Platelets are the smallest of the blood cells, yet they are one of the main players during the process of thrombus formation (thrombogenesis). Furthermore, the traditional belief that the endothelium exists simply to provide an inert interface between the blood and the vessel wall is no longer accurate. Indeed, the endothelium produces a large number of substances that affect blood flow and in turn are affected by changes in the blood and the pressure of blood flow.

Despite many therapeutic advances that have lead to increasingly effective antihypertensive drug treatments, the precise pathophysiological mechanisms of hypertension and its complications are still poorly understood. In hypertension, the delicate balance between the vasodilators and the vasoconstrictors is upset, leading to changes that then take place in the vascular beds, setting up a vicious cycle that further maintains the high blood pressure. There is also increasing evidence that platelets and the endothelium, which both get activated in hypertension, have a crucial role in the increased thrombotic tendency seen in hypertension. Indeed, despite exposure of the blood vessels to high pressures, the main complications of hypertension (that is, myocardial infarction and stroke) are paradoxically thrombotic in nature rather than hemorrhagic—“the thrombotic paradox of hypertension” or “Birmingham paradox.”

The processes of thrombogenesis and atherogenesis are also intimately related. Many components of the coagulation and fibrinolytic pathways are primary and secondary predictors of cardiovascular events. The close association of these markers with cardiac outcomes and common cardiovascular risk factors raises the possibility that such indices are not merely markers or consequences of thrombosis, but may significantly contribute to the pathogenesis of arterial thrombotic disease.

In this issue of Hypertension, Preston et al report on the presence of circulating endothelial and platelet microparticles in hypertension. Based on this cross-sectional study of 24 severe hypertensives, 19 mild hypertensives, and 16 control subjects, they suggest that these markers may be useful and specific for pressure-induced endothelial and platelet activation in hypertension. These micro-particles may also play a pathogenic role in mediating target organ injury in severe hypertension.

Although these indices are associated with blood pressure, a relationship to hypertensive target organ damage or prognosis should convincingly be present, and these indices should also be favorably altered by therapy. Preston et al classify their hypertensive patient groups based on diastolic blood pressure in patients admitted to the emergency department, because diastolic blood pressure was used in triage guidelines. Certainly, it is well established that systolic blood pressure is the better predictor of cardiovascular risk, even after adjusting for underlying diastolic blood pressure, and indeed, patients with isolated systolic hypertension exhibit similar abnormalities of the prothrombotic state compared with patients with systolic-diastolic hypertension.

The possibility also remains that the high diastolic blood pressures in the emergency room were a “white coat effect”; 24-hour ambulatory blood pressure monitoring (ABPM) would have established a much better relationship to blood pressure “load.” In fact, 24-hour ABPM has been correlated to target organ damage. However, Preston et al did find significant correlations between circulating endothelial and platelet microparticles and systolic blood pressure.

Nevertheless, target organ damage is not examined in the present paper by Preston et al. 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 μg/min), have been shown to have a modest correlation to some markers of endothelial damage/dysfunction, such as von Willebrand factor (vWF) levels. In a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Spencer et al recently showed that patients with hypertensive target organ damage had significantly higher plasma vWF, but there were no statistically significant differences in platelet count or soluble P-selectin (an index of platelet activation) between those with and those without target organ damage. Importantly, vWF levels were still a significant independent predictor of target organ damage on multivariate analysis, and intensified cardiovascular risk factor management (including blood pressure reduction) resulted in improvements in indices of hemorheology and endothelial and platelet function.

Preston et al may be using circulating endothelial and platelet microparticles as “novel” indices of endothelial and platelet activation, but a very important aspect would be a comparison with

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Hypertension. 2003;41:199-200.)

