The Prothrombotic Paradox of Hypertension
Role of the Renin-Angiotensin and Kallikrein-Kinin Systems

Arne W.J.H. Dielis, Machiel Smid, Henri M.H. Spronk, Karly Hamulyak, Abraham A. Kroon, Hugo ten Cate, Peter W. de Leeuw

Abstract—Despite increased pulsatile stress, thrombotic rather than hemorrhagic events represent a major complication of hypertension. The pathophysiology of thrombosis in hypertension involves the interaction among vascular endothelium and particularly the renin-angiotensin and kallikrein-kinin systems. Because hypertension is often associated with some degree of inflammation, the combination of chronic inflammation and chronic shear stress may convert the normal anticoagulant endothelium into a procoagulant surface, expressing tissue factor. Activation of the renin-angiotensin system leads to activation of nuclear factor κB–dependent proinflammatory genes, also accelerating the expression of tissue factor. Renin-angiotensin and kallikrein-kinin systems interact at several levels to modulate coagulation, fibrinolysis, and vasodilatation in such a way that these 2 systems could have a major influence on the occurrence of thrombotic complications. Treatment with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists may favorably influence the balance between the renin-angiotensin and kallikrein-kinin axis, regulating blood pressure as well as reducing the risk of thrombosis, which may explain part of the clinical efficacy of these drugs. (Hypertension. 2005;46:1236-1242.)

Key Words: renin-angiotensin system □ kallikrein-kinin systems □ blood pressure

Although hypertension exposes blood vessels to increased pulsatile stress, thrombotic rather than hemorrhagic events represent a major complication in hypertensive patients. This apparent contradiction is known as the thrombotic paradox of hypertension or “Birmingham paradox.” Nevertheless, in hypertension, several thrombogenic abnormalities occur and evidence is emerging that the condition confers a “prothrombotic state.” Just as is the case in venous thrombosis, abnormalities in the vessel wall, blood constituents (such as hemostatic and fibrinolytic factors and platelets), and blood flow can precipitate and explain most thrombotic complications. All of the components of this arterial variant of Virchow’s triad are dependent on endothelial function. Indeed, vascular endothelium maintains blood fluidity, modulates blood coagulation, promotes or prevents vascular growth, modulates inflammation, and regulates vasomotor tone. The renin-angiotensin and the kallikrein-kinin systems are powerful regulators of these processes. Therefore, in this brief review, we discuss the possible endothelial origin of the prothrombotic state in hypertension in relation to these 2 regulatory systems. As a PubMed search strategy, we selected relevant articles by entering as key words hypertension, renin-angiotensin, aldosterone, kallikrein, (brady)kinin, coagulation, fibrinolysis, and their various combinations.

Endothelial Function and Blood Fluidity
Under physiological conditions, balanced coagulation and fibrinolysis ensure blood fluidity. In most patients with hypertension, a certain degree of atherosclerotic vascular disease is present that is associated with increased plasma concentrations of C-reactive protein. These elevated C-reactive protein concentrations may activate inflammation as well as coagulation. Increased activity of proinflammatory mediators potentially activates vascular endothelial cells to generate tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1), among a range of other proteins. TF is an integral membrane protein that is present in adventitial mesenchymal cells of blood vessels. Normally, endothelial cells contain little or no TF, but various stimuli can activate these cells to produce this protein. When expressed, TF binds to activated factor VII (FVIIa). The catalytic TF–FVIIa complex may directly activate factor X (FX) as well as factor IX (FIX), leading to thrombin generation, although at least physiologically, the activation of FIX is the dominant pathway. Under thrombotic conditions, the engagement of activated platelets and the cofactors FVa and FVIIa accelerate the rate of thrombin formation dramatically, ultimately leading to clot formation. TF pathway inhibitor (TFPI), which is produced by endothelial cells, inhibits TF–FVIIa by form-
Role of the Renin-Angiotensin System

Angiotensin II (Ang II) and, to some extent, Ang III, are the natural agonists for the AT1 and AT2 receptors. Both receptor types are found on the endothelium. Ang II may be degraded to Angiotensin I (1–7) (Ang(1–7)) by angiotensin-converting enzyme 2 (ACE2) as well as by the endothelial enzyme prolylcarboxypeptidase (PRCP). However, ACE2 is the preferred angiotensinase in heart, kidney, and testes. The degradation product has vasodilator properties because it induces the release of NO and prostacyclin after stimulation of the endothelial AT2 receptor. Recent data indicate that in the presence of Ang II, the vasodepressor effect of Ang(1–7) can only be demonstrated when the AT1 receptor is blocked. This suggests that the vasodilator effect of Ang(1–7) is not as potent as the vasoconstrictor effect of Ang II. In addition, the expression of the AT2 receptor is normally far less than that of the AT1 receptor.

