Effects of Severe Hypertension on Endothelial and Platelet Microparticles


Abstract—The molecular mechanisms by which extreme blood pressure elevation leads to vascular injury are not defined. To explore the hypothesis that activation of endothelium and platelets as manifested by increased concentrations of circulating endothelial microparticles and platelet microparticles could play a role in this target organ injury, we conducted a cross-sectional study of these markers in 3 groups: (1) untreated patients referred specifically for treatment of severe uncontrolled hypertension; (2) untreated patients with established mild hypertension; and (3) normotensive volunteer subjects. By ANOVA, endothelial (P=0.002) and platelet (P=0.01) microparticles were greatest in the severely hypertensive group. There was a significant correlation between both of these markers and blood pressure, even in the setting of multiple risk factors. Our results suggest that these markers may be useful and specific for pressure-induced endothelial and platelet activation in hypertension. Furthermore, because of the combined effects of endothelial and platelet microparticles on coagulation, leukocytes, and endothelium, it is possible that they may play a pathogenic role in mediating target organ injury in severe hypertension. (Hypertension. 2003;41:211-217.)

Key Words: hypertension, arterial ■ endothelium ■ platelets ■ endothelium-derived factors ■ cell adhesion molecules

Severe, uncontrolled hypertension is associated with high rates of target organ complications,1–6 but the molecular mechanisms by which extreme blood pressure elevation leads to vascular injury are not well defined. Increased evidence suggests that hypertension confers a prothrombotic state, characterized by abnormalities of endothelial function and platelet activation.7–24 This dysfunction is conferred by isolated systemic hypertension as well as simultaneous systolic and diastolic hypertension.9 Consequently, investigative interest has recently focused on endothelial and platelet activation as important mediators of hypertensive vascular injury.

Endothelial microparticles (EMP) are small membrane vesicles that are shed from the surface of endothelial cells in response to activation, injury, and/or apoptosis. EMP release can be caused by a number of cytokines such as interleukin-1 and tumor necrosis factor and by elevated shear pressure.25–30 Assays for circulating EMP have recently been developed25–26 as potential means of quantifying endothelial cell injury. EMP are also known to be elevated in thrombotic thrombocytopenic purpura,26 a condition associated with endothelial injury, and in acute coronary syndromes.27,30 Increased EMP release has also been associated with endothelial injury in patients with multiple sclerosis and lupus anticoagulant.28–29

Circulating platelet microparticle (PMP) concentration is a marker of platelet activation.31–33 PMP are formed by platelet membrane vesicle formation and shedding.31 PMP are known to possess procoagulant activity and are elevated in severe thrombotic states such as acute myocardial infarction and stroke.31,34–38 PMP are also elevated in several states characterized by increased platelet activation/injury such as idiopathic thrombocytopenic purpura, heparin-induced thrombocytopenia, and systemic lupus erythematosus.31,38 Furthermore, chronic elevation of PMP may be linked to the development of vascular dementia. In addition, PMP exert a variety of stimulatory effects on a number of cell types including endothelial cells, leukocytes, neutrophils, monocytes, and other platelets.39–45 The effects of arterial hypertension on EMP and PMP concentrations have not been studied.

Pilot studies from our public teaching hospital suggest that patients with severe uncontrolled hypertension (criteria: diastolic blood pressure [DBP] >120 mm Hg and/or systolic blood pressure [SBP] >220 mm Hg) account for ≈800 emergency department visits per year and an extraordinary annual rate of target organ injury that approaches 30% to 40%.5–7 Whether extreme hypertension is associated with increased release of circulating EMP and PMP has not been investigated.

To explore the hypothesis that activation of endothelium and platelets as manifested by increased concentrations of circulating EMP and PMP could play a role in this acceler-
ated acute target organ injury, we conducted a cross-sectional study examining the relation between severe blood pressure elevation and these markers. The aim of our study was to determine the absolute effect of extreme elevation of blood pressure on EMP and PMP in the clinically relevant setting of multiple coexisting risk factors for endothelial and platelet activation/injury. By this approach, we sought to determine whether severe uncontrolled hypertension is associated with increased release of EMP and PMP in a pressure-dependent manner.