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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000049761.98155.7B
established markers of endothelial and platelet activation. In their study, endothelial microparticles (supposedly an endothelial marker) correlate more strongly with platelet CD62 (a platelet marker, r=0.36 and P=0.005) than with other established endothelial markers (vWF, soluble intercellular adhesion molecule-1 [sICAM-1], and soluble vascular cell adhesion molecule-1 [sVCAM-1]) that were studied. In fact, the only significant correlation between endothelial microparticles and sVCAM-1 was weak (r=0.26, P=0.04). Similarly, platelet microparticles (supposedly a platelet marker) did not correlate significantly with platelet CD62 (r=0.025, P=0.054), and if platelet microparticles truly reflected platelet activation, a better relationship would be preferred. This paradox raises issues about how valid these new indices are as endothelial and platelet markers. On a broader perspective, this issue highlights a long-standing problem: how best to measure or quantify abnormalities of platelets and the endothelium?

In general, the quantification of platelet abnormalities can be performed using a wide variety of measures, such as platelet volume, aggregometry, excretion of metabolites, flow cytometry to detect various platelet antigens, and the measurement of increased plasma levels of platelet-specific products, such as platelet factor 4, β-thromboglobulin (BTG), and the soluble adhesion molecule P-selectin. The choice of method may sometimes depend on the nature of the study. As an example, measurement of large numbers, say, in epidemiological studies may require the use of plasma markers rather than the more specialized, time-consuming techniques such as flow-cytometry.

Similarly, debate remains over how best to assess the endothelium. Various indices have been used to assess endothelial activation, dysfunction, and damage. The ideal one must not only be specific to the endothelium but must also be stable and easily measurable. Indeed, the “gold standard” still remains uncertain, as available indices quantify different aspects of endothelial physiology. In addition, words such as “damage,” “injury,” “dysfunction,” and “activation” are currently freely used in the study of the endothelium without a clear definition of, or even a consensus about, their meanings. A continuum is also likely to exist among endothelial activation (eg, by cytokines), endothelial dysfunction (resulting in thrombogenesis and atherogenesis), and endothelial damage (resulting in overt vascular damage and atherosclerosis). Endothelial (dys)function also implies some functional component to the endothelium, which may be rather different from that assessed by measurement of plasma markers or endothelial microparticles.

Therefore, are endothelial and platelet microparticles really a reflection of endothelial and platelet damage rather than activation, or are we simply detecting (platelet or endothelial?) cell debris from a severely damaged vascular tree? One could argue that perhaps the best proof of endothelial damage would be to observe desquamated, but not apoptotic, endothelial cells in circulating blood. A method to capture these cells has been developed and used to prove that endothelial injury occurs in acute myocardial infarction and unstable angina (but not in stable angina), confirming a separate mechanism in pathogenesis. Increased surface expression of markers such as E-selectin is probably a reflection of endothelial activation, rather than damage, and E-selectin is not expressed by normal resting endothelial cells.

Lastly, many of the patients in the study by Preston et al were previously taking antihypertensive drugs, and the "hangover" effect of these drugs may possibly be a confounder. Antihypertensive drugs may partly 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 also exhibit a number of nonhemodynamic effects, such as changes in serum electrolytes, lipids and carbohydrate metabolism, endothelial function, vascular smooth muscles, cardiomyocyte growth, and, possibly, fibrinolysis. Do different antihypertensive drugs differentially affect the endothelium or platelets, and if so, does it affect activation, (dys)function, or the integrity/damage of these cells? With a new technique to assess the endothelium and platelets in hypertension, we still need further large-scale comparisons with established methods of assessment, data on the relation to target organ damage and the effects of treatment, and a definition of which aspect of cellular pathophysiology we are studying (and why!).

Acknowledgment

We acknowledge the support of the City Hospital Research and Development program for the Hemostasis, Thrombosis, and Vascular Biology Unit.

References

Hypertension, Platelets, and the Endothelium: The "Thrombotic Paradox" of Hypertension (or "Birmingham Paradox") Revisited

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Hypertension. 2003;41:199-200; originally published online February 3, 2003;
doi: 10.1161/01.HYP.0000049761.98155.7B
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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