Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients

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Abstract

Background: Experimental data suggest that aldosterone has harmful effects promoting myocardial fibrosis and disturbing autonomic balance. There has been no evidence of these potential effects in intact man. **Methods and Results:** We report the findings in 31 patients with stable chronic heart failure (CHF) who were treated with spironolactone (50–100 mg/day) or placebo in addition to diuretics and angiotensin converting enzyme (ACE) inhibition. In a controlled randomised double-blind study, we found that spironolactone treatment reduced circulating levels of procollagen type III N-terminal amino peptide, a marker of vascular collagen turnover, and in addition increased time-domain parameters of heart rate variability ($n = 24$). These latter parameters suggest a parasympathomimetic effect for additional spironolactone. Spironolactone significantly reduced heart rate (prolonged RR interval) particularly during the dawn hours (06.00–09.00 h). In this unbalanced study it was not possible to provide a detailed diurnal assessment of the impact of spironolactone on heart rate variability, but the preliminary data suggest that there may be an interaction with the autonomic nervous system which varies in time. **Conclusions:** These are the first human data to show that use of the aldosterone antagonist, spironolactone, can positively improve time-domain heart rate variability and reduce myocardial collagen turnover, as reflected by further reductions in serum procollagen peptide, despite concurrent ACE inhibitor treatment. Residual aldosterone after ACE inhibitor treatment may therefore have a role promoting arrhythmia and cardiac death by two mechanisms. Effects of additional spironolactone on slowing heart rate (and potentially the detrimental effect of aldosterone) were most prominent between 6 a.m. and 10 a.m. when cardiac death is also known to be most prominent.

Keywords: ACE inhibitors; Aldosterone; Spironolactone; Heart failure; Sympathetic nervous system; Heart rate; Diurnal variation; Collagen; Human

1. Introduction

Neurohormonal suppression in heart failure patients has a major impact on morbidity and mortality [1]. It is likely that angiotensin converting enzyme (ACE) inhibitors produce their beneficial effects through a combination of vasodilatation and neurohormonal blockade [2]. Recent data suggest that the withdrawal of angiotensin II and aldosterone is not sustained during chronic therapy with ACE inhibitors: this is thought to be due to a combination of reactive hyper-reninaemia [3], alternative non-enzymatic pathways of angiotensin synthesis [4], confounding factors on angiotensin analysis [5] and partial compliance with ACE inhibitor treatment. This is important because, if ACE inhibitors do not maintain neurohormonal blockade, then other therapeutic opportunities arise. For example, the ACE-inhibitor-induced suppression of aldosterone in chronic heart failure is poor (20%), variable and unsustained. Therefore, if aldosterone is independently harmful, then there is plenty of residual aldosterone even in the presence of an ACE inhibitor for spironolactone to have a useful role, in addition to standard therapy with a diuretic and an ACE inhibitor. Spironolactone is currently being assessed for its efficacy in this setting in the RALES study [6].

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What harmful effects might aldosterone produce in heart failure? We have already shown that residual aldosterone causes magnesium loss and increased ventricular arrhythmia [7]. Experimental evidence shows clearly two other harmful effects for aldosterone. Firstly, aldosterone appears, independently of angiotensin II, to promote myocardial fibrosis. Secondly, aldosterone appears to exert parasympathetic effects as evidenced by the observations that aldosterone reduces baroreceptor discharge in the dog [8] and the observation that aldosterone reduces the bradycardia response to pressor stimuli in healthy man [9].

These effects of aldosterone on myocardial fibrosis and on the parasympathetic system could potentially increase mortality in heart failure, but there are as yet no human data to confirm these two potentially malignant effects of aldosterone in heart failure patients. In this paper, we sought evidence for such effects in man.

2. Methods

We report ECG data from 24 patients with symptomatic heart failure following previous myocardial infarction. This represents a subgroup of 31 individuals from an earlier study, the details of which have reported elsewhere [7]. Written and informed consent was given by all patients prior to study and the protocol was reviewed and passed by the local Research and Ethical Committee in the normal fashion prior to data collection. For the whole study population, mean left ventricular ejection fraction was considerably reduced at radionuclide scintigraphy ($20 \pm 5\%$; $n = 31$). All patients continued with current treatments including a diuretic and ACE inhibitor in every case. Patients were allocated to receive supplemental placebo or spironolactone for 8 weeks after a 1-month placebo run-in phase (data from the run-in phase were not used subsequently). The trial allocation was originally designed to assign 2 patients to active therapy for every one placebo control [7]. Plasma potassium and clinical status were monitored weekly. If tolerated, doubling of the medication from the second week while retaining double-blind conditions of treatment gave an active dose of spironolactone of 100 mg once daily compared to matched placebo.

