Effects of angiotensin II (AT₁) receptor blockade on cardiac vagal control in heart failure

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ABSTRACT

The objective of the present study was to determine the autonomic effects of angiotensin II (AT₁) receptor blocker therapy in heart failure. In a randomized double-blind cross-over study, we compared the effects of candesartan and placebo on baroreflex sensitivity and on heart rate variability at rest, during stress and during 24 h monitoring. Acute effects were assessed 4 h after oral candesartan (8 mg) and chronic effects after 4 weeks of treatment (dose titrated to 16 mg daily). The study group comprised 21 patients with heart failure [mean (S.E.M.) ejection fraction 33% (1%)] in the absence of angiotensin-converting enzyme (ACE) inhibitor therapy. We found that acute candesartan was not different from placebo in its effects on blood pressure or mean RR interval. Chronic candesartan significantly reduced blood pressure [placebo, 137 (3)/82 (3) mmHg; candesartan, 121 (4)/75 (2) mmHg; P < 0.001; values are mean (S.E.M.)], but had no effect on mean RR interval [placebo, 857 (25) ms; candesartan, 857 (21) ms]. Compared with placebo there were no significant effects of acute or chronic candesartan on heart rate variability in the time domain and no consistent effects in the frequency domain. Baroreflex sensitivity assessed by the phenylephrine bolus method was significantly increased after chronic candesartan [placebo, 3.5 (0.5) ms/mmHg; candesartan, 4.8 (0.7) ms/mmHg; P < 0.05], although there were no changes in cross-spectral baroreflex sensitivity. Thus, in contrast with previous results with ACE inhibitors, angiotensin II receptor blockade in heart failure did not increase heart rate variability, and there was no consistent effect on baroreflex sensitivity.

INTRODUCTION

Angiotensin II appears to play an important role in the pathophysiology of cardiac disease, as indicated by the beneficial prognostic effects of angiotensin-converting enzyme (ACE) inhibitors after myocardial infarction and in heart failure [1,2]. The effects of ACE inhibitors on mortality cannot be explained by haemodynamic actions alone, since other vasodilators are less effective [1]. We have suggested previously that the explanation may lie, in part, in the adverse effects of angiotensin II on cardiac vagal control [3]. Large trials have shown that impaired cardiac autonomic function is associated with an adverse prognosis in patients with heart failure and after myocardial infarction [4,5]. The mechanisms of cardiac autonomic control remain poorly defined, but there is abundant evidence from animal studies that angiotensin II has effects on both limbs of the autonomic nervous system, causing facilitation of sympathetic activity and inhibition of cardiac vagal activity [6–8]. These effects may be mediated both centrally and peripherally. In healthy human volunteers, we have shown previously that exogenous angiotensin II reduces the cardiac vagal modulation of heart rate [3]. Conversely, we and others

Key words: angiotensin, baroreflex sensitivity, heart failure, heart rate, heart rate variability, vagus nerve.

Abbreviations: ACE, angiotensin-converting enzyme; BRS, baroreflex sensitivity; HF, high frequency; x-HF, high-frequency x-index of BRS; HRV, heart rate variability; LF, low frequency; x-LF, low-frequency x-index of BRS; RMSSD, root mean square of successive RR interval differences; SDNN, S.D. of RR interval values.

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have shown that, in patients with heart failure, indices of cardiac vagal activity are increased by ACE inhibitors [9–12]. Despite effectively inhibiting ACE, treatment with ACE inhibitors is often associated with residually elevated levels of circulating angiotensin II, a phenomenon termed ‘angiotensin II re-activation’ and associated with a poor prognosis [13]. The development of AT₁ receptor blockers has enabled more specific and more complete blockade of the actions of angiotensin II, but the role of these agents in the management of heart failure remains unclear. We hypothesized that, like ACE inhibitors, AT₁ receptor blockers might exert important beneficial effects on cardiac autonomic control. In patients with heart failure, we have used laboratory and ambulatory studies of heart rate variability (HRV) and baroreflex sensitivity (BRS) to determine the autonomic effects of both acute and chronic therapy with the selective angiotensin II AT₁ receptor blocker candesartan cilexetil (‘candesartan’).