**Methods**

The study is a cross-sectional comparison of EMP and PMP among 3 blood pressure groups: (1) untreated emergency department patients with severe, uncontrolled hypertension (DBP ≥120 mm Hg; n=24), (2) untreated mildly hypertensive patients (DBP ≥95 and ≤100 mm Hg; n=19), and (3) normotensive healthy volunteers (DBP <90; n=16). The study protocol was approved by and conducted according to the institutional guidelines of the University of Miami Human Subjects Committee (Institutional Review Board). Written informed consent was obtained directly from all subjects by study personnel before entering the study.

**Study Subjects**

Subjects with severe, uncontrolled hypertension met the criteria: age 18 years or older, average of two supine DBP measurements taken 10 minutes apart was ≥120 mm Hg, and no antihypertensive drugs for ≥48 hours. Diastolic pressure was selected for study inclusion criteria for the practical reason that emergency department triage guidelines are based on diastolic rather than systolic pressure. Patients were excluded if there was documented or suspected secondary hypertension, acute hypertension related to a readily identifiable cause such as drug ingestion or an acute pain syndrome, or clinical findings of acute ongoing target organ damage requiring immediate treatment (ie, evidence of acute coronary syndrome, transient ischemic attack, congestive heart failure, atrial fibrillation, malignant hypertension, or acute kidney failure).

Subjects with mild hypertension were included if the average of two supine diastolic blood pressure measurements taken 10 minutes apart was ≥95 mm Hg and ≤100 mm Hg. Normotensive control subjects were included if they had no known history of medical illness or significant risk factors for cardiovascular disease, a normal (<140/90 mm Hg) blood pressure, and a normal physical examination.

Clinical and laboratory data collected from all subjects included body mass index (BMI), presence of diabetes mellitus (DM), smoking history, total cholesterol (TC) to HDL cholesterol ratio (TC/HDL), and triglycerides (TG).

**Laboratory and Bioanalytical Procedures**

Routine laboratory tests including complete blood count, blood urea nitrogen, serum creatinine, serum electrolytes, glucose, TC, HDL, TC/HDL ratio, and TG were determined by standard laboratory methods.

**Endothelial Microparticles**

Blood samples were drawn by venipuncture into blue-top Vacutainer tubes containing sodium citrate. Platelet poor plasma (PPP) was separated from whole blood within 1 hour by centrifuging at 1500g for 10 minutes. For EMP assay, 50 μL of PPP was incubated with 4 μL of PE-conjugated mAb to CD31 and 4 μL of FITC-conjugated mAb to CD42 (Pharmingen) for 20 minutes. The samples were diluted with 0.5 mL of PBS, then analyzed with Coulter EPICS XL flow cytometer, as previously published.25 The discriminator (triggering) was set with FL2 (ic, CD31 FL) at a predetermined FL threshold so that all CD31+ particles were included. Then, EMP regions are selected by plotting FL1 (CD42) versus FL2 (CD31).

EMP are defined as particles with size <1.5 μm that are positively labeled by CD31 mAbs and negative for CD42.

**Platelet Microparticles**

Fifty microliters of PPP was incubated with 4 μL of FITC-labeled CD41 for 20 minutes, then was fixed with paraformaldehyde (2%, final concentration) for 1 hour. After fixation, the number of PMP was diluted with 2 mL of PBS, then measured with flow cytometry.35 Soluble ICAM-1, soluble vascular adhesion molecule-1s (VCAM-1), and von Willebrand Factor (vWF) were measured as follows.46 Soluble ICAM-1 and sVCAM-1 were quantified by a colorimetric sandwich ELISA (R&D Systems), using monoclonal murine anti-human sVCAM-1 and soluble intercellular adhesion molecule-1 (sICAM-1) capture antibodies. A second antirecombinant human sICAM-1 or sVCAM-1 antibody was tagged with horseradish peroxidase, and the sandwich complex was visualized by enzyme action on the substrate tetramethylbenzidine.

vWF antigen was determined by an ELISA method (Asserachrom vWF, Diagnostica Stago) with F(ab')2 polyclonal rabbit anti-human antibody used for both capture and tagged antibodies. The second antibody was tagged with horseradish peroxidase; the bound enzyme acts on the substrate ortho-phenylenediamine (OPD/H2 O 2 ) and absorbance measured.

