


cardiovascular risk, even after adjusting for underlying diastolic blood pressure, suggests that these indices 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\(^\text{3}\) 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.\(^\text{5}\) 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 related to target organ damage.\(^\text{6}\) However, Preston et al\(^\text{3}\) 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.\(^\text{7,8}\) In a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Spencer et al\(^\text{9}\) 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\(^\text{3}\) 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
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.10 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.11 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 (dys)function also implies some dysfunction.

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