The influence of dose of angiotensin I-converting enzyme inhibitor on systolic blood pressure variability in heart failure: a substudy of the Assessment of Treatment with Lisinopril and Survival in heart failure (ATLAS) trial

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Heart failure is associated with a decreased variability in circadian systolic blood pressure. ACE inhibitors have been shown to be beneficial in CHF. However, the effect of the magnitude of the dose of ACE inhibitor on blood pressure variability has not been reported. The objective of this sub-study of the ATLAS trial was to determine if there was a difference in effect on systolic blood pressure variability of two doses (35 mg, 'high'; and, 5 mg, 'low') of the ACE inhibitor, lisinopril, in patients with heart failure (class II–IV; NYHA). Criteria for inclusion were: symptomatic heart failure (class II–IV; NYHA), left ventricular ejection fraction $\leq 30\%$, and 2 months of conventional therapy with diuretics with, or without, digoxin. Twenty-four hour ambulatory blood pressure was recorded prior to randomization and after peak titration (4 weeks) of the study drug for analysis of variability of systolic blood pressure variability. The high dose of lisinopril was associated with greater variability of 24 h systolic blood pressure as noted by inspection of the 24 h recordings or calculation of the blood pressure variability index ($P < 0.05$). The greater variability in SBP was not associated with a difference in mean 24 h arterial blood pressure.

Conclusions Variation in circadian systolic blood pressure is useful in reflecting the influence of the magnitude of dose of the ACE inhibitor lisinopril on the pharmacodynamics of patients with heart failure. *Blood Press Monit* 6:81–84 © 2001 Lippicott Williams & Wilkins.

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Heart failure is associated with abnormalities in variability of blood pressure [1–5]. Physical activity and alterations in autonomic nervous system (ANS) activity play a major role in the observed changes in variability of systolic blood pressure. Decreased activity of the parasympathetic nervous system (PNS) is one of the earliest abnormalities noted in the natural history of the syndrome [6,7]. A decrease in systolic blood pressure and heart rate variability is accompanied by neurohormonal activation [8].

Treatment of heart failure with angiotensin I-converting enzyme (ACE) inhibitors has resulted in improvement in morbidity and mortality [9]. Treatment of heart failure with the ACE inhibitors lisinopril and captopril resulted in an increase in the absolute amplitude of circadian systolic blood pressure variation [10]. To the best of our knowledge, a dose–effect relationship between ACE inhibitors and variability of blood pressure and heart rate has not been reported.

The Assessment of Treatment with Lisinopril and Survival in Heart Failure (ATLAS) trial [11] afforded us an opportunity to study the effect of two doses of the ACE inhibitor, lisinopril, on circadian variability in blood pressure in patients with heart failure (class II–IV; New York Association). The objectives of the ATLAS trial were to compare the effect on mortality of a low (clinical practice) dose of an ACE inhibitor, which provides relief of symptoms of congestive heart failure (CHF) with a high dose of the same drug which better reflects the doses used in mortality trials. We hypothesized that the higher dose of the ACE inhibitor lisinopril would be associated with greater circadian variability in systolic BP.

Methods

Fifty-four subjects qualified for enrolment into the ATLAS trial at our site. The protocol was approved by the Louisiana State University Health Sciences Center Institutional Review Board. The major entry criteria included: left ventricular ejection fraction $\leq 30\%$ and symptomatic heart failure (class II–IV; New York Association) despite 2 months of conventional therapy with diuretics with or without digoxin. The patients were required to have been treated with a diuretic for at least 60 days prior to entry and may have been receiving

ACE inhibitor therapy. Patients' eligibility was assessed during a 4-week screening phase in which incremental doses of lisinopril were added to their existing diuretic/digoxin therapy. Provided they tolerated lisinopril, patients were randomly allocated to once daily, double-blind treatment with lisinopril low dose (5 mg) or high dose (35 mg).

Twenty-four hour ambulatory blood pressure recording

Twenty-four hour ambulatory blood pressure and heart rate were recorded utilizing a digital blood pressure monitor (Smartlink, Wilmington, DL, USA). Recordings were made prior to randomization and after peak titration (4 weeks) of the study drug. The monitors were programmed to record blood pressure every 15 min from 06:00 to 24:00, and every 30 min from 24:00 until 06:00.

Blood pressure analysis

Criteria for acceptable blood pressure recordings included a minimum of 67 good readings from the total of 84 scheduled readings; at least two blood pressure readings per hour during 05:00 until 22:59 with not more than 3 h with 1 data point each; and one good reading per hour between 23:00 and 04:59 with not more than 1 h of missing data. The absolute amplitude of the 24 h time course for systolic BP was calculated as 50% of the difference between the daytime acrophase and the nighttime nadir, expressed in mmHg.

Statistical analysis

Differences between demographic data were tested for using Student's *t*-test (2-tailed). Differences between low and high dose lisinopril systolic blood pressure data was tested for using a two-way analysis of variance (dose, time) with repeated measures on one factor (time). Fisher's protected LSD post-hoc test was used to identify statistical differences between groups over time. Treatment effects for low and high dose lisinopril for variability index was determined using a paired *t*-test (1-tailed). Statistical significance was accepted at $P < 0.05$.