**METHODS**

**Patients**

This was a prospective, randomized, double-blind, placebo-controlled, cross-over study. We recruited patients with heart failure who were not on current ACE inhibitor therapy (either if previously intolerant of an ACE inhibitor or if an ACE inhibitor had not yet been started). Inclusion criteria were echocardiographic evidence of left ventricular impairment (ejection fraction ≤ 40%) and haemodynamic stability with concurrent therapy unchanged for a minimum of 2 weeks. Exclusion criteria were ACE inhibitor or AT₁ receptor blocker therapy within the previous 6 weeks, systolic blood pressure ≤ 90 mmHg, obstructive valvular disease, atrial fibrillation or renal impairment (serum creatinine ≥ 221 µmol/l). Each patient provided written consent, and the protocol was approved by the South Birmingham local research ethics committee. On completion of the study, all patients were treated with an ACE inhibitor, unless previously intolerant.

**Experimental protocol and study design**

All studies were performed in a clinical autonomic research laboratory with temperature maintained at 21–24 °C. Patients were instructed not to eat or drink for at least 2 h before attending, and to abstain from caffeine, alcohol and tobacco for the preceding 12 h. All medications were withheld on the day of the study until recordings were obtained. Subjects lay near-supine on a couch, and at the start of each study a venous cannula was inserted into an antecubital vein. Before the start of each test a 30 min rest period was allowed to enable blood pressure, heart rate and respiration to stabilize.

**Recording of ECG, blood pressure and respiratory signals**

The electrocardiographic signal was amplified, processed (high-frequency signal noise filter > 500 Hz) and digitized at 500 Hz using a National Instruments NB/M10/16XH/18 analogue-to-digital converter board (National Instruments Corp., Austin, TX, U.S.A.). A continuous arterial pressure signal was obtained using the Portapres device (TNO Biomedical Instrumentation, Amsterdam, The Netherlands) and was digitized similarly. In addition, brachial arterial pressure was measured by intermittent cuff sphygmomanometry with an automated oscillometric system (mean of at least three readings). A respiratory signal was recorded from the amplified output of a standard strain gauge attached to an elasticated strap around the subject’s chest. All signals were displayed on the screen of a personal computer (Power Macintosh 7100/80) running Lab View 5.0 software (National Instruments Corp.), and selected periods were stored to disk.

**Study design**

**Acute study**

After an initial screening and acclimatization visit, each patient attended for two acute-study visits, 5–10 days apart, in random order. Patients were studied before and 4 h after a single oral dose of candesartan (8 mg) or placebo. Both before and after dosage, ‘Oxford’ BRS was measured (see below) and steady-state recordings of at least 257 beats were acquired during breathing synchronized to a metronome, at a respiratory frequency individually adjusted to suit each subject at the initial visit and maintained constant in each arm of the study.

**Chronic study**

In a double-blind, randomized cross-over protocol with no washout period, each patient received 4 weeks of oral treatment with candesartan or placebo. The starting dose of candesartan was 8 mg (once daily); the dose was doubled after 2 weeks provided that systolic blood pressure exceeded 90 mmHg. Serum urea and electrolytes were checked at enrolment, and after 1 week and 4 weeks of each chronic treatment period. Patients attended for study visits at baseline and on completion of each treatment period. At each study visit, steady-state recordings of at least 257 beats were acquired under the following conditions: (a) during unrestricted breathing at rest; (b) during verbal mental arithmetic testing (serial subtraction, with the difficulty level titrated according to each subject); (c) during metronomic breathing as above, at the predetermined rate established in the acute limb of the study; and (d) during 70 ° head-up tilt, with metronomic breathing at the predetermined rate; recording began on stabilization of the heart rate, 5 min after assuming head-up position.
In addition Oxford BRS was measured at the end of the study visit, to avoid a confounding influence of the baroreflex-mediated effects of phenylephrine on heart rate. Finally, each patient underwent a Holter 24 h ECG recording using a three-channel tape recorder (Tracker; Reynolds Medical, Hertford, U.K.) at baseline and on completion of each 4-week treatment period.

