Do high doses of AT1-receptor blockers attenuate central sympathetic outflow in humans with chronic heart failure?

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Abstract

In patients with CHF (chronic heart failure) sympathetic activity increases as cardiac performance decreases and filling pressures increase. We hypothesized that in patients with mild-to-moderate CHF, higher than conventional doses of an AT1-receptor [AngII (angiotensin II) type 1 receptor] antagonist would achieve greater central AT1-receptor blockade, resulting in diminished MSNA (muscle sympathetic nerve activity) and augmented MSNA variability, two indices of central effects on sympathetic outflow. In total, 13 patients with ischaemic cardiomyopathy [NYHA (New York Heart Association) class II–III] were weaned off all pharmacological RAS (renin–angiotensin system) modifiers, and then randomized to receive a low (50 mg/day) or high (200 mg/day) dose of losartan. Central haemodynamics, MSNA and its variability, plasma catecholamines, AngI (angiotensin I) and AngII and aldosterone were assessed both before and 3 months after randomization. Neither dose altered BP (blood pressure), PCWP (pulmonary capillary wedge pressure) or CI (cardiac index) significantly. Compared with 50 mg daily, losartan 200 mg/day decreased MSNA significantly (\(P<0.05\)), by approximately 15 bursts/min, and increased MSNA variability within the 0.27–0.33 Hz high-frequency range by 0.11 units\(^2/Hz\) (\(P = 0.06\)). PNE [plasma noradrenaline (norepinephrine)] fell in parallel with changes in MSNA (\(r = 0.62; P < 0.05\)). These findings support the hypothesis that higher than conventional doses of lipophilic ARBs (AT1-receptor blockers) can modulate the intensity and variability of central sympathetic outflow in patients with CHF. The efficacy and safety of this conceptual change in the therapeutic approach to heart failure merits prospective testing in clinical trials.

Key words: angiotensin II type 1 receptor blocker (ARB), chronic heart failure, muscle sympathetic nerve activity (MSNA), noradrenaline

INTRODUCTION

In patients with CHF (chronic heart failure) caused by ischaemic heart disease, sympathetic activity increases as cardiac performance decreases, and sympathetic hyperactivity is a predictor and determinant of adverse cardiovascular outcomes [1]. Sympatho-excitation elicited by AngII (angiotensin II) and aldosterone is an important mechanism for sympathetic hyperactivity in CHF [2]. AngII may increase sympathetic activity via its excitatory central [3], ganglionic [4] and peripheral presynaptic effects [5].

Using a rabbit model of ventricular pacing, Zucker’s group demonstrated the importance for sympatho-excitation in heart failure of central AT1-receptors (AngII type 1 receptors) in areas such as the PVN (paraventricular nucleus) of the hypothalamus [6]. Our group has shown that, in rats with CHF post-MI (myocardial infarction), central infusion of the ARB (AT1-receptor blocker) losartan decreases renal sympathetic nerve activity, normalizes arterial baroreflex function and improves LV (left ventricular) function [3,7]. Moreover, in rats with CHF post-MI, high doses of ARBs administered systemically cause sympathoinhibitory effects similar to those achieved with direct central infusion [7].

There is little information in patients with CHF concerning the effect of ACEis [ACE (angiotensin-converting enzyme) inhibitors] on central sympathetic outflow. In patients with CHF, sympathetic activity is increased as cardiac performance decreases and filling pressures increase [1]. We hypothesized that in patients with mild-to-moderate CHF, higher than conventional doses of an AT1-receptor antagonist would achieve greater central AT1-receptor blockade, resulting in diminished MSNA and augmented MSNA variability, two indices of central effects on sympathetic outflow. In total, 13 patients with ischaemic cardiomyopathy [NYHA (New York Heart Association) class II–III] were weaned off all pharmacological RAS (renin–angiotensin system) modifiers, and then randomized to receive a low (50 mg/day) or high (200 mg/day) dose of losartan. Central haemodynamics, MSNA and its variability, plasma catecholamines, AngI (angiotensin I) and AngII and aldosterone were assessed both before and 3 months after randomization. Neither dose altered BP (blood pressure), PCWP (pulmonary capillary wedge pressure) or CI (cardiac index) significantly. Compared with 50 mg daily, losartan 200 mg/day decreased MSNA significantly (\(P<0.05\)), by approximately 15 bursts/min, and increased MSNA variability within the 0.27–0.33 Hz high-frequency range by 0.11 units\(^2/Hz\) (\(P = 0.06\)). PNE [plasma noradrenaline (norepinephrine)] fell in parallel with changes in MSNA (\(r = 0.62; P < 0.05\)). These findings support the hypothesis that higher than conventional doses of lipophilic ARBs (AT1-receptor blockers) can modulate the intensity and variability of central sympathetic outflow in patients with CHF. The efficacy and safety of this conceptual change in the therapeutic approach to heart failure merits prospective testing in clinical trials.