**Platelet CD62P**

Fifty microliters of blood was incubated with 5 μL of FITC-CD41, PE-CD62P, and PE-Cy5-CD45 for 10 minutes, fixed by adding 65 μL of 4% PFA, incubated for an additional 10 minutes, diluted with 1 mL of PBS, and then left to stand for 2 hours or long enough to visually observe that hemolysis was complete. The expression of CD62P was be measured with a flow cytometer.37

**Statistical Methods**

A sample size of 15 study subjects per group was calculated to allow detection of a difference in EMP and PMP of ~1 SD with 80% power and α-level of 0.05. EMP and PMP have not been previously studied in hypertension. The sample size of 15 per group is in the range of that required to demonstrate significant differences between normotensive and hypertensive groups in commonly used soluble markers such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (sICAM-1).9,12,16 The sample size estimation is also based on the statistical power of previous studies of EMP and PMP in normal subjects versus several disease entities such as thrombotic thrombocytopenic purpura and multiple sclerosis.26,29

Baseline demographic, clinical, blood pressure, and biochemical measures (total cholesterol, LDL cholesterol, and total cholesterol to HDL ratio) were compared between the mild hypertension group and the severe hypertension group by means of a 2-sample t test. Nonparametric baseline data were compared by means of the Fisher exact test.

Differences in EMP and PMP among the 3 study groups were evaluated by 1-way ANOVA followed by the Tukey test for pairwise comparisons. Relations between EMP and PMP considered as dependent variables and both SBP and DBP were evaluated by standard regression methods. Multiple regression analysis was then applied to evaluate clinical and biochemical variables (age, BMI, smoking, diabetes mellitus, and TC/HDL ratio) evaluated as independent variables in regression models of the dependent variables EMP and PMP. Statistical significance was considered as a level of P<0.05. All data are presented as mean±SD.

**Results**

Results (Table 1 and Figures 1 through 3) are expressed as mean±SD. Demographic, clinical, blood pressure, and laboratory data are displayed in Table 1 for the 3 blood pressure groups. The mild hypertension (n=19) and the severe hypertension (n=24) groups did not differ with regard to age, gender, BMI, hemoglobin, hematocrit, blood urea nitrogen,
creatinine, total cholesterol, LDL cholesterol, TC/HDL ratio, number of patients who smoked, or the number of patients with diabetes mellitus. By ANOVA, there were small but statistically significant differences between the hypertensive groups and the normotensive control group in hemoglobin ($P<0.05$), hematocrit ($P=0.02$), and creatinine ($P=0.03$), hematocrit ($P=0.02$), and creatinine ($P=0.02$).

The mean level of endothelial microparticles was highest in severe hypertension ($P=0.002$, versus control subjects), followed by mild hypertension (Figure 1). However, the difference between severe hypertension versus mild hypertension and control subjects versus mild hypertension did not reach statistical significance. EMP showed a significant positive correlation with both SBP ($P=0.006$; $r=0.36$) and DBP ($P=0.001$; $r=0.42$). EMP also demonstrated significant correlations with the presence of diabetes mellitus ($P=0.03$; $r=0.28$) and smoking ($P=0.02$; $r=0.32$). EMP did not correlate with age ($P=0.20$), BMI ($P=0.89$), TG ($P=0.54$), or TC/HDL cholesterol ratio ($P=0.37$). The model containing SBP, smoking, and diabetes mellitus had values of $P=0.0008$ and $r=0.51$. The model containing DBP, smoking, and diabetes mellitus had values of $P=0.0003$ and $r=0.54$.

