate fluctuations were assessed by fast Fourier spectral analysis. The effects on systemic haemodynamics in supine and standing position were also studied. We treated 11 patients with 3 mg and 13 patients with 12 mg spirapril for 8 weeks.

2 Overall blood pressure variability was not changed by spirapril. By spectral analysis the changes in blood pressure and heart rate variability in various frequency bands can be assessed, which may be related to changes in activity of the autonomic nervous system. The relative power in the mid-frequency band (0.08–0.12 Hz) of supine systolic pressure was 23±10% during placebo and decreased during treatment with 12 mg to 11±4% (P<0.01 vs placebo, first dose) and to 13±6% (P<0.01, chronic treatment). Standing systolic mid-frequency power was 38±12% during placebo and decreased to 27±9% (P<0.01 vs placebo) after the first dose of 12 mg, but it did not decrease after chronic treatment (29±13%). Treatment with 3 mg induced no changes in mid-frequency blood pressure variability. A decrease in power of the mid-frequency band may point to a decrease in sympathetic vascular drive. The power in the high-frequency band (0.15–0.40 Hz) of heart rate did not change after treatment, suggesting that there is no change in the vagal cardiac drive.

3 Supine blood pressure decreased by a decrease in vascular resistance by 16±23% (3 mg) and 14±19% (12 mg) after 8 weeks treatment. Heart rate, stroke volume and cardiac output did not change. No orthostatic hypotension occurred after the first dose. In the 12 mg group the orthostatic induced rise in heart rate (compared with supine) increased from +9±5 beats min⁻¹ (placebo) to +14±4 beats min⁻¹ (P<0.05) after the first dose. No changes in the orthostatic heart rate increase occurred in the 3 mg group. The orthostatic changes in stroke volume, cardiac output and vascular resistance were not influenced by spirapril.

4 In conclusion, the decrease in mid-frequency blood pressure variability may suggest an inhibitory effect of acute and chronic ACE inhibition upon sympathetic vasomotor control. Vagal activity was not influenced as high-frequency heart rate variability did not change. Acute and chronic ACE inhibition did not blunt important cardiovascular reflexes, as the haemodynamic response to orthostasis remained intact.

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Keywords hypertension ACE inhibition blood pressure variability autonomic nervous system orthostasis

Introduction

Angiotensin converting enzyme (ACE) inhibitors are an important class of drugs for the treatment of essential hypertension and congestive heart failure [1,2]. Although extensive investigations on their mechanisms of action have been performed, there are still some unresolved questions. By inhibiting the angiotensin converting enzyme levels they decrease the levels of circulating angiotensin II and aldosterone [1,2], thereby inhibiting vasoconstriction and salt and water retention. ACE inhibitors also exert an influence on the autonomic nervous system [3,4] which may contribute to their blood pressure lowering effect and could explain the absence of reflex tachycardia. However, there is a vast body of conflicting data whether ACE inhibition enhances parasympathetic activity without a concomitant influence on sympathetic activity [5,6], or whether sympathetic activity is diminished by ACE inhibition [7-9]. An alternative explanation for the absence of reflex tachycardia may be that ACE inhibitors increase venous compliance, thereby reducing preload [1,10].

The aim of this study was to examine the effects of ACE inhibition on autonomic nervous function by studying heart rate variations during forced breathing (which is a measure of vagal tone) and by studying blood pressure and heart rate variations by spectral analysis. Spectral analysis breaks down a signal to its constituent frequency components, and quantifies the power of these components. Modulation of blood pressure and heart rate by baroreflex and sympathetic and parasympathetic nervous activity has been shown to be involved in the genesis of the various frequency components of blood pressure and heart rate variability [11]. We also studied the haemodynamic changes upon standing during ACE inhibition as these changes are largely influenced by adjustments in vagal and sympathetic activity [12]. As ACE inhibitors can occasionally cause a pronounced drop in blood pressure after a first dose [13,14] we examined the effects of both acute (first dose) and chronic treatment. We studied these effects in patients with essential mild to moderate hypertension by using the ACE inhibitor spirapril (TI 211-950, Sandoz, Basel, Switzerland) which is a new non-sulphhydryl ACE inhibitor. Spirapril itself is inactive, but is rapidly de-esterified after absorption to its active diacid metabolite spiraprilat. Spirapril has been shown to be a potent blood pressure lowering agent with a long duration of action [15].