Ang I, Ang II, and Ang III all induce expression of TF mRNA in cultured rat endothelial cells via stimulation of the AT1 receptor and subsequent intracellular activation of transcription factors NF-κB and activator protein-1. As a result, TF becomes predominant over TFPI, thereby rendering the endothelium prothrombotic. Ang II also stimulates the expression of PAI-1 mRNA in endothelial cells and increases plasma PAI-1 levels in a dose-dependent manner. The mechanism of this effect is still unclear. Possible explanations include increased PAI-1 expression by direct stimulation of AT1 or AT2 receptors and stimulation of the angiotensin subtype 4 (AT4) receptor after conversion of Ang I or II into Ang IV. There is conflicting data as to whether agonists of AT1 and AT2 receptor subtypes influence PAI-1 expression in endothelial cells. In cultured cells, Ang I and Ang II seem to be able to induce increased expression of PAI-1 mRNA levels, but this may also be attributable to conversion of these peptides into Ang IV. This conversion involves aminopeptidases A and M, membrane proteins of vascular endothelial cells. Angiotensin II (Ang II) and, to some extent, Ang III, are the natural agonists for the AT1 and AT2 receptors. Both receptor types are found on the endothelium. Ang II may be degraded to Angiotensin I (1–7) (Ang(1–7)) by angiotensin-converting enzyme 2 (ACE2) as well as by the endothelial enzyme prolylcarboxypeptidase (PRCP). However, ACE2 is the preferred angiotensinase in heart, kidney, and testes. The degradation product has vasodilator properties because it induces the release of NO and prostacyclin after stimulation of the endothelial AT2 receptor. Recent data indicate that in the presence of Ang II, the vasodepressor effect of Ang(1–7) can only be demonstrated when the AT1 receptor is blocked. This suggests that the vasodilator effect of Ang(1–7) is not as potent as the vasoconstrictor effect of Ang II. In addition, the expression of the AT2 receptor is normally far less than that of the AT1 receptor.

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Endothelial Function and Blood Flow

Vascular endothelial cells are pivotal in the association between hypertension and vascular thrombotic complications. Vessel walls are exposed to 2 distinct mechanical forces: cyclic strain and shear stress. Cyclic strain results from transmural pressure and leads to dilatation and increased wall stress. The latter develops in all structural components of the vessel wall. Cyclic strain not only augments endothelial-derived NO synthase (eNOS) expression and subsequent NO production but also the production of superoxide anions.

Shear stress, on the other hand, is a frictional force to which only endothelial cells are exposed. It is influenced by transmural pressure gradients and vessel diameter and causes cell deformation and cytoskeletal tension. Mean shear stress is highest in small arterioles and venules. Acute shear stress activates Ca²⁺ channels with subsequent Ca²⁺ mobilization. This leads to release of arachidonic acid and production of NO and prostaglandin I2 (PGI2) via cascades involving inositol 1,4,5-triphosphate, diacylglycerol, protein kinase B, and phospholipase A2. Acute shear stress is likely to be the most important physiological regulator of PGI2 and NO. Sustained shear stress induces cytoskeletal remodeling of endothelial cells. Cells become flatter and they align in direction of the flow to minimize shear stress. Cell differentiation increases and cells become hypertrophic. Activation of nuclear factor κB (NF-κB) may lead to enhanced transcriptional stimulation of a wide variety of factors such as platelet-derived growth factor-β, transforming growth factor-β1, t-PA, cyclooxygenase, eNOS, prostacyclin synthase, and TF. Thus, whereas acute shear stress enhances vasodilation and fibrinolysis, chronic shear may favor thrombus formation by increased TF expression (Figure 1).

