Target Organ Damage and the Prothrombotic State in Hypertension

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Hypertension causes target organ damage by the direct physical effect of increased blood pressure, as well as the active promotion of atherosclerosis and thrombogenesis. More importantly, the processes of thrombogenesis and atherogenesis are intimately related, and many of the basic concepts of thrombogenesis can be applied to atherogenesis.

Over 150 years ago, Virchow postulated that a triad of conditions are needed to predispose to thrombus formation, that is, abnormalities in blood flow, blood constituents, and the vessel wall. Although Virchow was referring to venous thrombosis, the same concepts could essentially be applied to arterial thrombosis. A modern viewpoint of Virchow’s triad includes abnormalities of hemorheology and turbulence at bifurcations and stenotic regions (that is, “abnormal blood flow”), abnormalities in platelets and the coagulation and fibrinolytic pathways (“abnormal blood constituents”), and, finally, abnormalities in the endothelium (“abnormal vessel wall”). This may explain an important pathophysiological paradox in hypertension, in which despite the blood vessels being exposed to high pressures, the main complications of hypertension are generally thrombotic in nature rather than hemorrhagic.

Evidence for the prothrombotic or hypercoagulable state in hypertension has been extensively reviewed. However, we all recognize that the presence of target organ damage makes a dramatic difference to clinical outcome in hypertension. The “target organ” effects of hypertension are particularly manifest in the heart, brain, kidney, peripheral arteries, and the eye. Indeed, hypertensive patients with evidence of target organ damage are well recognized to be at high risk of cardiovascular and cerebrovascular events, and they should be targeted for aggressive blood pressure and risk factor management.

Indeed, one may postulate that the “high-risk” hypertensives with evidence of target organ damage are more likely to exhibit a greater prothrombotic or hypercoagulable state. It is therefore of little surprise that the abnormalities in the prothrombotic or hypercoagulable state in hypertensives have previously been related to the presence of left ventricular hypertrophy on echocardiography, and high von Willebrand factor levels, an established index of endothelial damage, has been shown to be related to microalbuminuria (defined as the excretion of urine albumin between 20 and 200 μg/min), another surrogate manifestation of hypertensive target organ damage. In this issue of Hypertension, Sechi et al extend this relationship further by reporting another large cross-sectional study investigating the relationship between hemostatic factors and target organ damage in hypertension. They find that plasma fibrinogen, fibrin D-dimer, and prothrombin fragment 1+2 were significantly related to the presence and severity of target organ damage on univariate analysis.

These observations that link the prothrombotic state and target organ damage in hypertensives are important in view of the relationship between these markers and prognosis. For example, 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 in the Lehigh general practice study. Fibrin D-dimer is an index of thrombogenesis and fibrin turnover, and data from the Edinburgh Artery Study has shown an independent predictive value for mortality and cardiovascular events in patients with atherosclerotic disease. The cohort study by Agewall et al found that prothrombin fragment 1+2 levels were an independent predictor of major coronary events in treated hypertensive patients. With the use of a similar design, our cohort study also found that patients with hypertension who developed cardiovascular or cerebrovascular events at 4 years’ follow-up had higher baseline von Willebrand factor and fibrin D-dimer levels, although on a Cox multivariate proportional hazards analysis, plasma fibrinogen and blood pressure levels emerged as independent predictors.

In their study, Sechi et al stage target organ damage in their hypertensives according the WHO guidelines, but it is likely that the abnormalities in various prothrombotic indices can also be related to the degree, and possibly the duration of hypertension. Indeed, patients with mild hypertension or lower blood pressures and more recent onset hypertension (which is usually more difficult to precisely quantify) may perhaps show less abnormalities, and such patients are also less likely to have target organ damage. For example, patients with severe hypertension (defined as >160/95 mm Hg) demonstrate high plasma von Willebrand factor levels, which
does not appear to be present in patients with milder elevations of blood pressure.13