Methods

Patients

This study was part of a larger multicentre study (4 centres) in which the efficacy and tolerability of two dosages (3 and 12 mg once daily) of spirapril on 24 h ambulatory blood pressure was studied in patients with mild to moderate essential hypertension [15]. All patients who participated in that study from our institutions also took part in the present study.

The study group comprised 30 patients, aged between 20 and 60 years, all having essential hypertension. The sitting diastolic blood pressure (Korotkoff phase V) of all patients was between 100 and 120 mmHg (average of three office readings) after a period of 4 weeks placebo treatment. Secondary hypertension and overt target organ damage were excluded by physical examination, routine laboratory investigations, ECG and chest X-ray. All antihypertensive and other medications which might influence the cardiovascular system were discontinued at the start of the placebo phase of the study. Patients were instructed to refrain from changing their usual diet and level of physical activity and also to abstain from using NSAIDs for the duration of the study. Basic characteristics of all patients are listed in Table 1. No patients showed signs of left ventricular hypertrophy on the ECG. The protocol was drafted in accordance with the declaration of Helsinki (1989), approved by the local hospital ethics committees and all subjects gave written informed consent.

Study design

The complete duration of the study was 12 weeks: 4 weeks placebo treatment was followed by an active treatment phase of 8 weeks during which patients were treated with either 3 or 12 mg of spirapril in a double-blind randomized fashion. Patients were instructed to take one identical capsule every morning before breakfast at the same time.

During the study three measurement cycles were performed. The first after 4 weeks placebo treatment (baseline). The second measurement cycle was performed...
4 h after the first active medication was taken, which was ingested immediately after the first measurement cycle (acute treatment, first dose). The third and also last measurement cycle was performed after 8 weeks active treatment, again 4 h after ingestion of the active medication (chronic treatment). Blood samples were taken on both measurement days prior to and 4 h after ingestion of the medication for determination of plasma ACE concentrations by a colour kinetic assay.

Measurements

Beat-to-beat noninvasive finger arterial pressure was recorded by Finapres during all three above mentioned measurement cycles [16–18]. Every measurement cycle started with a test for forced respiratory sinus arrhythmia (FRSA) during which the patient was requested to perform six maximal inspirations and expirations consecutively for 60 s. Thereafter the patient remained in the supine position for 10 min. The patient was then asked to stand up within 2 to 3 s and remain standing quietly for 5 min. A marker pulse identified the onset of the inspirations during FRSA, as well as the onset of the supine and standing periods. Care was taken to keep the hand, on which the finger blood pressure was measured, at heart level (4th intercostal space in the midaxillar line) during the complete measurement cycle applied to finger and intrabrachial arterial pressure measured at the same finger at all times.

The manoeuvres were performed in the morning in a room with a constant temperature of 22–24°C. All subjects abstained from coffee, tea and smoking starting the evening before the experiments. The continuous blood pressure recording and the marker pulse signal were on line analogue-to-digital converted by a personal computer at 100 Hz per signal.

Data analysis

By means of a signal analysis program the time of the systolic upstroke was identified for each beat, as were the actual systolic, mean and diastolic pressures and the interbeat interval (resolution 10 ms). The registration of six patients was not suitable for analysis due to technical reasons. Of the remaining 24 patients 11 patients were treated with 3 mg and 13 patients with 12 mg of spirapril.

FRSA The largest of the six differences between inspiration and expiration (I/E) in pulse interval were determined for each patient during baseline, acute and chronic treatment [19].

