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MEHMET AĞIRBASLI

DOUGLAS E. VAUGHAN

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Review

Mehmet AGIRBASLI
Douglas E. VAUGHAN

The Role of Renin-Angiotensin System in Regulating Fibrinolytic Balance: Potential Mechanism in Prevention of Myocardial Infarction

Cardiology Division
Departments of Medicine and Pharmacology
Vanderbilt University Medical Center
Veterans Administration Medical Center
Nashville, Tennessee

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Introduction

Over the last two decades, there has been an impressive growth of experimental and clinical evidence defining a role for the renin-angiotensin system (RAS) in the development of ischemic cardiovascular disease. It is now widely appreciated that activation of the RAS is associated with a vascular toxicity that is independent of its effects on blood pressure. This association predicted the cardiovascular risk among treated hypertensive patients. A long-term prospective trial by Alderman et al. examined the relationship between the renin-sodium profile and subsequent myocardial infarction in >1,700 patients entering a hypertension control program. After an average of 8.3 years of follow-up, the risk of myocardial infarction (MI) increased nearly 5-fold in patients with a high renin-sodium profile at baseline compared to those with a low profile, despite equivalent success in managing hypertension (1). Another prospective study by the same group demonstrated that plasma renin activity (PRA), without monitoring urinary sodium, also predicted the risk of MI in 2902 hypertensive patients during an average of 3.6 years follow-up (2). There was, for every 2 unit increase in PRA, an overall 25% increase in MI incidence. These observations fueled the hypothesis that pharmacological interruption of the RAS reduces the risk of ischemic heart disease.

Survivors of acute myocardial infarction (AMI) are at increased risk of fatal and non-fatal ischemic events. Long-term survival of patients after AMI remains a major public health objective. Important advances in secondary prevention of AMI have been made in recent years. Several survival studies investigated the effects of five different angiotensin converting enzyme (ACE) inhibitors in more than 100.000 patients after AMI (3-10). In all but the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardica (GISSI-3) trial, double-blind, placebo-controlled methods were used to randomize the patients to receive either active or control treatments. This, comprehensive investigation has revealed that ACE inhibition on average, reduced the risk of recurrent MI by approximately 8% per year of treatment. Recently published follow-up study of (AIRE) trial (Randomly Allocated Ramipril or Placebo for Heart Failure after Acute Myocardial Infarction) provided robust evidence that administration of ramipril to patients with clinically defined heart failure after AMI results in a survival benefit that is not only large (11.4% absolute reduction in mortality), but also sustained over many years (11).

The mechanisms through which ACE inhibitors reduce reinfarction is an active area of research. Blood pressure reduction, reduced myocardial demand with improved loading conditions, reduced left ventricular remodeling, reduced sympathetic activity, reduced arterial permeability and lipoprotein entry, growth factor inhibition (Angiotensin II, platelet derived growth factor, transforming growth factor β), bradykinin accumulation, prevention of atherosclerosis, free radical scavenging, and anti-inflammatory effects are some of the mechanisms invoked to explain the beneficial role of ACE inhibitors. It is likely that several of these mechanisms are operative simultaneously. If triggering of any or all of these mechanisms by the RAS contributes to precipitation of infarction, interruption of the RAS by ACE inhibition

could theoretically reduce the risk of myocardial infarction. It is unlikely that simple improvement in left ventricular loading conditions is the primary mechanism, as treatment for a certain period is necessary to observe this reduction in the incidence of acute coronary syndromes. Recent research has demonstrated an interesting interaction between the RAS and fibrinolytic system (12). Accumulating data suggest that angiotensin II (Ang II) modulates fibrinolysis (12, 13). This interaction may be the mechanism to explain the indisputable impact of ACE inhibitors in prevention of myocardial infarction. In this review, we will try to define the close relation between these two systems by dissecting into the components of the fibrinolytic and renin-angiotensin systems.