Figure 1. Endothelial responses to shear stress. AA indicates arachidonic acid.
excluded that this is attributable to t-PA autoregulation in response to increased PAI-1 levels.28

**Role of the Kallikrein-Kinin System**

The kallikrein-kinin system, in part, counteracts the effects of the renin-angiotensin system.22 Under physiological conditions, endothelial cells and their matrix provide the serine protease PRCP that activates prekallikrein (PK) to kallikrein. Next, kallikrein activates FXII.32–34 Inactive prekallikrein is converted to kallikrein after binding to kininogen, the precursor of bradykinin. In turn, PRCP-mediated conversion to kallikrein generates bradykinin from kininogen.33 In addition, PRCP also degrades Ang II. The vasodilator peptide bradykinin acts on the endothelial B2 receptor to stimulate intracellular Ca\(^{2+}\)/H\(_{1001}\) mobilization and subsequent release of NO and prostaglandins. Through the same receptor, bradykinin also enhances the release of endothelial storage pool-derived t-PA, the aforementioned activator of fibrinolysis.11,12,35,36 Receptor blockade reduces t-PA release but to a lesser extent than the reduction of the vasodilator response.35

In addition to activating the kinin system, kallikrein could theoretically stimulate intrinsic coagulation through the formation of FXIIa. However, in current models of blood coagulation, this reaction is not regarded as important, an idea that is based mainly on the lack of any hemostatic consequences of the absence of FXII, PK, or high molecular weight kininogen (HMWK) in humans.37 In fact, only in conditions of sepsis or exposure to artificial surfaces (eg, during cardiopulmonary bypass), FXII-dependent activation of the intrinsic route of coagulation may be observed. Of interest, recent studies suggest that elevated concentrations of FXIIa are associated with an increased risk of cardiovascular complications including myocardial infarction,38–40 but the pathophysiological mechanisms remain to be established. The generation of kallikrein is associated with increased bradykinin and t-PA antigen production,41 and there are convincing data to suggest that FXIIa is a weak activator of plasminogen and, hence, fibrinolysis.42,43

In addition to their respective direct roles in coagulation and fibrinolysis, the renin-angiotensin and kallikrein-kinin systems interact with each other at 3 additional levels (Figure 3). First, the enzyme PRCP, which is expressed on endothelial cell membranes, is involved in the conversion of prekallikrein to kallikrein and the degradation of Ang II to Ang(1–7). Thus, PRCP activity results in vasodilation. Second, ACE degrades bradykinin to the degradation product bradykinin(1–5) and converts Ang I to Ang II. As a result, ACE activity leads to enhanced vasoconstriction and inhibition of fibrinolysis through both systems.44 Interestingly, bradykinin(1–5) is not an inert degradation product, but it inhibits thrombin-induced platelet aggregation through binding to the thrombin cleavage site on protease activated receptors 1 and 4.45,46 Finally, stimulation of AT2 receptors enhances bradykinin formation through an yet unknown pathway.22,44

In the past, an additional interaction has been proposed in the sense that kallikrein would act as a physiological activator of prorenin,47,48 but recent data have negated that hypothesis.49

A summary of the biological actions of the renin-angiotensin system and kallikrein-kinin systems on vascular functions, coagulation, and fibrinolysis is given in Table 1.

**Clinical Implications**

Essential hypertension causes an earlier onset of the age-related decline in endothelial function.21,50 Because this abnormality also occurs in subjects with a positive family history of hypertension, it seems to be, at least partially, genetically determined. Endothelial dysfunction does not only occur in normal aging and hypertension, but also in atherosclerosis, diabetes mellitus, chronic heart failure, menopause, vasospasm, and coronary artery disease, each of which is frequently coexisting in hypertension. A continuously elevated blood pressure increases shear stress and hence causes morphological alterations of vessels, so-called vascular remodeling with hypertrophic endothelial cells, and an increased media-to-lumen ratio, with further loss of normal endothelial function and a further rise in blood pressure.51