Power spectra Power spectra were estimated by means of fast Fourier transformation [11,20,21] of supine and standing blood pressure and heart rate. The first minute of standing was omitted from the analysis as stabilization of blood pressure and heart rate takes some time. Integration of the curve for specific frequency-bands yields variance for that particular frequency band. We calculated the power in two frequency bands: the mid-frequency band (0.08–0.12 Hz) and the high-frequency band (0.15–0.40 Hz). The power of these frequency bands is considered to reflect sympathetic and vagal activity respectively [11.20–22]. Total variance and percentual variance (power) of the mid-frequency and high-frequency band of blood pressure and pulse interval in supine and standing position were determined for the three different measurement cycles: the placebo phase (P), after the first dose (A) and after chronic treatment (C).

Haemodynamics The signal analysis program calculates the beat-to-beat values of left ventricular stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) using the pulse contour algorithm of Wesseling [23]. In short, SV is calculated from the aortic characteristic impedance and the arterial pressure waveform as the integral of the pressure pulse over the arterial systolic period [24,25]. On comparison of CO by this method with thermodilution during changes in blood pressure and heart rate in open heart surgery, a standard deviation of the difference between the two methods of 10.6% (=0.54 l min⁻¹) was found [25]. To obtain absolute SV values, calibration with a standard method such as thermodilution is needed, but without such calibration the relative changes in SV can be used [23,24]. When comparing the pulse contour algorithm applied to finger and intrabrachial arterial pressure waveforms [12], we obtained almost identical results.

We determined the absolute changes in mean arterial pressure (MAP) and heart rate (HR) and the relative changes in SV, CO and TPR induced by acute and chronic ACE inhibition after 10 min in the supine position compared with the placebo phase. Also, the absolute and relative changes in these parameters induced by standing were assessed. The values of all beats during the last minute of the supine position before standing up and during the fifth minute of standing were averaged for all individual patients. We determined the changes induced by standing in the placebo period, after the first dose and after 8 weeks treatment.

Statistics

Statistical analysis was performed with Biomedical Programs (BMDP) statistical software (University of California, Los Angeles, CA, USA). Results are presented as mean ± s.d. A Kruskall-Wallis one-way analysis of variance by ranks was used to compare dosage groups and the effect of acute and chronic treatment. This was followed in case of significance by a Mann-Whitney U-test or a Wilcoxon signed rank test in case of paired data. A P <0.05 was considered significant.

Results

Haemodynamic changes induced by ACE inhibition are summarized in Table 2. Spirapril caused a reduction in
blood pressure in both dosage groups, which was already significant after the first dose. Mean supine (Finapres) arterial pressure in the placebo phase was 101 ± 9 mmHg in the 3 mg and 101 ± 15 mmHg in the 12 mg group. Compared with placebo vascular resistance did not decrease significantly after the first dose, but during chronic treatment its decrease by 16 ± 23% (P < 0.05) in the 3 mg group and by 14 ± 19% (P < 0.05) in the 12 mg group. The changes in heart rate, stroke volume and cardiac output after treatment with spirapril were not significant. Compared with the placebo phase plasma ACE decreased from 12.5 ± 1.2 μU ml⁻¹ to 2.9 ± 1.1 μU ml⁻¹ (P < 0.01) in the 3 mg and from 14.3 ± 3.0 μU ml⁻¹ to 2.2 ± 4.0 μU ml⁻¹ (P < 0.01) in the 12 mg group after the first dose. Pre-dose ACE concentrations after 8 weeks treatment were 10.5 ± 3.4 μU ml⁻¹ (3 mg, P > 0.05 vs placebo) and 7.2 ± 2.8 μU ml⁻¹ (12 mg, P < 0.05 vs placebo). ACE levels 4 h post-dose were 3.2 ± 1.1 μU ml⁻¹ (3 mg, P < 0.01 vs placebo) and 1.4 ± 0.6 μU ml⁻¹ (12 mg, P < 0.01 vs placebo). The decrease in plasma ACE concentrations did not differ between the 3 and 12 mg groups, except for the pre-dose ACE concentration after 8 weeks treatment. This ACE level was significantly lower in the 12 mg group than in the 3 mg group (P < 0.05).