The fibrinolytic balance

The fibrinolytic system represents a crucial defense mechanism against intravascular thrombosis. The initiation of fibrinolysis is regulated by a dynamic balance between the plasminogen activators and inhibitors in the region of thrombus. Two major plasminogen activators (PA) have been identified; tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). While both of these activators are synthesized in the endothelium, t-PA is felt to be the primary PA in the blood. The concentration of active t-PA is determined by the rate of endothelial secretion, hepatic clearance and inhibition by a specific, rapid-acting plasminogen activator inhibitor (PAI-1). Vascular fibrinolysis is largely modulated by the balance between t-PA and PAI-1. PAI-1 is derived from multiple sources, including the endothelium, vascular smooth muscle cells, the liver, adipose tissue and platelets. t-PA and PAI-1 react to form an inactive t-PA/PAI-1 complex. Under physiological circumstances, there is abundant supply of plasminogen in the circulation available for activation and conversion into plasmin. However, only small portion of plasminogen is converted into plasmin for three reasons a) t-PA circulates in trace concentrations in plasma, b) t-PA is relatively inefficient PA in solution in the absence of fibrin, and c) t-PA is inhibited by the presence of PAI-1.

Therefore, circulating levels of active t-PA, active PAI-1, and t-PA/PAI-1 complex are crucial in regulation of fibrinolysis. An imbalance between plasminogen activators and PAI-1 can lead to clinical consequences. For example, PAI-1 deficiency or t-PA excess can result in abnormal bleeding (14,15), conversely, an elevated PAI-1 level is associated with myocardial infarction (16,17). Increased plasma levels of PAI-1 have been detected in young survivors of myocardial infarction in comparison with healthy age-matched controls (16). Elevated PAI-1 levels in young survivors of myocardial infarction have also been associated with an increased risk of recurrent infarction (17). Interestingly, there is a temporal association between plasma PAI-1 levels which exhibit a marked circadian variation and peak in the early morning hours coincident with the reported peak incidence of MI (18). Recent studies with thrombolytic agents (mainly t-PA or streptokinase) in the setting of AMI have shed light into the clinical importance of this marked circadian variation in plasma PAI-1 levels. Becker et al. found in a group of 28 patients that coronary artery patency 90 minutes after the beginning of treatment with t-PA was 27% between midnight and noon compared with 82% for treatment between noon and midnight (19). These interesting findings were confirmed in a larger study by Kurnik (20). In this study, the onset of myocardial infarction was confirmed to have a marked circadian variation with a peak incidence around 10 AM. The peak efficacy of t-PA was about 8 PM, representing a phase difference of about 10 hours after peak infarction incidence. Diminished efficacy of t-PA early in the day may be explained with elevated PAI-1 levels in the morning hours.

Experimental data also support a direct relationship between increased levels of PAI-1 and thrombotic events. Transgenic mice engineered to overexpress PAI-1 develop spontaneous thrombosis (21). High concentrations of active PAI-1 were observed in porcine coronary artery thrombi as an important determinant of the resistance to clot lysis by t-PA (22). Anti-PAI-1 monoclonal antibodies accelerate fibrinolysis within the clots (23).

The renin angiotensin system and fibrinolysis

Hormonal systems like RAS have evolved as a protector against acute fluid volume loss. In addition to causing vasoconstriction and the retention of salt and water, it appears that angiotensin inhibits fibrinolysis, thereby promoting clot formation and protecting against hemorrhage and volume loss. Activation of the renin-angiotensin system (RAS) can disturb the balance of the fibrinolytic system by stimulating excess production of plasminogen activator inhibitor type 1 (PAI-1) and increasing the risk of thrombotic events. Circadian variation of these parameters support the role of hormonal influence on fibrinolytic system (18).

Experimental and clinical studies have been designed to define the relationship between the RAS and the fibrinolytic system. In addition to its well-known vasoconstrictor effects, Angiotensin II (Ang II) also modulates fibrinolysis. Ang II stimulates PAI-1 production

in cultured endothelial cells in a dose dependent manner (12). Interestingly, specific Ang II receptor blockers could not inhibit the effects of Ang II on PAI-1 production (24).

Prior work described a mechanism through which A II may contribute to a prothrombotic state by reducing the activity of the endogenous fibrinolytic system (25). This investigation reported a dose-dependent increase in plasma PAI-1 in healthy human volunteers infused with graded doses of A II, whereas no change occurred in control subjects given a 5% dextrose infusion. No significant effect on t-PA concentrations resulted from A II infusion, indicating a very selective and specific action on PAI-1. The doses of A II used in this study simulated plasma A II levels generated by assumption of an upright posture. Thus, the increase in PAI-1 occurred at physiologic levels of A II.

