Despite advances in pharmacology that have led to increasingly effective antihypertensive drug treatments, the precise pathophysiological mechanisms of hypertension and its complications are still poorly understood. Increasing clinical and laboratory evidence suggests that hypertension per se may confer a prothrombotic or hypercoagulable state.1 This may explain in part why, despite exposure of the blood vessels to high pressures, the main complications of hypertension (that is, heart attacks and strokes) are paradoxically thrombotic in nature rather than hemorrhagic.

In recent years, it has become increasingly evident that components of the coagulation and fibrinolytic pathways are primary and secondary predictors of cardiovascular events.2 The close association of these markers with cardiac outcome and the common cardiovascular risks factors raises the possibility that such indices are not merely markers or consequences of thrombosis but rather may significantly contribute to the pathogenesis of arterial thrombotic disease. Indeed, the processes of thrombogenesis and atherogenesis are intimately related.3

As long as 150 years ago, Virchow suggested 3 components that should be fulfilled for thrombus formation (thrombogenesis). These are now referred to as Virchow’s triad: abnormalities of the vessel wall (which we today recognize as endothelial dysfunction or damage), blood constituents (with abnormal levels of hemostatic and fibrinolytic factors and platelet activation), and blood flow (focusing on rheology and flow reserve). For hypertension to confer a hypercoagulable or prothrombotic state, each of these components must be adequately fulfilled. These components also need to be related to hypertensive target organ damage, long-term prognosis, and alteration by treatment.

The main rheological property of blood is its resistance to flow, or viscosity; at high shear rates, blood viscosity is low, but in conditions of low shear rates (with high viscosity), atherogenesis, endothelial cell dysfunction, thrombogenesis, and ischemia may all occur in relation to local hyperviscosity. Abnormalities in blood flow have been well recognized in hypertensives, with abnormalities in arterial compliance,4 hemorheological factors,1 and reduced coronary flow reserve.5 Hypertension may also cause damage to the endothelium (“blood vessel abnormalities”), as demonstrated by well-documented abnormalities in both flow-mediated and pharmacological arterial vasodilatation and abnormalities of levels of specific plasma markers of endothelial damage or dysfunction, such as von Willebrand factor (vWF) and soluble thrombomodulin.6,7 These abnormalities of rheology and endothelial dysfunction may be related to the complications of hypertension and the determination of blood pressure itself.

The third and final component of Virchow’s triad refers to abnormalities in blood constituents, such as clotting or hemostatic factors and platelet activation. Many of the blood constituents associated with hypertension and its complications are components of the coagulation and fibrinolytic pathways. Indeed, the process of thrombogenesis is a fine balance between these 2 systems. The fibrinolytic system, in turn, is influenced primarily by the interaction between plasminogen activators, such as tissue plasminogen activator (tPA), which promote fibrinolysis, and inhibitors that modulate this activity, such as plasminogen activator inhibitor-1 (PAI-1). The ratio of active tPA to active PAI is 1:8 in healthy male subjects, but in men with atherothrombotic disease, this ratio is severely disturbed, at 1:50.8

In this issue of Circulation, the Framingham Offspring Study reports an association between blood pressure and plasma PAI-1 and tPA antigen levels in a large (2500-person) cohort of essentially healthy middle-aged men and women, suggesting that increasing blood pressure conferred a state of impaired fibrinolysis.9 They also found that the plasma viscosity data, although obtained from frozen plasma, were positively related to systolic and diastolic blood pressure, but in women only. The association between viscosity and blood pressure is in keeping with previous epidemiological studies, such as the Edinburgh Artery Study and the Scottish Heart Health Study.10,11 Interestingly, however, the Framingham Offspring Study found no significant associations between blood pressure and fibrinogen, factor VII, or vWF, in contrast to the wide body of clinical and epidemiological studies.1,12 For example, in one study of hypertensive diabetics, plasma fibrinogen was the strongest predictor of both systolic and diastolic blood pressure, followed by blood viscosity and body mass index.13 Similarly, increased vWF levels have been associated with hypertension, with some prognostic value, being predictive of cardiovascular disease progression.14–16
One reason for the contrasting results of the Framingham Offspring Study with previous studies may be its use of very mild criteria for defining hypertension, that is, a systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. The failure of Poli et al\textsuperscript{9} to confirm (for instance) raised fibrinogen or vWF levels in hypertension could easily be explained by the higher blood pressure profiles of subjects in previous studies (for example, >160/95 mm Hg) and the fact that the patients were often recruited from individuals referred to hospital or specialist clinics.\textsuperscript{14–16} Subjects in the Framingham Offspring Study who were taking antihypertensive therapy were also excluded to avoid the confounding influence of these drugs on prothrombotic markers,\textsuperscript{1,14,15} but this suggests that only the mildest untreated hypertensives may have been included in the analysis; the mean and range of blood pressures for the (hypertensive) study population were not stated, and differences in patients with isolated systolic hypertension or isolated diastolic hypertension were not examined. This is of particular relevance because a rise in diastolic blood pressure is associated with a relatively smaller increase in cardiovascular risk compared with a corresponding proportional rise in systolic blood pressure.\textsuperscript{17} Indeed, data from the SYST-EUR study\textsuperscript{18} demonstrate how devastating isolated systolic hypertension can be, in terms of the number of thrombosis-related complications (that is, strokes and heart attacks) in the placebo group, which was reduced by antihypertensive therapy. If the prothrombotic state and endothelial damage or dysfunction in hypertension are related to the degree and possibly the duration of hypertension, then those with mild hypertension or lower blood pressures (as in the Framingham Offspring Study) and hypertension of more recent onset (which is usually more difficult to precisely quantify) may have lower levels of established prothrombotic markers. Furthermore, in the Framingham Offspring Study, 71\% of those 496 subjects were hypertensive at \( \geq 1 \) examinations. With an average duration of 11 years from the examination at which hypertension was first documented to (presumed) venipuncture, this implies very strongly that these subjects could not have had life-threatening hypertension, target organ damage, or other complications; otherwise, antihypertensive therapy would have been prescribed.