**Table 2** Haemodynamic changes. Haemodynamic changes at rest induced by spirapril 4 h after the first dose (acute) and after 8 weeks treatment (chronic) compared to the placebo phase. The changes in mean arterial pressure (MAP) and heart rate (HR) and the relative changes in stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were determined after 10 min in the supine position. Results are mean ± s.d.; *P < 0.05 compared to placebo, Wilcoxon signed rank test.

<table>
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<tr>
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<th>Acute</th>
<th>Chronic</th>
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<tr>
<td>ΔMAP (mmHg)</td>
<td>-10 ± 7*</td>
<td>-8 ± 6*</td>
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<tr>
<td>ΔHR (beats min⁻¹)</td>
<td>-11 ± 10</td>
<td>-11 ± 6*</td>
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<tr>
<td>ΔSV (%)</td>
<td>+14 ± 24</td>
<td>+7 ± 26</td>
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<tr>
<td>ΔCO (%)</td>
<td>+11 ± 28</td>
<td>+8 ± 30</td>
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<tr>
<td>ΔTPR (%)</td>
<td>-14 ± 22</td>
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3 mg (n=11)     12 mg (n=13)

Orthostatic haemodynamics

The haemodynamic changes upon standing are summarized in Figure 2. Standing from supine induced an increase in HR and MAP. In the 12 mg group the increase in HR after the first dose, but not after chronic treatment, was significantly larger than in the placebo phase (placebo 9 ± 5; first dose 14 ± 4, P < 0.05; chronic treatment 12 ± 6 beats min⁻¹, P > 0.05). Increase in HR after standing in the 3 mg group was not different from placebo phase (placebo 9 ± 5; first dose 14 ± 4, P < 0.05; chronic treatment 12 ± 6 beats min⁻¹, P > 0.05). Plasma ACE increased from 12.5 ± 1.2 μU ml⁻¹ to 2.9 ± 1.1 μU ml⁻¹ (P < 0.01) in the 3 mg and from 14.3 ± 3.0 μU ml⁻¹ to 2.2 ± 4.0 μU ml⁻¹ (P < 0.01) in the 12 mg group after the first dose. Pre-dose ACE concentrations after 8 weeks treatment were 10.5 ± 3.4 μU ml⁻¹ (3 mg, P > 0.05 vs placebo) and 7.2 ± 2.8 μU ml⁻¹ (12 mg, P < 0.05 vs placebo). ACE levels 4 h post-dose were 3.2 ± 1.1 μU ml⁻¹ (3 mg, P < 0.01 vs placebo) and 1.4 ± 0.6 μU ml⁻¹ (12 mg, P < 0.01 vs placebo). The decrease in plasma ACE concentrations did not differ between the 3 and 12 mg groups, except for the pre-dose ACE concentration after 8 weeks treatment. This ACE level was significantly lower in the 12 mg group than in the 3 mg group (P < 0.05).

**Discussion**

The present analysis showed no difference in the blood pressure lowering effects of 3 and 12 mg spirapril (Table 2) or in the decrease of plasma ACE levels. Blood pressure was decreased by a decrease in total peripheral resistance (Table 2). Despite the spirapril induced vaso-dilation, we found no reflex increase in stroke volume, cardiac output or heart rate. The haemodynamic profile

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ACE inhibition and cardiovascular regulation

Figure 1 Percentual powers of the mid-frequency band (MF: 0.08-0.12 Hz) and the high-frequency band (HF: 0.15-0.40 Hz) of systolic (PS) and diastolic (PD) blood pressure (supine •; standing ○) and pulse interval (INT) before (Placebo = P), after the first dose, (Acute = A) and after 8 weeks treatment (Chronic = C) with 3 mg (n=11) or 12 mg (n=13) of the ACE inhibitor spirapril. Results are group averages, bars represent standard deviations. A star indicates a statistical difference vs placebo (*P<0.01).

of spirapril thus appears to be comparable with other ACE inhibitors [1]. Since reflex cardio-stimulation by vasodilators may favour left ventricular hypertrophy [26], the absence of a heart rate or stroke volume increase during treatment with ACE inhibitors may be considered as an important advantage from a clinical point of view.