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INTRODUCTION

In patients with CHF (chronic heart failure) caused by ischaemic heart disease, sympathetic activity increases as cardiac performance decreases, and sympathetic hyperactivity is a predictor and determinant of adverse cardiovascular outcomes [1]. Sympatho-excitation elicited by AngII (angiotensin II) and aldosterone is an important mechanism for sympathetic hyperactivity in CHF [2]. AngII may increase sympathetic activity via its excitatory central [3], ganglionic [4] and peripheral presynaptic effects [5].

Using a rabbit model of ventricular pacing, Zucker’s group demonstrated the importance for sympatho-excitation in heart
inhibitors] or ARBs on directly measured indices of central sympathetic outflow such as MSNA (muscle sympathetic nerve activity). In 12 patients with mild CHF, MSNA and PNE [plasma noradrenaline (norepinephrine)] decreased by 30 ± 5% after 2 months of treatment with a low dose (10 mg/day) of the lipophilic ACEi benazepril [8]. Much less impact on central sympathetic outflow however was reported after treatment for 4 weeks with a low dose (8 mg/day) of a hydrophilic ARB, candesartan. MSNA decreased by 19 ± 7% as compared with placebo (P < 0.01; n = 10/group) [9]. Considering that MSNA in untreated CHF subjects is in general 2–3-fold greater than in healthy age-matched control subjects [10,11], these represent rather modest decrements in MSNA. One potential explanation for these observations is that conventional doses of ACEis or ARBs may not achieve concentrations in the brain sufficient to cause interruption of central neural AngII generation or achieve central AT1-receptor blockade.

In the present study, we assessed whether in patients with mild-to-moderate CHF, treatment with a high dose of hydrophilic losartan will achieve central AT1-receptor blockade sufficient to cause a more pronounced decrease in MSNA, an index of central sympathetic outflow, than the dose evaluated in clinical trials [12]. Because a high dose of losartan might attenuate the cardiac sympathetic afferent reflex and/or increase catecholamine clearance by causing a greater decrease in LV-filling pressure and/or a larger increase in cardiac output, central haemodynamics were determined before and after the treatment [13]. Advanced heart failure is characterized, in addition, by loss of the variability of central sympathetic outflow, determined using spectral analysis [14–16]. MSNA spectral power within the low-frequency range can be augmented or restored by acute infusion of atrial natriuretic peptide (but not nitroglycerine) or, independently of any effect on MSNA burst frequency or incidence, by 4–6 months of treatment with the centrally acting β-adrenoreceptor antagonists carvedilol and metoprolol [17,18]. We therefore submitted the MSNA signal to spectral analysis, as an additional test of the hypothesis that the higher dose of the ARB would have greater effect on the central generation and modulation of sympathetic discharge.

MATERIALS AND METHODS

Study population
Patients aged 21–75 years with CHF class II–IIIa NYHA (New York Heart Association) and LVEF (LV ejection fraction) 25–40% on echocardiogram, secondary to coronary artery disease, were eligible. Other inclusion criteria included sinus rhythm and no cardiac ischaemic event or clinical exacerbation of CHF in the 3 months before the study. Excluded were patients with chronic kidney disease [defined as eGFR (estimated glomerular filtration rate) < 60 ml·min⁻¹·1.73 m⁻² or kidney disease irrespective of eGFR], endocrine or liver disease, hypertension [BP (blood pressure) > 140/90 mmHg at rest] or with other conditions possibly affecting cardiovascular regulation and sympathetic activity. Patients prescribed coumadin, a mineralocorticoid receptor blocker or central sympatholytic agent such as clonidine were excluded. Treatment with metoprolol or carvedilol, which do not alter MSNA when taken daily for 3–6 months [19], was permitted. We also excluded patients with any previous adverse reaction to an ARB as well as pregnant and lactating women, and patients with history of alcoholism, drug abuse, psychiatric disorders, or with peroneal nerve injuries. The Research Ethics Board of the University of Ottawa Heart Institute approved the study. All patients gave written informed consent to participate in the study after its nature and purpose had been explained.