The suggestion that impaired fibrinolysis may play an important role in the pathogenesis of cardiovascular disease and hypertension needs to be further qualified by whether measurements of tPA and PAI-1 antigens or activity are performed. Both tPA and PAI-1 molecules can be assayed by immunological techniques (ELISA) and by a functional technique. Consequently, the problem of structural versus functional presence arises, and the possibility of (inactive?) tPA/PAI complexes being quantified remains. In the Framingham Offspring Study, levels of PAI-1 and tPA antigen were positively related to blood pressure, although others have reported increased PAI-1 levels and tPA activity in hypertensives compared with normotensives, whereas tPA antigen levels were not significantly different.\textsuperscript{1,19} Indeed, Ridker et al\textsuperscript{20} have even suggested that elevations of tPA antigen are the result rather than a cause of atherosclerotic coronary disease. Rather than being a measure of fibrinolysis, tPA antigen levels may thus be simply a surrogate for vascular injury, without taking part in hemostasis. Measurement of tPA antigen could therefore be another measure of endothelial cell damage or dysfunction, although this may be a premature assumption, because some plasma levels may, like levels of PAI-1, arise from platelets.\textsuperscript{21}

As Poli and colleagues\textsuperscript{9} suggest, another caveat is that the fibrinolytic pathway in hypertension may also be affected by the interaction between metabolic risk factors, such as glucose and lipoproteins, and such confounders have to be taken into account in such studies.\textsuperscript{22} It could be hypothesized that subjects with higher or uncontrolled blood pressures and other metabolic disturbances, or smokers, are more likely to exhibit greater abnormalities of hemostasis and fibrinolysis, as are evidenced by more thrombosis-related complications, such as strokes and heart attacks, in patients with poorly controlled hypertension. It is likely, therefore, that the link between impaired fibrinolysis and hypertension may involve other variables, such as insulin resistance and hyperinsulinemia, and the hypothesis that these insulting stimuli are synergistic is attractive, if unproven.

Although various components of the coagulation and fibrinolytic pathways are associated with blood pressure, a relationship to hypertensive target organ damage or prognosis should be present, and these indices should also be favorably altered by therapy. These aspects were not examined in the present article from the Framingham Offspring study, although it is unlikely that a large enough group of complicated, severely hypertensive subjects would be available in the present study to warrant analysis. The typical surrogate indices of hypertensive target-organ damage, such as left ventricular hypertrophy and microalbuminuria (defined as the excretion of urine albumin between 20 and 200 \( \mu \)g/min), have been shown to have a modest correlation to some markers, such as vWF levels.\textsuperscript{14,23} The Framingham Offspring Study nevertheless does suggest some degree of a dose-response relationship for fibrinolytic indices. In a cross-sectional study of 178 patients with hypertension, we recently reported that patients with left ventricular hypertrophy had higher plasma fibrinogen than those without it; left ventricular mass and left atrial size were also correlated with fibrinogen levels,\textsuperscript{14} which may be an important factor influencing coronary flow reserve in hypertensives.\textsuperscript{4,5} Indeed, plasma fibrinogen may have prognostic implications in hypertension, as illustrated by the Leigh general practice study, in which hypertensive subjects with plasma fibrinogen levels >3.5 g/L had a 12-fold higher cardiovascular risk than those with plasma fibrinogen levels <2.9 g/L.\textsuperscript{24} Plasma vWF and prothrombin fragment F1+2 levels are also predictive of cardiovascular disease progression in hypertensives.\textsuperscript{4,25}

Antihypertensive drugs may perhaps act by influencing both the coagulation and fibrinolytic systems in hypertension, adding to their protective potential with respect to cardiovascular end points. Beyond their blood pressure–lowering potential, some antihypertensive agents may exhibit a number of nonhemodynamic effects, such as changes in serum electrolytes, lipid and carbohydrate metabolism, endothelial function, vascular smooth muscle and cardiomyocyte growth, and possible fibrinolysis (reviewed in Reference 1). A major
controversy in antihypertensive drug treatment therefore concerns the question of whether, given a comparable blood pressure, antihypertensive drugs offer different degrees of protection from stroke and thromboembolism. A study into abnormalities leading to the hypercoagulable or prothrombotic state in hypertension may provide clues to dissect these points.

Hypertension may thus confer a hypercoagulable or prothrombotic state, and this may perhaps represent an abnormal balance between the coagulation and fibrinolytic pathways. We need more studies looking at a wide range of patients with differing elevations of blood pressure to demonstrate whether or not these abnormalities are related to the pathogenesis of hypertension, its complications, and its long-term outcome. However, the exact mechanisms through which these prothrombotic factors act are still unclear, although hypertension fulfills the components of Virchow’s triad, leading to a hypercoagulable state. The observation that blood pressure reduction with nondrug intervention and various classes of antihypertensive drugs does not always lead to a similar reduction in complications (heart attacks and strokes) may possibly relate to different effects on the abnormalities of hemostasis and fibrinolysis that lead to the hypercoagulable or prothrombotic state in hypertension. Evidence from the many epidemiological studies, such as the Framingham Offspring Study, suggests that more attention to the prothrombotic state in hypertension is still needed.

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References

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Gregory Y. H. Lip and Andrew D. Blann

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