Platelet microparticles were significantly higher ($P=0.01$) in severe hypertension than both mild hypertension and control subjects. Furthermore, PMP did not differ between mild hypertension and control subjects. There was a significant positive correlation between PMP and SBP ($P=0.005$; $r=0.36$) and DBP ($P=0.002$; $r=0.40$). There was no correlation between PMP and the other parameters of age ($P=0.47$), BMI ($P=0.67$), DM ($P=0.96$), smoking ($P=0.85$), TG ($P=0.39$), or TC/HDL cholesterol ratio ($P=0.17$).

We compared EMP with the more widely used markers of endothelial and platelet activation, sVCAM-1 and sICAM-1, and with the marker of endothelial injury/dysfunction, vWF. We compared PMP with platelet surface CD62P. Table 2 contains the results of correlations carried out between EMP, PMP, and these markers. The correlations between EMP and sVCAM-1 ($r=0.26$, $P=0.04$) achieved statistical significance, whereas the correlation between EMP and vWF approached significance ($r=0.24$, $P=0.06$). The correlation of PMP with the platelet activation marker CD62P also approached statistical significance ($r=0.25$, $P=0.054$). We also observed a correlation between EMP and platelet CD62 ($r=0.36$, $P=0.005$); both markers had strong correlation with SBP (CD62: $r=0.36$, $P=0.006$).

### Discussion

We investigated the effects of extreme blood pressure elevation on two recently developed markers of endothelial and platelet activation: EMP and PMP. We compared EMP and PMP values between 2 blood pressure groups matched for coexisting risk factors plus normotensive control subjects. We observed that the EMP values were elevated in the severe hypertension group at highest risk for acute vascular target organ injury compared with the mild hypertension and control groups. We found a strong, positive correlation of EMP with the absolute level of both systolic and diastolic blood pressures. This finding is consistent with existing literature that suggests both systolic and diastolic hypertension confer abnormalities of endothelial function and platelet activation.$^9$ EMP also correlated with the presence of diabetes mellitus and smoking, factors also known to produce endothelial activation/injury. The correlation of EMP with blood pressure persisted in the presence of multiple coexisting risk factors for endothelial injury/activation. This finding

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### TABLE 1. Demographic and Clinical Data for the Three Blood Pressure Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normotensive (n=16)</th>
<th>Mild Hypertension (n=19)</th>
<th>Severe Hypertension (n=24)</th>
<th>P (MHT vs SHT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>46.3 (13)</td>
<td>53.6 (8.1)</td>
<td>52.9 (10.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>3/13</td>
<td>6/13</td>
<td>8/16</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI</td>
<td>26 (3.6)</td>
<td>29.4 (4.4)</td>
<td>28.9 (4.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122 (9)</td>
<td>142 (10)</td>
<td>195 (26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80 (5)</td>
<td>96 (1)</td>
<td>127 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>41 (6)</td>
<td>46 (10)</td>
<td>68 (23)</td>
<td>0.0003</td>
</tr>
<tr>
<td>DM</td>
<td>0</td>
<td>5/19</td>
<td>5/24</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
<td>6/19</td>
<td>6/24</td>
<td>0.48</td>
</tr>
<tr>
<td>History of MI</td>
<td>0</td>
<td>2/19</td>
<td>1/24</td>
<td>0.36</td>
</tr>
<tr>
<td>History of stroke</td>
<td>0</td>
<td>1/19</td>
<td>1/24</td>
<td>0.67</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>39.0 (3.9)</td>
<td>43.1 (4.1)</td>
<td>42.3 (5.7)</td>
<td>0.51</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>14 (3.7)</td>
<td>15 (5.9)</td>
<td>15 (4.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9 (0.16)</td>
<td>1.12 (0.25)</td>
<td>1.1 (0.31)</td>
<td>0.70</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>193 (40)</td>
<td>217 (51)</td>
<td>219 (41)</td>
<td>0.887</td>
</tr>
<tr>
<td>TC/HDL, mg/dL</td>
<td>3.94 (0.85)</td>
<td>4.74 (1.36)</td>
<td>4.31 (1.29)</td>
<td>0.290</td>
</tr>
<tr>
<td>Dipstick proteinuria</td>
<td>0</td>
<td>0</td>
<td>14/24</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are mean (SD). BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; DM, diabetes mellitus; MI, myocardial infarction; TC, total cholesterol; LDL, low density lipoprotein cholesterol; and TC/HDL, total cholesterol to high density lipoprotein cholesterol ratio.
suggests that EMP may be a marker of the effects of blood pressure per se on the endothelium.