Study design and procedure
The present study was designed and executed as a single blind randomized clinical trial. One investigator and patients were not blinded, but all other investigators and research personnel involved were blinded to the allotted dose. After screening, patients receiving dihydroxy had this medication discontinued over 1 week. Once stable dihydroxy for 2 weeks, longer acting ACEis were replaced by captopril in equivalent doses. Subsequently, over the next 1–2 weeks doses of captopril and any ARB were gradually decreased and then discontinued. Dry weight was monitored closely and the furosemide dose adjusted accordingly. Once off RAS (renin–angiotensin system) blockers for a minimum of 3 days, during a 3–5 days run-in period, each patient participated in ‘a mock study’ (without insertion of the flow-directed balloon-tipped pulmonary artery catheter, assessment of MSNA, and blood sampling) to acquaint them with the laboratory, research personnel and experimental procedures.

The baseline study included assessment of central haemodynamics, MSNA, plasma catecholamines, renin, AngII, and aldosterone. Patients were then randomized to receive either a conventional, low (50 mg/day) or high (200 mg/day) dose of losartan. The starting dose was the same for both groups (25 mg twice a day), but those randomized to high dose of losartan had their dose increased by 25 mg twice a day every 2 weeks. The baseline pre-treatment study protocol was replicated 3 months after randomization.

As preparation for both study days, patients abstained from alcohol, smoking, solid food and caffeine-containing drinks from 20:00 h on the evening before. They were asked to hold the morning dose of furosemide on the day of the study, and to take their losartan dose in the morning prior to the second study. All studies were performed in the morning. Instrumentation included placement of a flow-directed balloon-tipped pulmonary artery catheter (Edwards LifeSciences) via the right internal jugular vein, coupling of the flow-directed balloon-tipped pulmonary artery catheter to a cardiac monitor and Ponemah acquisition system, application of ECG electrodes (ECG/Biotach Amplifier; Gould), and BP monitor for cuff–BP and at radial artery for beat-to-beat BP measurement (both Colin 7000), application of a respiration belt (Pneumotrace Respirator Belt connected to a Bioelectric Amplifier; Gould), placement of an indwelling venous catheter (BD Insyte Autoguard, Becton Dickinson Infusion Therapy Systems) into a forearm vein, and placement of a tungsten micro-electrode into a muscle fascicle of the peroneal nerve at the fibular head with a reference electrode placed subcutaneously 1–2 cm away as described previously [20]. After 30 min of rest, MSNA was recorded for 10 min with simultaneous recording of
RESULTS

Demographic data
In total, 15 patients were enrolled and 13 patients were randomized and completed the study. Two patients withdrew consent during the run-in phase. There were no differences in gender, age, BMI (body mass index) and baseline LVEF between the two groups (Table 1). The majority of patients in each treatment arm were taking diuretics and a β-blocker (all metoprolol). Body weight was maintained throughout the study within the range of 1 kg from the body weight at baseline by adjusting the dose of furosemide.

Peripheral and central haemodynamics
At baseline, systolic and diastolic BPs were similar in the two groups (Table 2). Decreases in systolic and diastolic BP in response to losartan tended (not significantly) to be greater with the low dose. HR was similar in the groups at baseline, and did not change in response to losartan in either group. Both groups had similar PCWP (pulmonary capillary wedge pressure), CVP (central venous pressure), CI (cardiac index) and TPR at baseline. Neither dose of losartan had a significant effect on these haemodynamic variables (Table 2). For both groups together, TPR decreased significantly.

Table 1 Baseline data of study patients

<table>
<thead>
<tr>
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<th>Losartan treatment</th>
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<tr>
<td></td>
<td>50 mg/day</td>
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<tr>
<td></td>
<td>200 mg/day</td>
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<tr>
<td>Gender (n) (male/female)</td>
<td>5/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57±3</td>
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<tr>
<td>Weight (kg)</td>
<td>96±8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30±1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31±2</td>
</tr>
<tr>
<td>Type 2 diabetes (n)</td>
<td>1 (female)</td>
</tr>
<tr>
<td>Medication (n)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>4</td>
</tr>
<tr>
<td>Diuretic</td>
<td>4</td>
</tr>
<tr>
<td>Statin</td>
<td>5</td>
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Figure 1 Changes from baseline in MSNA and PNE
Black bars, losartan 50 mg/day; grey bars, losartan 200 mg/day. Values are means ± S.E.M. #P < 0.05 compared with baseline; +P < 0.05 compared with losartan 50 mg/day.