It should not be forgotten that many of the common disorders associated with hypertension can also be related to a prothrombotic state, and these conditions could also be regarded as target organ damage. For example, hypertension is a common cause of atrial fibrillation and is additive to the risk of stroke and thromboembolism in this common arrhythmia.14 Atrial fibrillation per se is also known to be associated with abnormalities of hemostasis and endothelial dysfunction, which are independent of underlying causes or structural heart disease.15 Hypertension is also an important cause of heart failure, and the evidence also points toward a prothrombotic state in heart failure.16 Indeed, left ventricular dysfunction is often forgotten as an important contributor to thromboembolism, with an inverse relationship between ejection fraction and stroke and thromboembolic events in the SAVE study.17 In patients with atrial fibrillation, the presence of clinical congestive heart failure and echocardiographic left ventricular dysfunction are independent risk factors for stroke.14

However, many antihypertensive agents can influence the prothrombotic state in hypertension (as reviewed by Lee3). In the study by Sechi et al.,7 concomitant treatment may be an important confounder, although the authors have tried to limit this by stopping antihypertensive therapy for 1 to 3 weeks. Nevertheless, 1 to 3 weeks may be insufficient to fully exclude the residual effects of antihypertensive drugs and several indices may even be in a state of flux, altering further over the time while drug free. A subgroup comparison of patients previously untreated and those treated, as well as a comparison of levels of the measured indices in their previously treated cohort when on treatment and off treatment apparently did not show any significant differences in fibrinogen, D-dimer, and prothrombin fragment 1 + 2 levels.7 Indeed, in severe, uncontrolled hypertension (that is, >160/95 mm Hg), there appears to be little difference in levels of various prothrombotic indices between treated and untreated patients.5 Perhaps it is simply the effect of getting blood pressure to well-controlled levels that actually normalize the prothrombotic indices.18 Indeed, we have recently shown that platelet and hemorheological markers in high-risk hypertensives are improved by tighter blood pressure control and cardiovascular risk management, irrespective of antihypertensive drug regimes used.19

Perhaps the relationship between the prothrombotic state and target organ damage is simply confounded by the presence of other preexisting vascular disorders, which are themselves associated with abnormal hemostasis. For example, Sechi et al.20 report a significant relationship of fibrinogen and fibrin D-dimer with cardiac, cerebrovascular, peripheral vascular, and renal damage. This therefore raises the issue whether these abnormalities are cause or effect, which is not answered by the cross-sectional design of their study.2 It is likely that a continuum exists between normality, “statistically increased” levels of hemostatic markers, and overt thrombosis. If so, it is also likely that those with high levels of hemostatic markers are predictive of subsequent vascular events, as discussed above. It has also been suggested that these associations may be explained by a reactive or secondary rise in plasma hemostatic factors, either as an acute phase response or as a hypertension-related “hematological stress syndrome,” in a similar way noted in atherosclerosis.20 Because the processes of thrombogenesis and atherogenesis have many similarities to inflammatory disease, the elevations in various indices may reflect the severity of vascular disorders as a secondary phenomenon rather than act as a true prognostic factor. Indeed, the role of potential pathogens needs to be defined, in view of possible relationships between hypertension and Chlamydia pneumoniae21 and Helicobacter pylori.22–23 The precise mechanisms for the elevated levels of various prothrombotic markers in hypertension also remain uncertain, although a cytokine-mediated increase in synthesis may possibly be the common pathway.24

The close relationship of the prothrombotic or hypercoagulable state to hypertensive target organ damage as well as their prognostic value in predicting cardiovascular events and mortality raises the possibility that they are not merely markers or consequences of atherothrombotic disease but may contribute to the pathogenesis of hypertension and its complications. Indeed, the close relationship between the prothrombotic state and hypertension raises the possibility of using these indices for cardiovascular risk stratification in hypertension, and preliminary data suggests that this is possible, with a close relationship to the Framingham risk scores.25 Clearly, more information from longitudinal studies on prognosis and the effects of treatment are needed to clarify the additional value of measuring prothrombotic markers as indices of hypertensive target organ damage and/or as an aid to risk stratification.

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References
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