Our findings are in marked distinction to what we have previously reported for the more widely utilized markers sVCAM-1, sICAM-1, and vWF.46 In the clinically relevant setting of multiple concomitant risk factors, we found no correlation between the level of blood pressure and sVCAM-1 ($r=0.15, P=0.24$ for SBP; $r=0.20, P=0.11$ for DBP); sICAM-1 ($r=0.01, P=0.91$ for SBP; $r=0.10, P=0.45$ for DBP); and vWF ($r=0.16, P=0.23$ for SBP; $r=0.22, P=0.09$ for DBP).46 The correlations between these markers observed in studies of patients with mild-to-moderate levels of hypertension did not persist in severely hypertensive patients with multiple concomitant risk factor for endothelial injury/activation. Because sVCAM-1 and sICAM-1 correlated primarily with other risk factors such as smoking and DM, we proposed that these markers may depend more strongly on metabolic factors in the hypertensive microenvironment rather than the absolute level of blood pressure per se.46 Finally, although we observed a correlation between EMP and sVCAM-1 that achieved significance ($r=0.26, P=0.04$), the correlations of EMP with sICAM-1 and vWF did not reach statistical significance. Furthermore, the correlation carried out between PMP and CD62P approached but did not achieve significance, suggesting that there may be qualitative differences in the mechanisms whereby blood pressure and other factors lead to elevation of PMP versus CD62.

Taken together, these data are consistent with the hypothesis that release of EMP and expression of the more widely utilized markers sVCAM-1, sICAM-1, and vWF are differentially modulated by the various risk factors that lead to endothelial dysfunction. EMP may therefore be a more specific marker for pressure-induced effects on the endothelium than sVCAM-1, sICAM-1, and vWF. Elevated EMP may therefore better distinguish patients at risk for impending hypertensive vascular injury.

Our in vitro studies26,48 suggest that EMP positive for CD31 are indicative of microvascular endothelial apoptosis. The persistent elevation of CD31 + EMP observed in patients with severe hypertension may suggest diffuse endothelial apoptosis. Focal areas of denuded endothelium could possibly lead to platelet and/or microparticle adhesion and consequent thrombosis.

PMP values were elevated in the high-risk, severe hypertension group but not the mild hypertension and control groups. PMP therefore identifies the high-risk group of patients at risk for impending hypertensive vascular injury. We also found a strong, positive correlation of PMP with the absolute level of blood pressure, suggesting that PMP may be a marker of the effects of blood pressure per se on platelet activation. We have also found the more widely used marker
platelet surface CD62P to be elevated in the high-risk patients with severe hypertension and to have a correlation with blood pressure level (SBP: \( r=0.43, P=0.002; \) DBP: \( r=0.37, P=0.002 \)). Moreover, there is a correlation of PMP and CD62P that approaches significance \( (P=0.054; r=0.24) \). This finding is consistent with the hypothesis that platelet activation may play a role in hypertension-induced vascular injury, although there may be qualitative differences whereby blood pressure leads to elevation of PMP versus CD62P.