Numerous papers show an effect of ACE inhibitors on the autonomic nervous system, and this may at least partly explain the absence of reflex counter-regulatory reactions [1,2]. However, there is no consensus whether this effect concerns an increased parasympathetic or a decreased sympathetic activity or both.

Several studies showed an increase in respiratory induced heart rate variability [27] or an increased bradycardia during the diving reflex [5,28] after administration of an ACE inhibitor. This was interpreted to represent an increased vagal tone. However, other studies showed a smaller decrease in heart rate during facial immersion in water ('diving') [6,29]. This last finding was also considered to express an increase in vagal tone through ACE inhibition. Thus, opposite results are supposed to be caused by the same change in vagal activity. This suggests that no consensus on this topic is reached in the literature.

Changes in sympathetic nervous system activity after treatment with ACE inhibitors have also been studied by studying cardiovascular responses to standardized manoeuvres. In several studies no changes in the cardiovascular reactions to handgrip, mental stress or cold pressor have been reported [5,28-30]. Another study reported a decreased tachycardia during cold pressor and a decreased blood pressure fall due to α-adrenergic receptor blockade after ACE inhibition, and this was interpreted to indicate a decrease in sympathetogenesis [8]. Although angiotensin II facilitates noradrenaline release from terminal nerve endings [3], a number of studies reported no decrease in plasma catecholamines during treatment with an ACE inhibitor [6,27,28]. However, Philipp et al. [7] demonstrated a significant decrease in plasma noradrenaline during ACE inhibition.

In the present study we aimed to assess changes in vagal and sympathetic tone after acute and chronic ACE inhibition by studying pulse interval variability during forced respiration (FRSA) [19], and by studying the variability of blood pressure and pulse interval in the mid- and high-frequency bands by spectral analysis. Several factors influence the blood pressure and pulse interval spectra. Neural mechanisms are considered to be the most important, and most of the spectral components are probably generated by sympathetic and parasympathetic nervous activity and the baroreflex [11,20-22]. Blood pressure variations which cause baroreflex modulation of pulse interval by parasympathetic nerves affect both high-frequency and mid-frequency powers, although mid-frequency power of pulse interval is also influenced by sympathetic nervous activity due to the time delay of baroreflex action in the mid-frequency range [11,31]. Thus, the high-frequency pulse interval variability may be considered to have the closest relation to vagal cardiac tone. Experiments with pharmacological vagal blockade corroborate this notion [22,32].

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There is much discussion on the origin of the blood pressure variability in the 0.1 Hz frequency range. Sympathetic vasomotor activity probably plays an important role as well as the baroreflex, as shown by the fact that blood pressure variability around this frequency decreases after sino-aortic denervation, while total blood pressure variability increases (mainly by an increase in lower frequency variability) [33]. Moreover, there are theoretical arguments for the existence of a 0.1 Hz resonance phenomenon in the feedback arterial baroreceptor–sympathetic vasomotor loop [34]. Much simplified, mid-frequency oscillations in blood pressure may be the result of the delayed sympathetic vasomotor reaction on blood pressure changes sensed by the baroreceptor and thus impose a specific rhythm on distensibility increases in response to administration of ACE inhibitors, forearm venous dilatation caused by ACE inhibitors, and when baroreflex sensitivity is decreased [35].

An advantage of this technique as compared with studying cardiovascular reflex responses is that spectral analysis may give an estimate of vagal and sympathetic activity during steady state circumstances, whilst the magnitude of vagally or sympathetically steered reflex responses may also be dependent on the unknown level of resting vagal or sympathetic tone.