The terms “endothelial dysfunction” and “vascular disease” are generally used to describe deterioration of vasodi-
lator function and subsequent changes in the vessel wall.\textsuperscript{11,19,52} By and large, vasoconstrictor responses are not impaired in endothelial dysfunction. Thus, mechanisms resulting in endothelial dysfunction include decreased secretion of or sensitivity to vasodilator agents and increased production of or sensitivity to vasoconstrictor agents.\textsuperscript{3,19,21,52} However, remarkably, disturbances in coagulation and fibrinolysis are not often considered when dealing with endothelial dysfunction. Nevertheless, several lines of evidence indicate that regardless of plasma levels, the renin-angiotensin system is activated in a considerable number of patients with essential hypertension. Indeed, experiments with inhibitors of the renin-angiotensin system have made it clear that this system is critically involved in the regulation of resting vascular tone. In addition, reduced responsiveness to vasodilator prostaglandins may result in a greater sensitivity to Ang II, at least in the kidney.\textsuperscript{53} However, whether the kallikrein-kinin system plays any role in the regulation of basal vascular tone remains open to debate. Under a variety of circumstances, blockade of bradykinin receptors has no or only minimal effects, and it seems quite possible that increased activity of the kallikrein-kinin system stems from its interaction with the renin-angiotensin system. At any rate, the apparent predominance of the effects of angiotensin is likely to shift the coagulation–fibrinolysis balance toward an unfavorable position.

Cardiovascular and cerebrovascular complications of hypertension like myocardial infarction, cardiac arrhythmias, sudden cardiac death, and stroke appear to have a peak incidence between 6 AM and noon, with a lower incidence at night.\textsuperscript{13} Although this rhythm coincides with morning peaks in blood pressure and higher urinary output of epinephrine, norepinephrine, aldosterone, and cortisol, PAI-1 and t-PA plasma levels also vary during the day.\textsuperscript{13,14,29} PAI-1 levels peak at 3 AM, have a nadir at 5 PM to 11 PM, and fall by 50% between 10 AM and 4 PM. t-PA levels show an opposite pattern with a peak at 6 PM and a nadir at 3 AM.\textsuperscript{13,14,29,36} These variations in fibrinolytic activity favor thrombus formation in the early morning and might reflect a hypercoagulable state in hypertension (Figure 4). Interestingly, elevated t-PA antigen levels but not activity are associated with an increased risk for myocardial infarction and stroke, although high t-PA levels would protect against coronary events.\textsuperscript{54,55} This merely reflects t-PA/PAI-1 complex formation. In fluid phase, PAI-1 forms a complex with t-PA, causing a slower clearance of t-PA and an elevation of t-PA antigen levels.\textsuperscript{11,30,54} Furthermore, hyperaggregability of platelets is also associated with hypertension, especially in established cardiovascular disease with fatty streaks and plaques.\textsuperscript{56}

### Effect of Interference With the Renin-Angiotensin System

The rationale of antihypertensive treatment with ACE inhibitors (ACEIs) and AT1 receptor antagonists is to establish a decrease in the activity of the renin-angiotensin system and to diminish the number of atherosclerotic complications. ACEIs have been shown to lower the risk of reinfarction and to decrease overall mortality and cardiovascular mortality in hypertension by 16% to 27% and 18% to 21%, respectively.\textsuperscript{14,22,27} Myocardial infarction and stroke are reduced by 20% during ACE inhibition.\textsuperscript{22} ACEIs ameliorate all 3 components of Virchow’s triad through the renin-angiotensin

### Table 1: Biological Actions of the Renin-Angiotensin and Kallikrein-Kinin Systems on Vascular Functions, Coagulation, and Fibrinolysis

<table>
<thead>
<tr>
<th>Effector System</th>
<th>Endothelial Function</th>
<th>Fibrinolysis</th>
<th>Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin-angiotensin</td>
<td>Ang II via AT1 receptor (human)</td>
<td>Ang II via AT1 receptor: increased</td>
<td>Ang I/II/III via AT1 receptor: TF mRNA (mouse)</td>
</tr>
<tr>
<td>system</td>
<td>Ang(1–7) via AT1 receptor: production of NO and PGI2 (human)</td>
<td>t-PA mRNA (human)</td>
<td>plasma PAI-1 (human)</td>
</tr>
<tr>
<td>Kallikrein-kinin</td>
<td>Bradykinin via BKB2R: release of NO and PGI2 (human)</td>
<td>Bradykinin via BKB2R: release of t-PA (human)</td>
<td>Kallikrein activates FXI (theoretically) Inhibition</td>
</tr>
<tr>
<td>system</td>
<td></td>
<td></td>
<td>Bradykinin 1–5 inhibits platelet aggregation by thrombin</td>
</tr>
</tbody>
</table>

BKB2R indicates bradykinin B2 receptor.