Both PMP and EMP are known to have the procoagulant activity of platelet factor 3 (PF3).\(^{26,49–50}\) This activity is due to exposure on the vesicle surface of normally in-facing anionic phospholipids such as phosphatidyl serine, which support the assembly of coagulation factors.\(^{50}\) Our data indicate that the absolute numbers of PMP are much higher than EMP in plasma (Figure 1), suggesting that PMP contribute most of the PF3 activity. However, EMP but not PMP have been demonstrated to express tissue factor,\(^{25}\) which can initiate the coagulation cascade. Therefore, it is possible that EMP and PMP work synergistically to achieve maximal procoagulant activity. Tissue factor on EMP initiates the coagulation cascade; PMP subsequently accelerate the process through PF3 activity. In addition, it has been demonstrated that PMP can bind and activate leukocytes,\(^{44}\) suggesting a potential role in inflammation as well. Circulating microparticles are also capable of producing impairment of endothelial vasodilator function.\(^{30}\) EMP and PMP may therefore be more than markers for endothelial injury/activation and may actually contribute to the pathogenesis of vascular injury observed in patients with uncontrolled severe hypertension.

Limitations of our study include its cross-sectional design, small sample size, and lack of prospective data, which limit our ability to infer causal relations among the variables. Our preliminary data will require confirmation and further study by larger prospective investigations. Nevertheless, our findings may have important implications. Despite the high rates of target organ injury in patients with severe uncontrolled hypertension, the mechanisms leading to this injury are not established. The current report demonstrates a significant and positive relation between blood pressure and both EMP and PMP that persists in the presence of extreme blood pressure elevation, consistent with the hypothesis that endothelial and platelet activation may play a role in the pathogenesis of the accelerated target organ injury observed in patients with severe uncontrolled hypertension.

Our results suggest that the new markers EMP and PMP are increased at a high blood pressure threshold in a subgroup of patients at risk for acute target organ injury. These markers may prove to be useful and specific indicators for hypertension-induced endothelial and platelet activation/injury. Specifically, EMP correlated with blood pressure, smoking, and coexisting DM, whereas PMP elevation correlated solely with blood pressure. Both markers are significantly elevated in the high-risk patients with severe hypertension. Furthermore, because of the combined effects of EMP and PMP on coagulation, leukocytes, and endothelium, it is possible that EMP and PMP may play a pathogenic role in mediating target organ injury in severe hypertension. Further investigation of the roles of EMP and PMP in mediating hypertensive vascular injury is warranted.

**Perspectives**

The current report demonstrates that the recently developed markers EMP and PMP are significantly elevated in high-risk patients with severe hypertension. Furthermore, there is a significant and positive correlation between blood pressure and both EMP and PMP that persists in the presence of multiple risk factors and extreme blood pressure elevation. This finding is consistent with the hypothesis that endothelial and platelet activation may play a role in the pathogenesis of the accelerated target organ injury observed in patients with severe hypertension.

### TABLE 2. Correlations Between Endothelial Microparticles and Platelet Microparticles and Commonly Used Markers of Endothelial and Platelet Activation

<table>
<thead>
<tr>
<th>Marker</th>
<th>Endothelial</th>
<th>Microparticles</th>
<th>Platelet</th>
<th>Microparticles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r )</td>
<td>( P )</td>
<td>( r )</td>
<td>( P )</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.26</td>
<td>0.04</td>
<td>0.08</td>
<td>0.54</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.16</td>
<td>0.21</td>
<td>0.14</td>
<td>0.29</td>
</tr>
<tr>
<td>vWF</td>
<td>0.24</td>
<td>0.06</td>
<td>0.07</td>
<td>0.62</td>
</tr>
<tr>
<td>Platelet CD62</td>
<td>0.36</td>
<td>0.005</td>
<td>0.25</td>
<td>0.054</td>
</tr>
</tbody>
</table>

sVCAM-1 indicates soluble vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; and vWF, von Willebrand factor.
severe uncontrolled hypertension. EMP and PMP have diverse effects on coagulation, leukocytes, platelets, and endothelium that could ultimately contribute to the pathogenesis of the acute vascular injury observed in patients with uncontrolled severe hypertension. EMP and PMP may therefore be mediators of as well as markers for endothelial and platelet activation and hypertensive target organ injury. Further investigation of the mechanisms of release of EMP and PMP in hypertension and the potential roles of these microparticles in mediating hypertensive vascular injury are warranted.

References


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