Sympathetic activity
MSNA was somewhat lower (not significantly) at baseline in patients randomized to the low dose of losartan (42±4 bursts/min) as compared with the group randomized to the high dose of losartan (49±3 bursts/min). During the treatment with the low dose of losartan MSNA increased by 15% (P<0.05). In contrast, a high dose of losartan decreased MSNA by 10% (P<0.05). These opposite responses were significantly (P<0.05) different from each other (Figure 1).

Ten MSNA recordings were suitable for spectral analysis: from four subjects who received 50 mg/day and from six who received 200 mg/day. Average MSNA frequency–power relationships derived before and after low-dose and high-dose losartan
Table 2  Haemodynamic changes in response to a low compared with high dose of losartan
Values are means ± S.E.M. For both groups together TPR decreased (P<0.05) after losartan.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Losartan treatment</th>
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<tr>
<td></td>
<td>50 mg/day</td>
<td>200 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>Baseline 12 weeks</td>
<td>Baseline 12 weeks</td>
<td></td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>129 ± 7/80 ± 6</td>
<td>−6 ± 8/−9 ± 5</td>
<td>127 ± 4/76 ± 3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>63 ± 4</td>
<td>1 ± 2</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>CI (litres · min⁻¹ · m⁻²)</td>
<td>2.2 ± 0.2</td>
<td>0.1 ± 0.2</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>10 ± 2</td>
<td>1 ± 2</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>5 ± 1</td>
<td>1 ± 2</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>TPR (mmHg. · min⁻¹ · min⁻¹)</td>
<td>20 ± 1</td>
<td>−3 ± 1</td>
<td>23 ± 4</td>
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Figure 2 Effects of losartan on MSNA variability
Values are means ± S.E.M. for MSNA harmonic power (units²/Hz), across the frequency range of 0–0.5 Hz, derived using CGSA before (closed circles) and after (open circles) losartan 50 mg/day (A) or losartan 200 mg/day (B). With high, but not low, dose of losartan, there is no significant effect on MSNA spectral power at lower-frequency ranges, but augmentation of MSNA spectral power across the frequency range of 0.27–0.33 Hz (P = 0.06).

Table 3  Changes in plasma AngI, AngII and aldosterone in response to a low compared with high dose of losartan
Values are means ± S.E.M. For both groups together AngII increased (P<0.05) and aldosterone decreased (P<0.05) after losartan.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Losartan treatment</th>
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<td></td>
<td>50 mg/day</td>
<td>200 mg/day</td>
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<tr>
<td></td>
<td>Baseline 12 weeks</td>
<td>Baseline 12 weeks</td>
<td></td>
</tr>
<tr>
<td>AngI (pg/ml)</td>
<td>7 ± 3</td>
<td>+8 ± 5</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>AngII (pg/ml)</td>
<td>4 ± 2</td>
<td>+4 ± 3</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>168 ± 52</td>
<td>−43 ± 69</td>
<td>135 ± 29</td>
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</table>

(349 ± 36 pg/ml). Compared with baseline, the low dose of losartan caused a small increase in PNE and a high dose of losartan a small decrease. Although these changes were not statistically significant, differences between them were (P<0.05). Changes in PNE during treatment with the low and high dose of losartan correlated directly (r = 0.62; P<0.05) with changes in MSNA. Plasma adrenaline (epinephrine) at baseline was similar in the two groups. Both doses of losartan tended (not significantly) to decrease plasma adrenaline.

Renin–angiotensin–aldosterone system
At baseline, plasma AngII and aldosterone did not differ between the two groups (Table 3). Plasma AngII increased in response to low (by 100%) and high dose (by 300%) of losartan. Plasma aldosterone decreased by approximately 25 and 50% in response to low and high doses of losartan, respectively. Increases in plasma AngII and decreases in aldosterone were statistically significant (P<0.05) when responses to losartan from both groups were combined.

6-Min walk test
At baseline, performance on walk test was similar in the low-dose (444 ± 29 m) and high-dose (439 ± 30 m) losartan groups. Neither high nor low dose of losartan caused significant changes in walk test distance (+7 ± 22 m and +30 ± 15 m respectively).