Twenty-four-hour ambulatory ECG monitoring was performed at baseline and during the day prior to end of the treatment phase. The effects of treatment on rhythm and ventricular premature beat analysis have been previously reported [7]. Recordings were made in the community with subjects undertaking normal daily activities (excluding employment) in all instances. Assessment of the effects of treatment on the autonomic nervous system were obtained by interpretation of the RR interval tachogram from the 24-hour ECG records. Heart rate variability can be used as a qualified reflection of autonomic effects in intact man [9]. All evaluable 24-hour ambulatory ECG recordings were subjected to standardised heart rate variability analysis using time-domain parameters (Reynolds Medical Pathfinder 600 Analyser, Ware, Hertfordshire, UK). All analysis were performed on complete 24-hour recordings visually edited for correct identification of aberrant beats. Patients with unsatisfactory technical quality recordings ($n = 4$) or chronic atrial fibrillation ($n = 10$) were excluded.

The impact of treatment on myocardial fibrosis was estimated using serum measurements of procollagen type III amino terminal peptide (PIIINP) using standard commercial radio-immunoassay [10]. The intra-assay coefficient of variation is 3% and the interassay coefficient of variation 7.5% in our laboratory. All samples from this study were processed together in one analysis. Due to the availability of a larger data set for the PIIINP assay observations are included for 16 patients who received placebo and 21 patients who received spironolactone from the original experiment [7].

2.1. Statistical analysis

Drug effects were calculated as the change in parameters between baseline and the end of the treatment phase. All data are expressed as mean ± 1 standard deviation. Due to the uneven group sizes treatment effects were compared using repeated Student t-test (two-tailed) with statistical significance accepted at $P < 0.05$. Correlation between parameters was assessed using standardised linear regression.

3. Results

There were no differences between the baseline clinical characteristics of those patients treated with placebo compared to those treated with spironolactone (Table 1). There was no evidence of a significant diuretic effect of spironolactone as judged by body weight although there was a variation in individual response as indicated by the large standard deviation (Table 1).

There was no difference in baseline or diurnal heart rate between the placebo or spironolactone-treated group determined from 24-hour recordings. Hourly mean RR interval at the end of the 8-week treatment phase was generally increased in the spironolactone-treated group compared to placebo (Fig. 1). The treatment effect of spironolactone was statistically significant between 06.00 and 09.00 h.

Standardised time-domain indices of heart rate variability (24-hour mean data) showed small but significant increases in ΔSDNN (the change in standard deviation of normal-to-normal RR intervals between baseline and day 56 tapes), ΔSDNN$_i$ (the change in standard deviation of consecutive normal-to-normal intervals showing increases between baseline and day 56 tapes), and ΔSDANN (the change in 24-hour standard deviation of averaged NN intervals over 5 min samples between baseline and day 56

Table 1
Clinical characteristics of patients studied

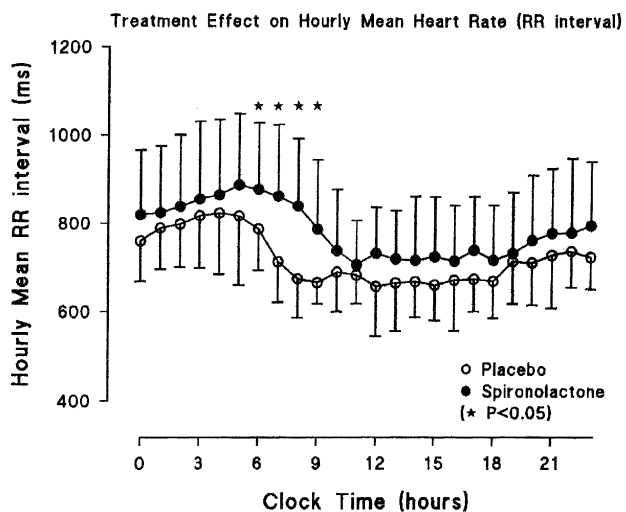|	Placebo	Spironolactone
n	16	21
Age (yr)	67.1 ± 8	64 ± 9
Male (n)	10	16
Duration CHF (yr)	2.6 ± 1.5	2.7 ± 2.8
Total dose diuretic (frusemide equivalent/day)	92 ± 33	82 ± 44
ACE inhibition (enalapril equivalent mg/day)	17 ± 10	15 ± 6
NYHA class II	11	12
(n) class III	4	7
class IV	1	2
Δ body weight (kg) (baseline–8 wk)	− 0.07 ± 2	− 1.1 ± 4

Fig. 1. Effect of placebo (○) or spironolactone (●) therapy on hourly mean RR interval at the end of 8 weeks therapy. * $P < 0.05$ placebo versus spironolactone.

tapes) which were statistically significant. There was a trend towards an increase in the composite time-domain triangular index, a measure of the distribution of normal NN intervals, again expressed as the change in index between baseline and day 56 tapes (ΔTINN) [9]. This effect was not statistically significant (Table 2).