Data analysis
All data were analysed by an investigator who remained blinded to the study agent.

Analysis of laboratory HRV
All ECG series were reviewed and, if necessary, edited before analysis to exclude ectopic and artefact signals. No signal containing > 3% ectopic beats was used for analysis; less frequent ectopics were deleted, and the RR intervals before and after the ectopics were replaced by interpolation from the previous and subsequent sinus intervals. As described previously, time-domain analysis was used to determine SDNN (S.D. of RR interval values) and RMSSD (root mean square of successive RR interval differences), and frequency-domain analysis (autoregressive modelling) was used to determine low-frequency (LF) power at \( \sim 0.1 \) Hz (reflecting both sympathetic and vagal activity), and high-frequency (HF) power at the measured respiratory frequency (providing an index of cardiac vagal tone) [14].

Analysis of 24 h tape recordings
The 24 h tape recordings were replayed and analysed offline using a Pathfinder analyser (Reynolds Medical). The system automatically detected and labelled each QRS complex, identifying artefact and ectopic beats; in addition, the recording and the results of the automated analysis were reviewed and edited by a physician, to ensure that QRS complexes and RR intervals were selected and measured correctly. This physician remained blinded to the study protocol and treatments. Tapes of less than 18 h duration were excluded. Time-domain analysis was performed for each 1 h of the recording, excluding those hours where \( > 15\% \) of the recording consisted of ectopic beats or artefact. Mean values were calculated for RR interval (mean of all normal-to-normal RR intervals), SDNN and RMSSD. In addition, the HRV triangular index was calculated; this is a simple geometric index which is calculated by constructing a sample density histogram of all normal-to-normal RR intervals and dividing the total number of all intervals by the height of the histogram.

Measurement of BRS
BRS was assessed using a modification of the Oxford method [15]. Incremental bolus doses of intravenous phenylephrine of between 50 and 200 \( \mu \)g were administered, at intervals of no less than 10 min, until a pressor response of 15–40 mmHg was achieved. Measurements were taken during unrestricted breathing. Systolic blood pressure and RR interval were plotted on a tachogram. The beginning and end of the rise in blood pressure were identified manually, and plots of systolic blood pressure against RR interval were generated. A regression line was fitted to each plot, and the slope of the line was taken as baroreflex gain only where the correlation coefficient exceeded 0.6 or statistical significance was reached \( (P < 0.05) \). The measurement of Oxford BRS was repeated with the ‘working dose’ of phenylephrine until at least three values (chronic study) or two values (acute study) that met the above criteria were obtained (only two values were taken in the acute study in order to minimize the cumulative dose of phenylephrine). In addition, we employed cross-spectral analysis to determine the \( \alpha \)-index, describing the transfer function of the systolic pressure signal to variability in the RR interval. The recordings of RR interval and systolic blood pressure were interpolated (using a cubic spline) and then resampled at 1/(mean RR interval) to produce a uniform time base. The cross-spectrum of 256 samples was then analysed by fast Fourier transformation using a Hanning window on successive overlapping records of 128 samples each. The \( \alpha \)-index, regarded as an indicator of baroreflex gain, was calculated as the square root of the ratio of RR interval to systolic spectral power in both the HF (\( \alpha \)-HF) and LF (\( \alpha \)-LF) bands [16]. In each case the \( \alpha \)-index was computed only when the squared coherence between these signals was \( > 0.5 \).

Sample size and power
A cross-over study design was chosen to eliminate the problem of inter-patient variability in indices of HRV and BRS. Sample size was estimated using the method for cross-over studies described by Altman [17]. We designed the study on the assumption that the autonomic effects of candesartan would be at least equivalent in magnitude to the previously published results with ACE inhibitors. There have been five studies on the autonomic effects of chronic ACE inhibitor therapy in heart failure, which showed a median increase of 114\% (range 24–157\%) in BRS and measures of HF HRV during active treatment [9–12,18]. We calculated that a sample size of 14 patients would give 80\% power \( (\alpha = 0.05) \) to detect a 40\% increase in resting RMSSD, resting normalized HF power, 24 h RMSSD and Oxford BRS during chronic candesartan therapy.