Creatinine clearance and plasma potassium concentration
Both groups had normal creatinine clearance at baseline (>90 ml·min⁻¹·1.73·m⁻²), and neither dose of losartan changed creatinine clearance. There were no episodes of
hyperkalaemia (defined as plasma $[K^+] > 5.1$ mmol/l) throughout the study.

**Tolerability**
No adverse effects of losartan were identified in either group.

**DISCUSSION**

The present study in patients with CHF NYHA class II–III provides support for the hypothesis that larger doses of blockers of the RAS may be required to attenuate central sympato-excitation in patients with CHF. Compared with a conventional/low dose of losartan, a high dose caused parallel decreases in MSNA and in PNE and an increase in MSNA spectral power within the high-frequency range.

A unique aspect of the present study, in addition to its comparison of the effects of the low against high doses of losartan on MSNA, is the acquisition in parallel of data concerning central and peripheral haemodynamics. Neither dose of losartan caused significant changes in haemodynamics. A modest fall in TPR was associated with a small increase in CI and variable change in BP. Changes in haemodynamics were similar in extent to those reported by others in patients with CHF on low dose of losartan [24]. The absence of more clear changes in haemodynamics in response to losartan may be related to low/normal circulating AngII levels secondary to concomitant $\beta$-adrenoreceptor blockade.

In patients allocated to the low dose of losartan (50 mg/day), MSNA and PNE showed small non-significant changes over 3 months of follow-up, and there was no effect on the variability of MSNA. There have been no previous studies on effects of losartan at any dose on MSNA or MSNA spectral power in patients with CHF. On the other hand, similar to our results, PNE showed a non-significant increase at 12 weeks in patients with CHF enrolled in a substudy of ELITE and randomized to losartan 50 mg/day [24]. The findings, after high dose of losartan, of decreases in MSNA and in PNE and in parallel an increase in MSNA spectral power within the high-frequency range are consistent with the concept that AngII, acting through $\text{AT}_1$-receptors, is an important component of a modifiable sympato-excitatory pathway activated in CHF. The concordance between changes in MSNA and PNE, the neurotransmitter released from sympathetic nerve endings, indicates that this inhibitory action is mediated via blockade of central and/or ganglionic $\text{AT}_1$-receptors, rather than by blockade of peripheral presynaptic $\text{AT}_1$-receptors. Because PCWP and CVP did not fall significantly, it is unlikely that deactivation of the afferent limb of the excitatory cardiac sympathetic reflex [19] accounts for the observed reductions in MSNA, and because cardiac output did not increase, the fall in PNE cannot be attributed to increased catecholamine clearance from plasma. However, over a longer time period, a decrease in sympathetic activity induced by high dose of losartan might translate into a decrease in LV filling pressure, leading to a further decrease in sympathetic activity by deactivating the afferent limb of the cardiac sympathetic reflex [2].

There is good concordance between changes in MSNA and cardiac sympathetic outflow in healthy subjects [25]. However, in the present study changes in MSNA were not accompanied by parallel changes in HR, most likely because pre-existing $\beta$-adrenoreceptor blockade was maintained. In future studies, MSNA could be complimented by quantification of cardiac noradrenaline spillover, using radiotracer methods.

Attenuation of MSNA spectral power with advanced heart failure has been attributed to central impairment of autonomic cardiovascular regulation [15]. In previous experiments involving heart failure patients with average LVEF of 20%, chronic $\beta$-adrenoreceptor blockade with carvedilol or metoprolol increased significantly MSNA spectral power across the frequency range of 0.1–0.22 Hz [18]. This includes the low-frequency nadir resulting from impaired sympathetic neuro-vascular transduction. At higher frequencies, up to 0.30 Hz, there was only a non-significant trend to greater spectral power. Thus, in the present study, it is conceivable that the presence of background $\beta$-adrenoreceptor blockade obscured our capacity to detect an independent effect of high-dose losartan on MSNA spectral power at frequencies below 0.27 Hz, and also attenuated the capacity of losartan (with a cohort of six subjects) to demonstrate an increase in MSNA 0.27–0.33 Hz spectral power of either greater magnitude than presently observed or with a chance probability of less than 6%. Importantly, the observation that high-dose losartan targeted this higher-frequency range, rather than the 0.13 Hz heart failure nadir, is consistent with central neural, rather than a peripheral vascular influence on the renin-angiotensin system [14]. The present enhancement of MSNA spectral power at 0.27–0.33 Hz is consistent with restoration of oscillatory function of central networks in parallel with those involved in the generation or transduction of respiratory sinus arrhythmia, which modulates HR variability within a similar frequency range. If so, the present observation would be concordant with previous reports of increased cardiac vagal tone following ACE inhibition [26]. Of interest, in Figure 2(B), is the suggestion that high-dose losartan may attenuate MSNA spectral power within the 0.11–0.15 Hz range. If this non-significant finding were observed in a larger cohort, this would suggest that in heart failure $\text{AT}_1$-receptor blockade blunts peripheral vascular responsiveness as does blockade of the central $\beta$-adrenoreceptor.