In these stable CHF patients treated with both diuretic and ACE inhibitor, serum levels of PIIINP were similar at baseline. Placebo had little effect on these values although spironolactone showed an approximately 20% reduction following 8 weeks treatment (Table 1). In contrast to

placebo most patients receiving spironolactone showed a significant fall in serum PIIINP during treatment (Fig. 2).

There was no significant correlation for the change in PIIINP across all patients and change in body weight ($r = 0.296$, $P =$ n.s.). Change in heart rate variability showed statistically significant correlation to change in PIIINP for all parameters including triangular index
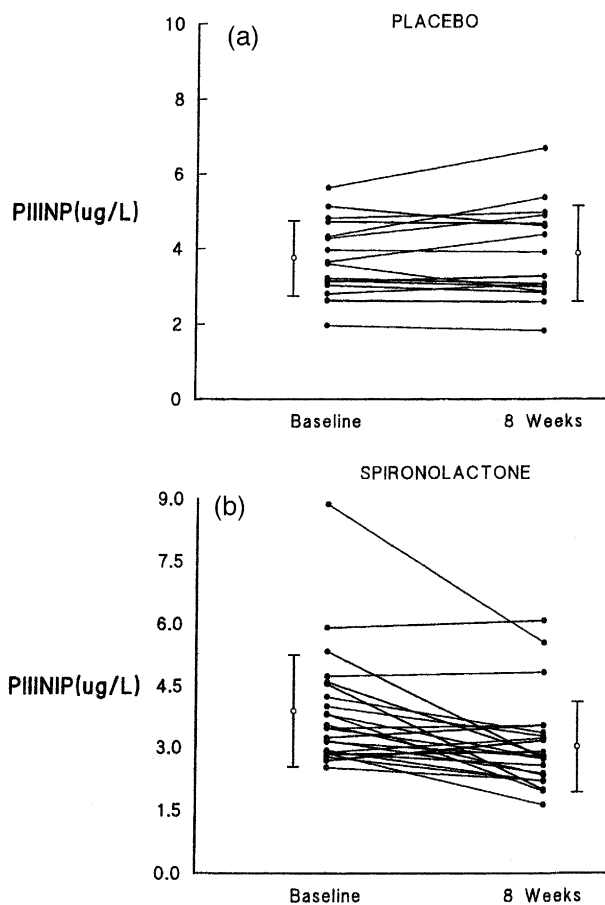

Fig. 2. Effect of placebo (a) or spironolactone (b) on serum PIIINP levels (μg/l) at baseline and following 8 weeks treatment in stable CHF. * $P > 0.05$ placebo versus spironolactone.

Table 2
Effect of treatments on time-domain heart rate variability parameters (change between baseline and 8 weeks treatment)

	ΔSDNN (ms)	ΔSDNNi (ms)	ΔSDAN (ms)	ΔTINN index
Placebo	− 1.2 ± 3.5	− 3.6 ± 7.9	0.4 ± 2.5	− 0.4 ± 8
Spironolactone	9.1 ± 4.5	4.1 ± 9	9.3 ± 6.0	1.8 ± 7
P	< 0.05	< 0.05	< 0.05	n.s.

(ΔSDNN, $r = 0.48$; ΔSDANN, $r = 0.41$; ΔSDNN$_i$, $r = 0.46$; ΔTINN, $r = 0.53$, all $P < 0.05$).

4. Discussion

There is now a large body of experimental data in laboratory animals and cell culture suggesting that angiotensin II and aldosterone are each independently capable of promoting myocardial fibrosis [11]. Until now, there have been no data to look at whether this also occurs in heart failure in man. To examine this question, we have used serum procollagen III amino terminal peptide (PIIINP) as a marker of myocardial collagen turnover. There is now accumulating evidence to show that serum PIIINP can be used as a marker for myocardial collagen turnover. It may also indicate a prognosis. Klappacher and colleagues [10] showed a close ($r = 0.784$, p = 0.0013) correlation between serum PIIINP and the amount of myocardial collagen type III on cardiac biopsy in heart failure patients. Furthermore, serum PIIINP was closely related to survival in these patients. Host et al. [12] showed that after a myocardial infarction serum PIIINP was higher in those patients with a poor outcome. Serum PIIINP has also been shown to increase temporarily after a myocardial infarction, which is in keeping with it being a marker of reparative fibrosis [13].