We found no changes in the FRSA after acute and chronic treatment with spirapril. Also, no changes in the power of the mid- and high-frequency band of heart rate were found in the present study. In the low-dose group (3 mg) the power of the mid-frequency band of blood pressure did not change, but in the higher-dose group (12 mg) a decrease in systolic blood pressure variability in this frequency band was observed both after acute and chronic treatment with spirapril. Thus, no increment of vagal tone during ACE inhibition and no change in cardiac sympathetic tone was found. However, we did find a decrease of sympathetic vasomotor tone during ACE inhibition in our patients by spectral analysis. This finding is in agreement with studies by Pagani et al. [37] and by Dutrey-Dupagne et al. [36] who also found a decrease of the mid-frequency band of blood pressure variability after ACE inhibition. As discussed above plasma noradrenaline does not decrease, but the pressor response of the end-organ (peripheral blood vessels) to sympathetic stimulation (noradrenaline) may be decreased after ACE inhibition [38,39]. Thus, a sympatho-modulating effect of ACE inhibitors appears to be related to an effect on the neurotransmission at the postjunctional site, leading to diminished facilitation of noradrenergic stimuli rather than to a direct effect on the sympathetic nervous system itself.

Although an increase in 'overall' sympathetic nervous activity is considered to have unfavourable effects in hypertension [40], the pathophysiological and clinical importance of sympathetic attenuation by ACE inhibitors remains doubtful. Although we found a decrease in blood pressure and plasma ACE concentrations in the 3 mg group we did not find an effect on the sympathetic nervous system in that group. Also, the increase in vascular resistance by sympathetic activation upon standing did not change after ACE inhibition. Moreover there is no agreement in the literature about the exact effect of ACE inhibitors on the autonomic nervous system, notwithstanding the large number of studies.

Occasionally, symptomatic hypotension is seen following a first dose of an ACE inhibitor [13,14], but in our patients the haemodynamic response to orthostasis remained intact and nobody complained about dizziness upon standing. Although ACE inhibition causes arterial vasodilatation, cardiac output does not increase after treatment with these drugs [1], as was confirmed by our results (Table 2). This may be related to venous dilatation caused by ACE inhibitors, forearm venous distensibility increases in response to administration of ACE inhibitors [41]. In our subjects the increase in heart rate upon standing was significantly larger after acute and chronic treatment with spirapril. Thus, no increment of vagal tone during ACE inhibition and no change in cardiac sympathetic tone was found. However, we did find a decrease of sympathetic vasomotor tone during ACE inhibition in our patients by spectral analysis. This finding is in agreement with studies by Pagani et al. [37] and by Dutrey-Dupagne et al. [36] who also found a decrease of the mid-frequency band of blood pressure variability after ACE inhibition. As discussed above plasma noradrenaline does not decrease, but the pressor response of the end-organ (peripheral blood vessels) to sympathetic stimulation (noradrenaline) may be decreased after ACE inhibition [38,39]. Thus, a sympatho-modulating effect of ACE inhibitors appears to be related to an effect on the neurotransmission at the postjunctional site, leading to diminished facilitation of noradrenergic stimuli rather than to a direct effect on the sympathetic nervous system itself.

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differences in the decrease in stroke volume upon standing. An ACE inhibition-induced decrease in stroke volume and increase in heart rate during tilt was found by Ibsen et al. [44]. However, during lower body negative pressure the increase in heart rate did not change after ACE inhibition, and the decrease in forearm blood flow was even smaller [45,46]. Thus, although there is some data to support the view that ACE inhibition increases venous compliance, as yet the evidence is far from conclusive.

In conclusion, spirapril decreases blood pressure by decreasing total peripheral resistance, without causing an increase in heart rate, stroke volume or cardiac output. There are some indications for an inhibitory effect of acute and chronic ACE inhibition by spirapril upon sympathetic vasomotor control, while parasympathetic cardiac drive was not influenced. The haemodynamic response to orthostasis remained intact, and no clear evidence for a venodilatatory response was found in our subjects.

We gratefully acknowledge the support for this study by Sandoz AG, Switzerland and Sandoz BV, Netherlands.

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(Received 6 January 1995, accepted 9 August 1995)