Although limited by the modest sample size, dictated by the complexity and invasiveness of these investigations, our findings provide support for the hypothesis that sympathetic hyperactivity in CHF is mediated – at least in part – through the central actions of AngII, and modifiable pharmacologically by high-dose lipo-philic $\text{AT}_1$-receptor blockade. The decrease in MSNA achieved with the supraclinical dose of losartan was relatively modest. If only a minor proportion of the sympato-excitation characteristic of untreated human heart failure is elicited via AngII-dependent mechanisms, such modest effects of a high dose of ARB would be anticipated. On the other hand, if this is indeed the predominant mechanism of sympathetic activation in human heart failure similar as it would appear to be in animal models [3,6,7], even higher doses and/or more lipophilic ARBs than used in the present study may be required to induce central sympathoinhibitory effects in areas such as the PVN of the hypothalamus. Either
way, a crucial aspect of this therapeutic approach is the attenuation of excess in central sympathetic outflow in CHF mediated via AngII-dependent mechanisms rather than non-specific central sympatholysis which may adversely affect outcomes in patients with CHF [27]. Results from the HEAAL study provide evidence of clinical benefit from such a therapeutic strategy in CHF in that, compared with losartan 50 mg/day, losartan 150 mg/day reduced the rate of death or heart failure admission [28].

Conclusions
Angiotensin receptor antagonists were developed for clinical application in heart failure in an era when therapeutics focused primarily on afterload reduction via direct peripheral vasodilatation. Doses evaluated in Phase II studies and the clinical trials that proved net benefit were set accordingly, with less attention paid to the potential effect of this class on the altered sympathetic and parasympathetic control of the heart and circulation characteristic of this condition. It was known from clinical investigation that sympathetic activity in heart failure increases as cardiac performance decreases, and that sympathetic hyperactivity is a predictor and determinant of mortality and adverse cardiovascular outcomes, but not until recently were the several central neural mechanisms by which AngII and aldosterone elicit important sympato-excitation in heart failure elucidated experimentally. Although limited by its modest sample size, dictated by the complexity and invasiveness of these investigations, the present findings in NYHA class II–III patients provide support for the hypothesis that sympathetic hyperactivity in human heart failure is mediated, at least in part, through the central actions of AngII, and modifiable pharmacologically if lipophilic AT1-receptor blockade is administered in a higher than conventional dose. Importantly, the dose selected was tolerated without adverse haemodynamic or other effects. Our study provides further insight into potential mechanisms responsible for the findings of the HEAAL trial that reported fewer death and heart failure admissions with losartan 150 mg/day as compared with losartan 50 mg/day. The hypothesis that the clinical course of class I–II patients will be modified favourably if high-dose lipophilic antagonist of central neural AngII-mediated sympathetic hyperactivity is interrupted by lipophilic antagonists given in higher than conventional doses merits testing in future clinical trials.

CLINICAL PERSPECTIVES

- In patients with CHF, sympathetic activity increases as cardiac performance decreases, and sympathetic hyperactivity is a predictor and determinant of adverse cardiovascular outcomes. This sympato-excitation may be elicited by central actions of AngII and aldosterone.
- In the present study in patients with CHF NYHA class II–III, treatment for 3 months with losartan at 50 mg/day or at 200 mg/day caused similar minor changes in central haemodynamics, but only the high dose caused parallel decreases in MSNA and in PNE and an increase in MSNA spectral power within the high-frequency range.

- These findings support the hypothesis that sympathetic hyperactivity in CHF is mediated, at least in part, through the central actions of AngII and is modifiable pharmacologically by high-dose AT1-receptor blocker. This mechanism may contribute to reduced mortality and heart failure admission rates in response to losartan at 150 mg/day compared with 50 mg/day shown in the HEAAL study.

REFERENCES


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