Statistical analysis
RR interval and HRV data were tested for normality of distribution. Frequency-domain data and values of BRS were skewed and were therefore logarithmically transformed before statistical analysis. The significance of the
differences between candesartan and placebo was determined using Student’s $t$ test for normally distributed data; otherwise the Wilcoxon signed rank test was used.

RESULTS

Patients and their characteristics
A total of 25 patients were recruited, of whom 21 participated in the study (two were excluded due to frequent ventricular ectopic beats, one developed atrial fibrillation and one required a change in loop diuretic dosing). The 21 participating patients comprised 15 men and six women, with a mean age of 66 years (range 53–77 years), and were in NYHA (New York Heart Association) class I ($n = 5$), II ($n = 10$) or III ($n = 6$) due to coronary artery disease (20 patients) or chronic valvular heart disease (one patient; stable after valve replacement). The mean ejection fraction (assessed by trans-thoracic echocardiography; modified Simpson method) was 33% (range 15–40%). All patients were in sinus rhythm and none had been treated previously with AT$_1$ receptor blockers. No patient was on current ACE inhibitor treatment; 18 had never received an ACE inhibitor, and three had previously been intolerant of an ACE inhibitor, which had been discontinued at least 6 weeks before recruitment. Concurrent therapy included loop diuretics ($n = 9$; frusemide dose range 40–160 mg), digoxin ($n = 1$), calcium antagonists ($n = 4$), $\alpha$-blockers ($n = 2$) and $\beta$-blockers ($n = 2$). Unless clinically indicated, all drugs were maintained at constant doses throughout the study (one patient required the addition of isosorbide mononitrate (30 mg daily) for stable-effort angina, and two patients required adjustment of amiloride (5 mg) to maintain normokalaemia). All drugs were withheld on the days of laboratory visits until recordings had been obtained.

Acute study
All 21 subjects completed the acute arm of the study. The first doses of candesartan and placebo were tolerated by all patients without adverse effects. The mean values of blood pressure and RR interval during metronomic breathing are shown Figure 1, and HRV and BRS data are shown in Table 1. There were no significant differences between the effects of candesartan and placebo in any of these parameters. HRV data are presented for 17 of the 21 patients (in four patients, frequent ectopic beats precluded analysis). Cross-spectral analysis with adequate coherence was possible in 10 and 16 patients for $\alpha$-LF and $\alpha$-HF power.

Table 1  RR variability and BRS at rest, during synchronized metronomic breathing
Values are means (S.E.M.). Significance of differences: * $P < 0.05$ compared with chronic placebo treatment. n.u., normalized units.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute study</th>
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<th>Chronic study</th>
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<tr>
<td></td>
<td>Placebo</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Candesartan</td>
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<tr>
<td>SDNN (ms)</td>
<td>20 (2)</td>
<td>20 (3)</td>
<td>17 (2)</td>
<td>19 (3)</td>
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<td></td>
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<tr>
<td>RMSSD (ms)</td>
<td>14 (2)</td>
<td>14 (2)</td>
<td>13 (2)</td>
<td>16 (3)</td>
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<td></td>
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<tr>
<td>LF power (n.u.)</td>
<td>0.35 (0.06)</td>
<td>0.33 (0.04)</td>
<td>0.31 (0.05)</td>
<td>0.21 (0.03)*</td>
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<tr>
<td>HF power (n.u.)</td>
<td>0.44 (0.05)</td>
<td>0.44 (0.04)</td>
<td>0.52 (0.05)</td>
<td>0.52 (0.04)</td>
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<tr>
<td>$\alpha$-LF (ms/mmHg)</td>
<td>4.6 (1.4)</td>
<td>4.3 (1.4)</td>
<td>3.3 (1.0)</td>
<td>3.2 (0.9)</td>
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<tr>
<td>$\alpha$-HF (ms/mmHg)</td>
<td>4.4 (1.1)</td>
<td>3.6 (0.9)</td>
<td>5.1 (1.3)</td>
<td>5.0 (1.2)</td>
<td></td>
<td></td>
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<tr>
<td>Oxford BRS (ms/mmHg)</td>
<td>3.7 (0.6)</td>
<td>4.0 (0.8)</td>
<td>3.5 (0.5)</td>
<td>4.8 (0.7)*</td>
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Table 2  RR interval and RR variability during mental arithmetic
Values are means (S.E.M.). There were no significant differences. n.u., normalized units.