Results

Patients

Fifty-four patients entered the trial and 42 patients had 24 h ambulatory blood pressure recordings suitable for analysis. The demographic and clinical characteristics of these patients are provided in Table 1. The characteristics of the high dose and low dose groups were similar except that the high-dose group had slightly more patients with diabetes mellitus.

Blood pressure analysis

Treatment with lisinopril did not result in significant differences in mean 24 h blood pressure between the high dose (94 ± 15 vs 95 ± 11 mmHg) and low dose (94 ± 13 vs 93 ± 10 mmHg) groups. However, the pattern of 24 h systolic blood pressure (SBP) was altered with the high dose associated with greater variability (Fig. 1). This variability was quantified by calculation of the absolute amplitude of SBP variability that revealed a greater variability in the high dose group as compared with the low dose group (Fig. 2).

Table 1 **Demographic and baseline clinical data**

	Low dose ($n = 21$)	High dose ($n = 21$)
Age (years)	56 ± 3	55 ± 3
Sex	14M/7F	16M/7F
Race	16B/5W	16B/5W
Etiology	9-IHD	8-IHD
	12-NIHD	13-NIHD
Diabetes mellitus	2	7
Hypertension	11	11
Digitalis	18	14
β-Blocker	2	2
Systolic BP (mmHg)	135 ± 6	138 ± 5
Diastolic BP (mmHg)	74 ± 3	73 ± 2
Heart rate (bpm)	82 ± 3	84 ± 3
LVEF (%)	19 ± 6	20 ± 8
Prior ACEI (mg/day)	10 ± 7	11 ± 9

IHD = ischaemic heart disease; NIHD = non-ischaemic heart disease; LVEF = left ventricular ejection fraction; ACEI = angiotensin converting enzyme inhibitor; values = mean ± SD.

