History of Hypertension and Enhanced Thrombogenic Activity in Postinfarction Patients

Yazid Y. Fadl, Wojciech Zareba, Arthur J. Moss, Victor J. Marder, Charles S. Sparks, Luc F. Miller Watelet, Elizabeth R. Carroll

Abstract—Hypertension is a risk factor for coronary thrombosis and death in cardiac patients mediated in part by endothelial damage or dysfunction and increased thrombogenicity. However, there are no data regarding the association between hypertension and thrombogenic activity in stable patients after myocardial infarction and limited data about the prognostic significance of thrombogenic factors in hypertensive patients after infarction. Therefore, levels of thrombogenic, lipid, and inflammatory factors were measured 2 months after an acute myocardial infarction in 461 hypertensive and 582 nonhypertensive patients. Thrombogenic factors included D-dimer, fibrinogen, plasminogen activator inhibitor-1, von Willebrand factor, factor VII, and factor VIIa. Lipid variables included cholesterol (total, HDL, LDL), triglyceride, lipoprotein (a), apolipoprotein-A1, and apolipoprotein-B. The prognostic significance of these factors for predicting cardiac events during a 2-year follow-up was evaluated in hypertensive and nonhypertensive patients. In comparison with nonhypertensive patients, those with hypertension had higher levels of D-dimer (607 versus 453 mg/L, \(P<0.001\)), fibrinogen (3.64 versus 3.43 g/L, \(P<0.001\)), plasminogen activator inhibitor-1 (29.7 versus 27.3 ng/mL, \(P=0.01\)), von Willebrand factor (159 versus 141 IU/dL; \(P<0.001\)), and higher levels of inflammatory markers (hsCRP and SAA). In multivariate analysis after adjustment for clinical covariates, elevated D-dimer was the only factor independently associated with a history of hypertension (OR, 1.38, \(P=0.05\)). D-Dimer was associated with an increased risk of recurrent cardiac events in both hypertensive (hazard ratio = 3.02, \(P=0.005\)) and nonhypertensive (hazard ratio = 2.42, \(P=0.02\)) patients. Thus, patients after infarction with a history of hypertension have enhanced thrombogenic activity, which predisposes them to recurrent cardiac events. (Hypertension. 2003;41:943-949.)

Key Words: hypertension, chronic ■ myocardial infarction ■ hemostasis ■ fibrinogen ■ lipids

Hypertension promotes atherosclerosis and cardiovascular disease and has deleterious effects on endothelial cells.1-7 Hypertension is reported in half of patients after myocardial infarction,8 and mechanisms related to cardiac events include enhanced atherosclerosis, thrombogenic potentiation, and proinflammatory influences. An association exists between hypertension and thrombogenic factors such as fibrinogen,9 but there is limited information regarding the thrombogenic and lipid profile of patients after infarction with a history of hypertension. This study aims to (1) evaluate levels of thrombogenic, lipid, and inflammatory factors in patients after infarction with and without a history of hypertension and (2) determine the prognostic significance of thrombogenic factors in postinfarction patients with a history of hypertension.

Methods

Study Population
The study population for this analysis used the 1045 patients enrolled in the prospective, multicenter Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study. From October 1, 1994, until June 30, 1997, the THROMBO study screened patients of either sex at the time of hospital discharge; however, blood pressure was not monitored throughout the hospital phase of the index event or those with significant comorbidities (malignancy or kidney or liver failure) were excluded from the study. Only patients who made the 2-month postdischarge follow-up visit were ultimately enrolled.

Demographic information and medical history including medication usage were obtained during the baseline visit 2 months after the index myocardial infarction. Ejection fraction was determined by an echocardiogram, a nuclear study, or angiography during the initial hospitalization after the myocardial infarction. Patients were categorized as having a history of hypertension if they were ever treated with antihypertensive medications before their index myocardial infarction. A single blood pressure measurement was taken before discharge; however, blood pressure was not monitored throughout the study because hypertension was not the primary scope of the original THROMBO study.

End Point Data
We performed 2 separate analyses examining different sets of end points predefined by the THROMBO protocol. The primary analysis...
end point was defined as nonfatal myocardial infarction (NFMI) or cardiac death, whichever occurred first. The secondary analysis end point was defined as NFMI, cardiac death, or unstable angina, whichever occurred first. The definition of NFMI was the same as the index myocardial infarction, that is, typical symptoms with an elevation of myocardial enzymes supported by ECG findings. Patients were categorized as having unstable angina if they were hospitalized during follow-up with an increase in either frequency or duration of anginal symptoms or with the development of new angina at rest. Both required ischemic ECG changes without enzyme elevation.

### Laboratory Variables

Fasting blood samples were obtained 2 months after hospital discharge from their index acute myocardial infarction. Assays of coagulation-related factors included factor VII, factor VIIa, fibrinogen, von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), and D-Dimer. Lipid and metabolic assays included the measurement of total cholesterol, HDL, triglycerides, apolipoprotein (apo) A1 and apo-B, lipoprotein (a), glucose, and insulin. LDL was calculated by use of the Friedewald formula. High-sensitivity C-reactive protein (hsCRP) and serum amyloid A (SAA) were also measured.

