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