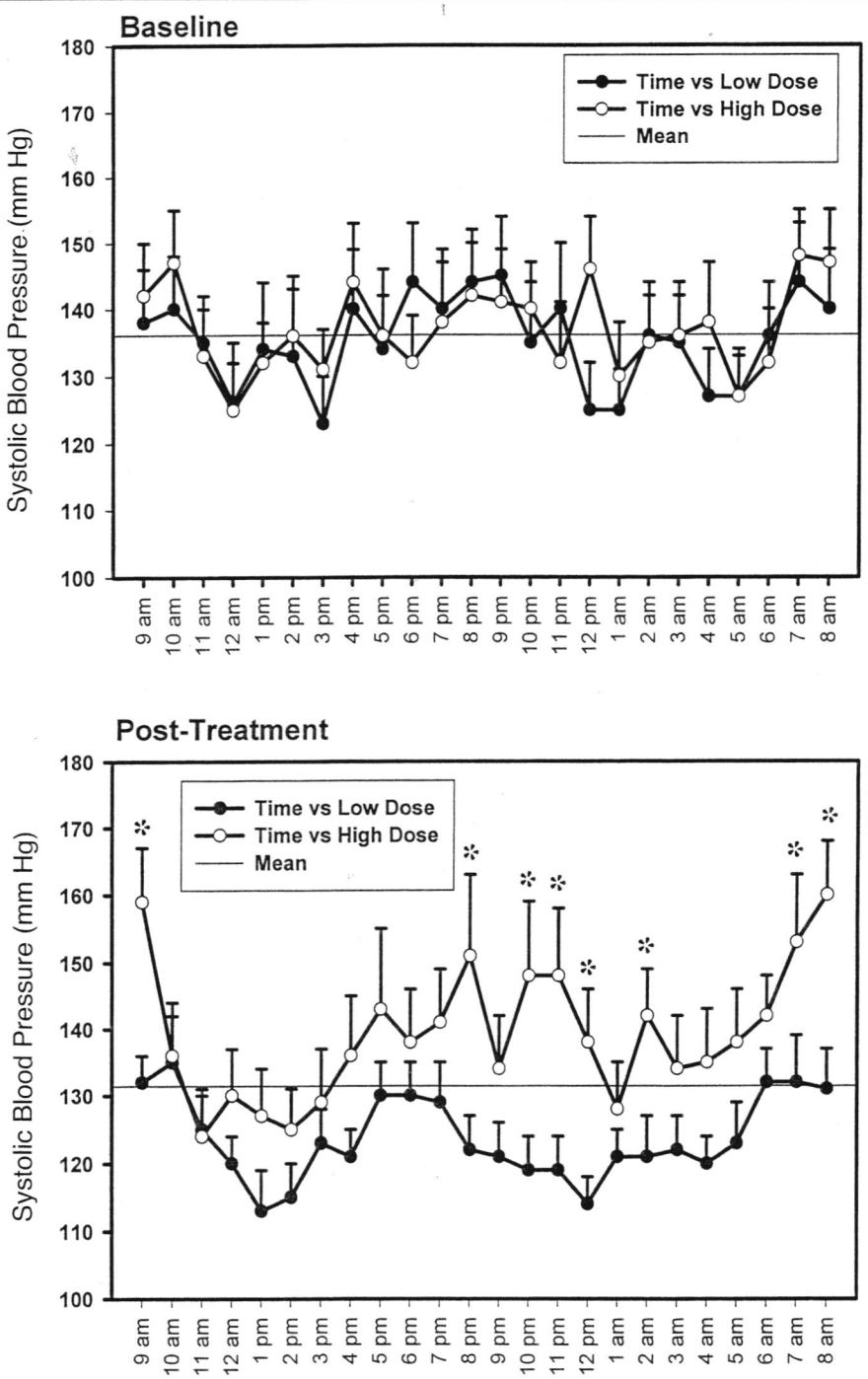
Discussion

This study reveals for the first time that systolic blood pressure variability increases with the treatment of heart failure with ACE inhibitors and is related to dose. This observation may be of particular importance since the beneficial effect of ACE inhibitors on clinical outcomes are dependent on dose [11], thus, systolic blood pressure variability may be a surrogate for improvement.

The degree of reduction in variability of the circadian time course of systolic blood pressure is correlated with the severity of the heart failure [2,3]. This reduction is likely due to the decreased physical activity and neurohormonal activation that are present in heart failure. Thus, the circadian variability of systolic blood pressure represents a multiplicity of factors, which characterize an integrated response of the cardiovascular system.

Information concerning the effect of ACE inhibitor treatment of heart failure on circadian blood pressure variability is limited. We have previously shown that treatment of heart failure with either lisinopril, or captopril increased the variability of systolic blood pressure as was found with this study [10]. The absolute amplitude of systolic blood pressure is inversely correlated with plasma norepinephrine and atrial natriuretic peptide in patients with heart failure [10]. Of note, even though the variability of 24 h systolic blood pressure was

Fig. 1



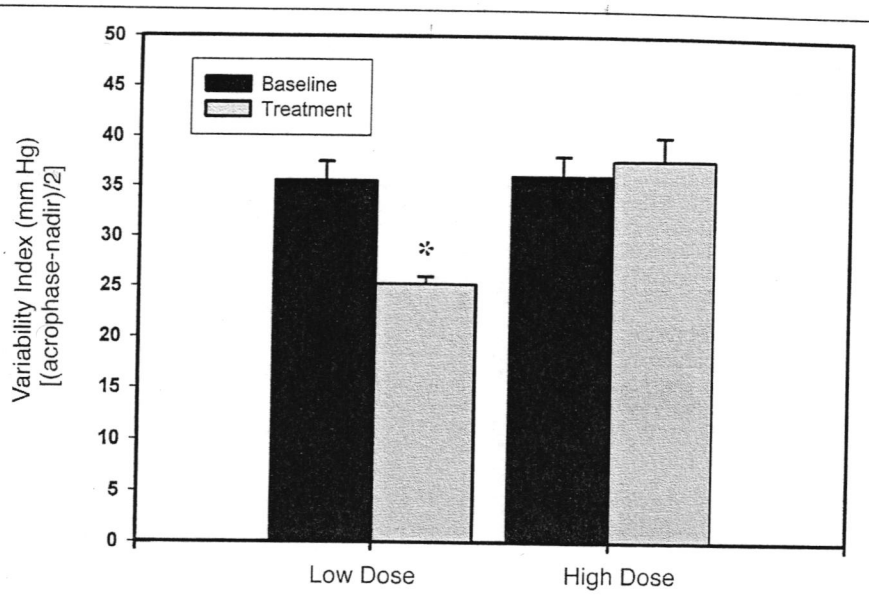
Twenty-four hour ambulatory systolic blood pressure (SBP) (mean ± SD) is shown at baseline and after randomization for patients receiving high dose ($n = 21$) and low dose ($n = 21$) lisinopril. Patients receiving the high dose of the ACE inhibitor have a higher SBP and exhibit more variability. * = $P < 0.05$.

greater in the high dose group, the mean 24 h blood pressure was not related to the dose of lisinopril.

Limitations of the study

We did not perform a full dose–effect study, and the range of dose of the ACE inhibitor in this trial was relatively narrow; larger doses may have shown further effects. Moreover, since all of our patients were on ACE inhibitor therapy prior to enrolment into this study, the low dose group represents withdrawal of drug. Although

Fig. 2



The increased variability of 24 h ambulatory systolic blood pressure in the group of patients receiving high dose lisinopril is shown by the calculation of the variability index (see text). *$=P < 0.05$.

the reason for the difference in systolic blood pressure variability appears to be a decline in the low-dose group, we are unable to determine the reason for the differences due to the lack of time-controls (i.e. a placebo group). Finally, we enrolled almost three times as many black patients as white patients.

Conclusion

Data from this study suggests that variation in 24 h systolic blood pressure reflects the dose effect of ACE inhibitors in patients with heart failure. The higher dose of the ACE inhibitor lisinopril was associated with a greater variability of systolic BP than the lower dose. Variability in circadian systolic BP may be useful for evaluating not only the efficacy, but also the dose, of drugs that are being evaluated for treatment of heart failure.

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