<table>
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<tr>
<th>Parameter</th>
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<th>Chronic candesartan</th>
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</thead>
<tbody>
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<td>RR interval (ms)</td>
<td>769 (25)</td>
<td>760 (26)</td>
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<td>SDNN (ms)</td>
<td>18 (2)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>11 (2)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>LF power (n.u.)</td>
<td>0.56 (0.06)</td>
<td>0.43 (0.08)</td>
</tr>
<tr>
<td>HF power (n.u.)</td>
<td>0.20 (0.04)</td>
<td>0.28 (0.05)</td>
</tr>
</tbody>
</table>

Table 3  RR interval and RR variability during head-up tilt testing
Values are means (S.E.M.). Significance of difference: *P < 0.05. n.u., normalized units.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic placebo</th>
<th>Chronic candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>777 (21)</td>
<td>769 (24)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>18 (3)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>10 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>LF power (n.u.)</td>
<td>0.35 (0.05)</td>
<td>0.31 (0.05)</td>
</tr>
<tr>
<td>HF power (n.u.)</td>
<td>0.35 (0.04)</td>
<td>0.43 (0.06)*</td>
</tr>
</tbody>
</table>

Table 4  24 h RR interval and RR variability
Values are means (S.E.M.). There were no significant differences. n.u., normalized units; HRVi, St George’s HRV index.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic placebo</th>
<th>Chronic candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>788 (17)</td>
<td>773 (17)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>93 (6)</td>
<td>95 (7)</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>34 (5)</td>
<td>32 (5)</td>
</tr>
<tr>
<td>HRVi (ms)</td>
<td>29 (2)</td>
<td>27 (2)</td>
</tr>
</tbody>
</table>

α-HF respectively. Adequate data for measurement of BRS by the Oxford method were available from 16 patients.

**Chronic study**

**Laboratory measurements at rest**

Altogether, 19 subjects completed the chronic arm of the study (of the initial 21 patients, two were excluded from the chronic study: one developed atrial fibrillation and another developed symptomatic postural hypotension while on concomitant α-blocker therapy). For the 19 subjects who completed both arms of the study, there were no serious adverse events, and there was no significant change in serum creatinine levels.

Compared with placebo, chronic therapy with candesartan was associated with a significant fall in blood pressure, but with no significant change in mean R-R interval (Figure 1). HRV data are presented for 17 of the 19 patients (in two patients, frequent ectopic beats precluded analysis); cross-spectral analysis with adequate coherence was possible in 12 patients for α-LF and 16 patients for α-HF (see Table 1). Despite the fall in blood pressure, there were no significant changes in time-domain parameters of HRV or in HF power. However, compared with placebo, LF power measured in normalized units was significantly lower during treatment with candesartan. BRS measured by the Oxford method was significantly greater with candesartan compared with placebo, but no such changes were seen for data obtained by cross-spectral analysis.

**Laboratory measurements under conditions of stress**

Of the 19 patients who participated in the chronic study, paired data were available from 14 patients who performed mental arithmetic and 15 patients who underwent head-up tilt. Conditions of mental and orthostatic stress were both associated with significant reductions in mean RR interval compared with baseline. During mental stress, there were no significant differences between the effects of candesartan and placebo on RR interval or HRV (Table 2). During orthostatic stress, there were no significant differences between the effects of candesartan and placebo on RR interval. Time-domain analysis revealed no significant differences in HRV between placebo and candesartan. In the frequency domain, HF power measured in normalized units was significantly greater during treatment with candesartan than with placebo (Table 3).