Another clinical study involving a subset of patients enrolled in the SAVE study examined the relationship of plasma t-PA-1 and PAI-1 to various neurohormones (26). No correlation was detected between concentrations of plasma t-PA and any of the neurohormonal parameters measured (e.g., catecholamines, markers of the RAS, atrial natriuretic factor, arginine, vasopressin). However, plasma aldosterone levels and plasma renin activity both correlated significantly with plasma PAI-1 levels (27).

Treatment with the ACE inhibitor captopril reduces basal vascular PAI-1 expression in the normal rat aorta, suggesting a fundamental role of angiotensin in regulating PAI-1 expression in healthy tissues (28). Such therapy also significantly reduces the vascular expression of PAI-1 in rats after balloon injury to the aorta.

The beneficial effects of ACE inhibition on fibrinolytic balance

The endothelial cell appears to regulate plasma fibrinolytic balance by producing PAI-1 and plasminogen activators. Via 2 parallel pathways, ACE plays a pivotal role in maintaining the balance between PAI-1 and t-PA. One of these pathways involves the conversion of AI to A II, which increases expression of PAI-1. The second pathway involves the degradation of bradykinin, an action that inhibits production of t-PA. In the presence of active ACE, the local increase in PAI-1 production and the decrease in t-PA might be expected to enhance the tendency toward thrombosis or development of atherosclerosis.

Angiotensin I converting enzyme (ACE) inhibitors were initially introduced as antihypertensives almost two decades ago. In addition to their extensive use for the treatment of arterial hypertension, ACE inhibitors have become a huge success in the treatment of congestive heart failure. Recently, their cardiac and vascular protective effects have become clear. As we discussed earlier, comprehensive investigation has revealed that ACE inhibition reduces the risk of recurrent MI in survivors of acute myocardial infarction. An effect of ACE inhibition on fibrinolytic balance may contribute to the reduction in the myocardial infarction rate achieved in these clinical trials. This potential mechanism is supported by the results of randomized, double-blind, placebo-controlled studies that evaluated changes in fibrinolytic variables after ACE inhibitor therapy in patients with myocardial infarction.

One of these studies measured t-PA antigen and PAI-1 antigen and activity in 15 men who had a recent, uncomplicated myocardial infarction. After 4 weeks of treatment with 75 mg/day of captopril, ACE inhibition was associated with a significant decrease in t-PA antigen and PAI-1 activity, compared to values during placebo administration. Although a median 18% reduction occurred, the change in PAI-1 antigen did not reach statistical significance (29). Jansson et al investigated antigen and activities of t-PA and PAI-1 in 81 survivors of myocardial infarction treated with enalapril or placebo for 3 months. ACE inhibition decreased t-PA antigen without altering other parameters (30).

A substudy of Survival and Ventricular Enlargement (SAVE) trial (2) demonstrated 30% higher t-PA levels in patients randomized to captopril compared to placebo group. Interestingly, this difference disappeared after cessation of captopril (27).

These same fibrinolytic variables were examined in a subset of 120 patients enrolled in the Healing and Early Afterload Reducing Therapy (HEART) study (31). Criteria for entry into the HEART trial were an anterior myocardial infarction and systolic blood pressure>100 mm Hg. Patients were randomized to receive placebo, 0.625 mg/day of ramipril, or 1.25 mg/day. Basal levels of PAI-1 activity as well as PAI-1 and t-PA antigens were essentially identical in the 3 treatment groups, and the PAI-1/t-PA ratio, an index of fibrinolytic balance, was normal. After 14 days of treatment with low or high-dose ramipril, PAI-1 activity was reduced by 22% and the PAI-1 antigen level was reduced by 44%, and the t-PA antigen levels were unchanged from baseline. Concentrations of neither PAI-1 nor t-PA changed significantly in the placebo group. The PAI-1/t-PA ratio increased>2-fold with placebo administration, indicating a shift toward thrombosis. In contrast, the normal ratio was preserved in patients treated with ramipril. Thus, ACE inhibition

appears to preserve the fibrinolytic balance in the recovery phase after an acute myocardial infarction.