Summary of observed actions of ACEIs and angiotensin receptor antagonists on endothelial function, fibrinolysis, coagulation, and platelet reactivity.

![Figure 4](http://hyper.ahajournals.org/)

**Figure 4.** Plasma levels of t-PA and PAI-1 during the day.
and kallikrein-kinin systems. Endothelial function, for instance, is improved by the reduction in Ang II levels as well as by the rise in bradykinin and Ang (1–7). Inhibition of ACE further leads to an improved fibrinolytic balance. Ang I– and Ang II–mediated PAI-1 expression and activity as well as antigen levels are blocked by ACEIs. Ang IV–mediated PAI-1 expression on the other hand is not influenced by ACEIs.14,27,30,31,44 Endothelial t-PA release is potentiated, which is thought to be the result of increased availability of bradykinin.16,35 Women are more sensitive to bradykinin-mediated effects of ACEIs because estrogen upregulates bradykinin receptors and sensitizes coronary arteries to bradykinin-mediated vasodilation.35 However, ACEIs do not block the renin-angiotensin system completely because the Ang II producing enzyme chymase is not inhibited.8 Furthermore, the ACEI ramipril has been found to reduce thrombin–antithrombin complex formation, an indicator of coagulation activation.15,57 Regarding hyperaggregability of platelets, ACE inhibition lowers platelet activation markers because of platelet-inhibiting PG12 and NO, resulting in diminished adhesion and aggregation.36 More related to atherosclerosis, ACEIs downregulate TF synthesis in monocytes, a mechanism possibly reflected in the preventive effect on thrombotic complications.58

AT1 receptor antagonists also lower the incidence of hypertension-related complications. Because Ang II concentrations increase during AT1 receptor antagonism, one may expect that PAI-1 would increase via stimulation of the AT4 receptor because there is more substrate for aminopeptidases A and M if this pathway is of importance. Yet, in human as well as in rat smooth muscle cells, AT1 receptor inhibition decreased PAI-1 activity and antigen levels in vascular smooth muscle cells. Remarkably, though, this effect is not found in vivo in salt-depleted normotensive subjects and postmenopausal women (normotensive and hypertensive).30,44,54,59 Data concerning patients with essential hypertension are conflicting. The AT1 receptor antagonists losartan and irbesartan have been found to achieve a significant lowering of PAI-1 levels compared with the ACEI perindopril and the β-blocker atenolol.54,55 Other results show no decrease of PAI-1 antigen after losartan treatment.60 Moreover, the PAI-1 antigen-lowering effect of losartan is not sustained beyond a period >6 weeks.9,54 AT1 receptor upregulation could account for this short period of action.9,61 In addition, there are more conflicting data as to whether losartan decreases t-PA activity and antigen.30,60 A decrease in t-PA antigen could be explained by the aforementioned complex formation because reduced PAI-1 levels result in higher levels of fluid phase t-PA that is cleared faster than complex-bound t-PA.30 Others have reported that t-PA activity increases in patients with heart failure.54 Because TF mRNA expression is solely regulated via the AT1 receptor, its inhibition prevents induction of TF mRNA. This effect may translate into a normalization of the hypercoagulable state in hypertension.9 As with ACEIs, AT1 receptor antagonists are found to inhibit platelet aggregability and adhesion by stimulating NO release from platelets and endothelial cells.62 In addition, losartan is able to counteract platelet activation ex vivo independently from the AT1 receptor, probably by blocking thromboxane A2 signaling directly.63

Table 2 summarizes the observed actions of ACEIs and AT1 receptor antagonists on endothelial function, fibrinolysis, coagulation, and platelet reactivity.

### Future Perspectives
It is becoming increasingly clear that essential hypertension may indeed be associated with a hypercoagulable state that may contribute to arterial thrombotic complications. The renin-angiotensin and kallikrein-kinin systems probably play a key role in causing this prothrombotic state. However, more research should be directed toward the precise mechanisms by which these systems become prothrombotic. In addition, it is worthwhile to explore in greater detail to what extent modulation of the thrombotic pathways by appropriate medication can reduce the incidence of thrombotic complications in hypertension. Although much of the favorable effects of antihypertensive drugs can be attributed to the fall in blood pressure per se, additional actions, however small, should not be overlooked.

### References


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