In essential hypertension, serum PIIINP was found to correlate not only with LV mass but also inversely with indices of diastolic filling. Furthermore, lisinopril was shown to normalise serum PIIINP at the same time as it reduced LV mass and improved diastolic filling [14]. These are strong indicators that serum PIIINP can be used as a marker for myocardial fibrosis. Our patients all had ischaemic cardiomyopathy already treated with ACE inhibitors and diuretics. Given this therapy is known to suppress the levels of serum PIIINP, it is reassuring to see that the circulating levels are comparable to the results recorded in patients who have hypertension and are being treated with ACE inhibitors [14]. These values are low and any further impact of additional aldosterone suppressive treatment would be expected to be small.

We saw a small but statistically significant fall in PIIINP following spironolactone compared to placebo. Our study is the first to confirm, albeit indirectly based on the specific and selective effect of spironolactone, that endogenous aldosterone over and above that remaining after ACE inhibitor treatment may have a role in the generation of continuing myocardial fibrosis in human heart failure.

Heart rate variability (HRV) is a novel and powerful prognostic indicator in patients following myocardial infarction and in patients with cardiac failure [9,15]. For example, at any given ejection fraction, a reduced HRV increases subsequent mortality by 2–3 times [16]. Although there is much debate as to the optimal interpretation or means of analysing RR interval data, broadly similar results are obtained with all techniques [9,17,18]. For all cardioactive drugs studied so far, the effect of drugs on survival is paralleled by their effects on HRV [19]. Cardiovascular drug effects on HRV are thought to be largely due to effects on vagal tone and to a lesser extent on sympathetic activity, although this remains controversial [20]. Experimental work suggests that aldosterone does possess autonomic effects, independent of angiotensin II. Aldosterone blunts the baroreceptor heart rate response to infused noradrenaline and increases sympathetic nervous activity [21,22]. The effects seen here of additional spironolactone on HRV are the first observations in heart failure patients. They suggest that aldosterone antagonism in these patients possibly exerts a parasympathomimetic effect. The effect seen here is small but is in keeping with patients who are already receiving ACE inhibitor treatment. A parasympathomimetic effect of spironolactone could may additionally suppress ventricular arrhythmia common in CHF. In ischaemic cats, vagal stimulation reduces the frequency of reperfusion induced ventricular fibrillation (VF) from 60 to 7%, while in ischaemic dogs vagal stimulation increases survival from 12 to 57% [23,24]. It is possible that the parasympathomimetic effects of spironolactone contribute to the 20% reduction in ventricular premature beats which we saw in our earlier study [7].

Spironolactone treatment had an interesting diurnal effect on heart rate. The particular effect on the 6–9 a.m. increase in heart rate may reduce the incidence of ischaemia at this time. Aldosterone under the influence of ACTH is known to peak at this time of day, as does cortisol [25] and therefore it is not surprising that the effects of spironolactone on heart rate and autonomic tone are most prominent at 6–9 a.m. Although the effect that we have documented is modest, the importance of the observation is that this is the same time of day when sudden cardiac death and myocardial infarctions are commonest [26,27]. In CHF, sudden death is 2.5 times as common in the few hours after 6 a.m. [27]. Our study raises the possibility that the ACTH-induced dawn increase in aldosterone alters autonomic balance in such a way as to increase ischaemia, arrhythmia and sudden death.

The beneficial effects of adding spironolactone to ACE inhibitor and diuretic treatment in this study did not appear to be related to any change in loading conditions through diuresis. Change in body weight, although variable within the patients, had no relationship either to changes in heart rate variability parameters or to changes in serum PIIINP. On analysis the changes in PIIINP appeared to correlate with changes in HRV. These may support other theoretical information described above that residual aldosterone after ACE inhibitor therapy still exerts a range of harmful effects in heart failure. Spironolactone, by blocking this residual aldosterone, may be a useful adjunct to standard diuretic/ACE inhibitor treatment. The question of whether

spironolactone will improve mortality in heart failure is more important and is currently being addressed by the ongoing RALES study. If this mortality study shows a positive drug effect, our observations suggest two further potential mechanisms for such an effect in man. Given the diurnal nature of our effect on HR our study would support a close circadian analysis of data from the RALES study and may give useful insight into the pathological role of residual aldosterone in human heart failure. While our study was too small to assess safety in a definitive fashion, we encountered few problems with additional spironolactone at the dose selected. It is important to note that the RALES study employs a lower dosage and will address safety which is obviously an important issue. Given the nature of current therapy for CHF, it is unlikely that additional spironolactone would be routinely used except in closely monitored patients where electrolyte disturbances were readily detected.

Acknowledgements

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