In addition to activating the conversion of A I to A II, ACE is responsible for the degradation of bradykinin, an important mediator of t-PA production at the level of the endothelial cell. Bradykinin therefore serves an essential role in the regulation of fibrinolytic balance. Experimental and clinical data support a potent stimulatory effect of bradykinin on t-PA secretion. For example, intra-arterial administration of bradykinin causes a dose-dependent increase in plasma t-PA levels in rats (32). Hypertensive human volunteers infused with graded doses of bradykinin while receiving an ACE inhibitor have demonstrated a striking dose-dependent increase in plasma t-PA levels (33). In the absence of an ACE inhibitor, however bradykinin administration had no effect on t-PA concentrations.

Along with these clinical studies enrolling cardiovascular patients, ACE inhibition also caused similar effects on fibrinolytic balance in healthy subjects. In a recent study, we examined the effect of salt depletion on tissue-type plasminogen activator (t-PA) antigen and plasminogen activator inhibitor-1 (PAI-1) activity and antigen in normal subjects in the presence and absence of ACE inhibition with quinapril 40 mg twice a day (34). Under low (10 mmol/day) and high (200 mmol/day) salt conditions there was significant diurnal variation in PAI-1 antigen and activity and t-PA antigen confirming previous observations. Morning PAI-1 antigen levels were significantly higher during low salt intake compared with high salt intake conditions. ACE inhibition significantly reduced 24 hour and morning PAI-1 antigen and activity level.

Angiotensin II receptor antagonists and fibrinolytic balance: Implications of Angiotensin II metabolism

As we discussed earlier, experimental work suggests that angiotensin II (Ang II) has a regulatory role on hemostasis. Recently developed Ang II receptor blockers interrupt renin angiotensin system by blocking the Ang II (type I) receptor (AT1). Hence, hypothesis develops that AT1 receptor blockers can also affect fibrinolytic balance in a favorable way like ACE inhibitors do. Despite ample evidence that suggests ACE inhibitors reduce PAI-1 levels, studies assessing PAI-1 levels after blocking AT1 receptor are in progress. Seljeflot et al. studied in vivo effects of Ang II on fibrinolysis by treating 20 hypertensive patients with losartan (a selective AT1 receptor antagonist) (35). Plasma levels of t-PA activity and antigen, and PAI-1 activity and antigen were unchanged after 4 weeks of treatment with losartan.

Data from our laboratory support the clinical observations of Seljeflot et al. The biologic activity of Ang II is limited by specific enzymes that promote its degradation. Octapeptide Ang II is cleaved to biologically active hexapeptide Ang IV by aminopeptidases. Ang IV binds receptors distinct from Ang II receptors. Data from our laboratory indicate that Ang IV is the peptide that stimulates endothelial expression of PAI-1 (24). The induction of PAI-1 expression could be blocked by Ang IV receptor antagonist but not Ang II receptor antagonism. Therefore, ACE inhibitors may have superior efficacy in reducing PAI-1 levels by blocking the generation of Ang II and Ang IV.

Conclusions

Hemostasis depends on an intricate relation between plasma coagulation and fibrinolytic factors, blood cells, vessel walls, extracellular matrix, blood viscosity and flow. Circadian variation and gender differences of fibrinolytic factors suggest an important hormonal influence in this process. Hormonal systems such as RAS act as a protector against acute fluid volume loss by inducing both vasoconstriction to maintain blood pressure and the retention of salt and water to restore normal fluid volume. Inhibition of the fibrinolytic system by A II (or A IV) further assists in maintaining vascular integrity by promoting clot formation. Studies have confirmed that these cascade of events are brought into action by RAS in coordination and sequentially. Inappropriate activation of the RAS may occur, however, in patients with left ventricular dysfunction and heart failure. In such patients, ACE-induced vasoconstriction may increase cardiac afterload, salt and water retention may increase cardiac preload as well as the symptoms of pulmonary congestion and edema. Additionally, inhibition of fibrinolysis by over-activated RAS may increase the thrombotic tendency. ACE inhibitors are indicated to counteract the vasoconstriction and salt and water retention associated with activation of the RAS. These drugs may also protect against thrombosis by reducing the expression of PAI-1 normally induced by angiotensin and by augmenting the bradykinin-induced production of t-PA.

It remains to be seen, however, whether interruption of renin-angiotensin cascade at other sites with AT 1 receptor blockers or renin inhibitors will have the therapeutic success of ACE inhibitors.

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