**DISCUSSION**

This study has demonstrated that, in patients with heart failure, acute treatment with candesartan does not result in changes in blood pressure, heart rate, HRV or BRS that are significantly different from those following placebo treatment. Chronic candesartan therapy caused a significant reduction in blood pressure, but no consistent changes in heart rate or HRV, at rest, during mental or orthostatic stress or during ambulatory monitoring. The absence of a reflex tachycardia despite the significant reduction in blood pressure with candesartan is a feature shared by ACE inhibitors, and suggests resetting of the baroreceptor heart rate reflex. This has not been described previously in patients with heart failure treated with AT₁.
receptor blockers, but is a consistent finding in hypertensive patients treated with these drugs [19]. BRS was measured in the present study by assessing the heart rate response both to an acute rise in arterial pressure (Oxford BRS) and to spontaneous oscillations in arterial pressure (cross-spectral BRS). No increase in BRS with candesartan was demonstrable by the cross-spectral method at either LF or HF power. The apparent increase in Oxford BRS is discrepant with the cross-spectral results and is difficult to explain, particularly as there was no change in HF HRV during candesartan therapy, a measure determined principally by baroreflex-mediated effects [20]. The physiological validity and reproducibility of the Oxford method in heart failure have been questioned strongly [21], and we are inclined to give more weight to the spontaneous relationship between RR interval and systolic pressure determined by the cross-spectral technique. In addition, the Oxford method is more susceptible to bias because of the need for acceptance or rejection of the slopes by the investigator (although it is difficult to explain our results by bias in the present blinded study).

In the present study there were no consistent effects of AT1 receptor blocker therapy on HRV indices of cardiac vagal control. In a previous study involving rabbits with experimental heart failure, Murakami and colleagues [22] found that AT1 receptor blockade partially restored abnormalities in the baroreflex control of heart rate; after using atropine and β-blockade, these workers attributed these effects to an attenuation of sympathetic activity rather than to enhancement of cardiac vagal control. In further studies involving rats and rabbits with heart failure, AT1 receptor blocker therapy was shown to enhance the baroreflex control of renal sympathetic nerve activity, although it should be acknowledged that these effects may not apply to the sympathetic control of other beds nor to the vagal component of heart rate control [23,24]. Thus the animal evidence suggests that AT1 receptor antagonists can modulate sympathetic nervous activity, although no consistent effects on cardiac vagal control have been shown. No comparable study of the effects of AT1 receptor antagonists in human heart failure exists, but previous data from studies of the effects of losartan in hypertensive patients [25] and healthy subjects [26] are consistent with our results. Thus 3 weeks of treatment with losartan in hypertensive patients resulted in a significant fall in blood pressure, but no significant changes in heart rate or HRV in the frequency domain, although cross-spectral analysis showed that BRS was significantly increased with losartan [25]. Rongen et al. [26] found that, in healthy subjects after 1 week of treatment, losartan was associated with a significant fall in blood pressure, but no significant changes in measures of HRV or BRS. The consistent lack of effect of AT1 receptor antagonists on measures of cardiac autonomic control in humans might be considered surprising in view of the well described actions of angiotensin II and the results of studies with ACE inhibitors. Animal and human studies have shown that angiotensin II has powerful influences upon the autonomic control of the cardiovascular system. Central and peripheral actions resulting in inhibition of cardiac parasympathetic control and facilitation of sympathetic activity have been demonstrated in animals [6–8]. In humans, our studies have shown that cardiac vagal control is reduced by angiotensin II [3], and a facilitatory action on the baroreflex control of sympathetic activity has also been described [27]. These actions appear to be mediated by AT1 receptors [28], and therefore pharmacological blockade might be expected to increase measures of cardiac vagal activity and reduce those related to sympathetic activity. Numerous studies of the cardiac autonomic effects of ACE inhibitor therapy in heart failure have shown increases in both HRV and BRS [9–12].

There are a number of possible explanations for the difference between the autonomic effects of inhibition of angiotensin II formation by ACE inhibitors and blockade of the AT1 receptor. First, it is possible that any increase in cardiac vagal activity due to candesartan was confounded by the reduction in blood pressure and consequent baroreflex-mediated vagal inhibition. The lack of a fall in measures of HF HRV with candesartan, despite the reduction in blood pressure, can be interpreted as suggesting that these agents may have some vagotonic influence. However, these effects appear to fall far short of the powerful and well documented vagotonic effects of ACE inhibitors [9–12], suggesting either that other measures are active or that ACE inhibitors cause smaller falls in blood pressure. No comparative data on the relative effects of ACE inhibitors and AT1 receptor blockers on blood pressure in heart failure are available, but there are data showing that ACE inhibitors have surprisingly modest effects on blood pressure in heart failure [12,29] and in a variety of other indications [30].

