Effects of Acute Angiotensin II Type 1 Receptor Antagonism and Angiotensin Converting Enzyme Inhibition on Plasma Fibrinolytic Parameters in Patients With Heart Failure

Nicholas E.R. Goodfield, MB, ChB, MRCP; David E. Newby, BA, BSc, BM, MRCP; Christopher A. Ludlam, MB, ChB, PhD, FRCP, FRCPath; Andrew D. Flapan, MB, ChB, MD, MRCP

Background—Angiotensin converting enzyme (ACE) inhibition after myocardial infarction is associated with an improvement in plasma fibrinolytic parameters. The aim of the present study was to determine whether acute ACE inhibition and angiotensin II type 1 (AT1) receptor antagonism have similar effects in patients with heart failure.

Methods and Results—Twenty patients with moderately severe chronic heart failure received enalapril 10 mg and losartan 50 mg on 2 separate occasions in a single-blind, randomized, crossover design. Plasma tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1) antigen and activity were measured at baseline and 6 hours after the dose. Acute administration of losartan but not of enalapril reduced plasma t-PA (11%; \(P < 0.003\)) and PAI-1 (38%; \(P < 0.001\)) antigen concentrations, which was associated with increases in t-PA (29%; \(P = 0.03\)) and decreases in PAI-1 (48%; \(P = 0.01\)) activity. Changes in plasma fibrinolytic parameters were more marked during losartan treatment (\(P < 0.02\)), with a 3-fold greater reduction in plasma PAI-1 antigen concentrations (\(P < 0.05\)).

Conclusions—Acute AT1 antagonism in patients with heart failure is associated with a significant improvement in plasma fibrinolytic parameters that is greater than during ACE inhibition. These beneficial effects of AT1 antagonism and ACE inhibition would therefore appear to be mediated principally through suppression of angiotensin II. (Circulation. 1999;99:2983-2985.)

Key Words: angiotensin ■ plasminogen activators ■ heart failure ■ fibrinolysis

It would be anticipated that high tissue plasminogen activator (t-PA) concentrations would protect against subsequent coronary events. However, paradoxically, epidemiological studies of total t-PA (antigen) concentrations in patients with ischemic heart disease\(^1\)\(^2\) have observed a positive correlation with future coronary events. This may be explained by the concomitant elevation of plasminogen activator inhibitor type 1 (PAI-1), which complexes with t-PA and therefore causes an overall reduction in free t-PA “activity.”\(^3\)\(^4\) It is this free and unbound t-PA that is physiologically active and leads to endogenous fibrinolysis.

Several large-scale heart failure and post–myocardial infarction trials (VHEFT-II [Veterans Administration Heart Failure Trial II], SAVE [Survival And Ventricular Enlargement], SOLVD [Studies Of Left Ventricular Dysfunction], AIREX [Acute Infarction Ramipril Efficacy eXtension Study], TRACE [TRAndolapril Cardiac Evaluation], and SMILE [Survival of Myocardial Infarction: Long-term Evaluation]) have suggested a reduction in reinfarction rates in patients treated with ACE inhibitors. The mechanisms underlying this reduction in coronary thrombotic events are unknown. However, given that angiotensin II\(^5\) and bradykinin\(^6\) are known to induce the release of PAI-1 and t-PA, respectively, the benefits of ACE inhibitor therapy may be mediated through increases in bradykinin-induced t-PA release or a reduction in angiotensin II–mediated PAI-1 release or both. Indeed, the use of ACE inhibitors after myocardial infarction is associated with a decrease in PAI-1 concentrations and a potential increase in t-PA activity.\(^7\)\(^8\) However, the effects of ACE inhibition on plasma fibrinolytic factors have not been assessed in patients with heart failure, and it is unknown whether these beneficial effects are also seen with angiotensin II type 1 (AT1) receptor antagonism. The aim of the present study, therefore, was to determine whether acute ACE inhibition and AT1 receptor antagonism have similar effects in patients with heart failure.

Methods

Subjects

Twenty patients with New York Heart Association (NYHA) grade II to III chronic heart failure and objective evidence of left ventricular
Changes in plasma t-PA (white bars) and PAI-1 (black bars) antigen (solid bars) and activity (hatched bars) after single oral dose of enalapril and losartan in patients with heart failure. *P = 0.016 (2-way ANOVA for changes in 4 plasma fibrinolytic parameters; losartan vs enalapril); †P = 0.047 (t test for changes in plasma PAI-1 antigen; losartan vs enalapril).

Data Analysis and Statistics
Data were examined by ANOVA and 2-tailed paired Student’s t test with Excel version 5.0 (Microsoft). All results are expressed as mean ± SEM. Statistical significance was taken at the 5% level.

Results
Patient characteristics are shown in Table 1. Baseline predose hemodynamic, plasma ANP, and fibrinolytic parameters were similar on the 2 study days, with no significant differences (Table 2) or time order effects.

After losartan therapy, plasma t-PA and PAI-1 antigen concentrations fell by 11% (P = 0.003) and 38% (P < 0.001), respectively (Table 2; Figure). Plasma t-PA activity increased by 29% (P = 0.03), whereas PAI-1 activity fell by 48% (P = 0.01). Enalapril therapy was associated with similar changes in fibrinolytic parameters (−6%, −14%, 21%, and −17%, respectively), but they were not statistically significant (P = 0.1 to 0.4). Changes in plasma fibrinolytic parame-
Acute angiotensin II inhibition with AT1 receptor antagonism produces a marked improvement in basal fibrinolytic balance through a reduction in PAI-1.

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References


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