A second explanation for the lack of change of HRV with candesartan is that the major effects of angiotensin II on autonomic control are mediated centrally and therefore may not be susceptible to AT1 receptor blockade. The central actions of angiotensin II appear to be mediated through the circumventricular organs such as the area postrema and subfornicular organ, which contain angiotensin II-sensitive neurons and which, lacking a blood–brain barrier, are accessible to circulating angiotensin II [6]. Reduction of circulating levels of angiotensin II by ACE inhibitor therapy would be expected to reduce the influence of angiotensin II at these sites, irrespective of whether ACE inhibitors are able to cross the blood–brain barrier. Conversely, AT1 receptor blockers do not reduce, and may even increase, circulating levels of angiotensin II [31], and require access to the AT1 receptor to exert their effect. It is not known whether candesartan, or indeed any of the AT1 receptor
AT_1 receptor blockade and cardiac vagal control

blockers, penetrates the blood–brain barrier in humans, although there is evidence of partial penetration into the central nervous system in rats at high doses [32,33]. Thus it is feasible that the central sites of cardiac autonomic control may remain exposed to the effects of high circulating levels of angiotensin II despite adequate peripheral AT_1 receptor blockade.

The third, but perhaps less likely, possible explanation is that the autonomic effects of ACE inhibitor therapy might be mediated by a mechanism independent of angiotensin II, for example via bradykinin or angiotensin [1–7]. ACE inhibitors increase plasma and tissue concentrations of these peptides [34], which have been shown to act centrally to facilitate the baroreflex control of heart rate in rats [35]. AT_1 receptor blockers are not thought to potentiate the bradykinin pathway directly; however, an indirect effect caused by unopposed AT_2 agonism cannot be excluded, as animal evidence shows that AT_2 receptors can stimulate bradykinin production and potentiate the bradykinin/nitric oxide/cGMP pathway [36,37]. The extent of this effect in humans is unknown, but in a recent study involving patients with heart failure, Davie et al. [38] found no differences between the effects of an ACE inhibitor and an AT_1 antagonist on endogenous bradykinin-mediated forearm vasodilatation. These findings are not directly applicable to the subject of cardiac autonomic control, but they do suggest that potentiation of endogenous bradykinins is unlikely to contribute significantly to the different effects of these two classes of drugs.

This was a small study because of necessarily strict quality criteria for ECG and blood pressure data sets. The ECGs of patients with heart failure tend to have a high incidence of ectopic activity, leading to the rejection of many otherwise suitable patients. The cross-over design allowed adequate statistical power to be achieved despite this problem. With a sample size of 19, the study had a power of 90% to detect changes of 40% in the parameters described above at a significance level of 5%. The sample size compares favourably with previous studies of ACE inhibitors and autonomic function, in which the median sample size receiving active treatment was 12 (range 8–20) [9–12,18].

The measurement of HRV and BRS in heart failure is of clinical importance, because low values are associated with high mortality, even in mild disease [5,39,40]. We have hypothesized previously that high circulating angiotensin II concentrations may explain the impairment in cardiac parasympathetic function in heart failure and, conversely, that ACE inhibitor therapy might reduce mortality by improving cardiac parasympathetic control [3]. The evidence from the present study suggests that AT_1 receptor blockers may not possess this protective autonomic action, although it remains uncertain whether this is a clinically important mechanism of action. It is still unclear whether AT_1 receptor blockers and ACE inhibitors are equally effective in reducing mortality in patients with heart failure – in the ELITE II study there were no differences in mortality between patients treated with losartan and captopril, but it should be acknowledged that ELITE II was not designed or empowered to prove equivalence [41]. The detailed results of further trials of AT_1 receptor blockers in heart failure are awaited.

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