### Table 1. Clinical Characteristics of Postinfarction Patients by History of Hypertension

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>No Hypertension (n=582)</th>
<th>Hypertension (n=461)</th>
<th>P</th>
<th>Adjusted P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics and prior history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>56.8±2</td>
<td>61.7±2</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥60</td>
<td>41</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>81</td>
<td>69</td>
<td>0.001</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82</td>
<td>65</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Black</td>
<td>10</td>
<td>26</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>10</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index, kg/m² (mean±SD)</td>
<td>27.6±0.6</td>
<td>28.6±0.9</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>27</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>17</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke</td>
<td>1</td>
<td>5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Prior angina pectoris†</td>
<td>29</td>
<td>37</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>26</td>
<td>21</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>45</td>
<td>40</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td><strong>Index myocardial infarction (MI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>56</td>
<td>46</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>30</td>
<td>40</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Unknown type</td>
<td>13</td>
<td>14</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Thrombolytic treatment</td>
<td>40</td>
<td>28</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Revascularization after MI</td>
<td>21</td>
<td>17</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Pulmonary congestion</td>
<td>15</td>
<td>25</td>
<td>0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>History of claudication</td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of abdominal aortic aneurysm</td>
<td>1</td>
<td>3</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction≤30%</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114</td>
<td>124</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69</td>
<td>72</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>Medications at enrollment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>29</td>
<td>47</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>86</td>
<td>77</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>19</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>77</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>15</td>
<td>28</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Lipid lowering medications</td>
<td>40</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>31</td>
<td>45</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

All variables are presented as percentages of the group, unless otherwise specified.

*From multivariate logistic regression analysis using hypertension as the dependent variable; only significant (<0.05) P values are shown.

†Angina less than 1 month before acute myocardial infarction.
measured. HsCRP levels were measured with the use of high-sensitivity CRP testing, as defined by Rifai et al.\textsuperscript{11}

**Statistical Analysis**

Baseline clinical characteristics were compared between patients with and without a history of hypertension using a 2-sided \( t \) test for the continuous variables and a \( \chi^2 \) test for the categoric variables. Because of the skewed distribution of several variables, comparisons between the blood values of the 2 groups were performed after logarithmic transformations of the variables. Multivariate logistic regression analysis was performed to identify differences in lipids and hemostatic factors after adjustment for relevant clinical covariates. The concentrations of the hemostatic factors, lipids, and hsCRP levels were recorded in their continuous form and dichotomized into the top versus lower 3 risk quartiles for use in survival analysis. The association between the dichotomized thrombogenic variables and cumulative probability of end points was examined graphically by the Kaplan-Meier method with the log-rank statistic. A Cox proportional-hazards survivorship model (SAS version 8.1 computer program, procedure PHREG) identified factors associated with cardiac events for hypertensive and nonhypertensive patients. Through the use of stepwise selection to identify the clinical variables associated with primary end points, a baseline clinical model was created, with a significance level of \( P < 0.10 \) for entering a variable into the model. After establishing the baseline model, 2 separate analyses were run with selected blood variables. The first analysis examined the predictability each individual blood variable added to the baseline model. The second analysis combined all blood variables to the baseline model, and, using forward selection to keep significant (\( P < 0.05 \)) variables in the model, provided those blood variables that significantly added to the predictability of the baseline model. We determined whether the hazard ratios for the blood variables of interest were equal or unequal across the hypertensive and nonhypertensive groups in all survivorship models. Probability values \(<0.05\) were considered significant.

**Results**

**Clinical Characteristics of Studied Patients**

A comparison of clinical characteristics between 582 nonhypertensive and 461 hypertensive patients is shown in Table 1. Patients after infarction with a history of hypertension were more likely to be older, nonwhite, female, and diabetic, with a higher frequency of prior angina, non-Q-wave myocardial infarction, and pulmonary congestion. The use of thrombolytic therapy during the acute myocardial infarction was significantly lower in those with a history of hypertension (28% versus 40%, \( P = 0.001 \)), and there was a suggestion of lower levels of revascularizations (CABG or PTCA) in the hypertensive group, although this did not achieve significance. Predischarge systolic blood pressures in those with a history of hypertension were on average 10 mm higher than those without a history of hypertension (124 versus 114 mm Hg, \( P < 0.001 \)), whereas hypertensive diastolic blood pressure measurements were only 3 mm higher (72 versus 69 mm Hg, \( P = 0.005 \)).

As expected, patients with hypertension were more frequently treated with ACE inhibitors, calcium channel blockers, and nitrates, but they received aspirin somewhat less frequently.

**Cardiac End Points**

There was no significant difference between nonhypertensive and hypertensive patients after infarction in the risk of cardiac death, primary analysis end points, and secondary analysis end points (Table 2). Figure 1 shows the cumulative probability of primary analysis end points in both groups. Kaplan-Meier curves for the cumulative probability of secondary analysis end points or of cardiac death did not reveal a significant difference in outcomes (not shown).

**Differences in Blood Variables Between Groups**

In comparison to nonhypertensive patients, hypertensive patients after infarction had significantly higher levels of d-dimer, fibrinogen, PAI-1, and vWF (Table 3). Factor VII and Factor VIIa did not show significant differences even after analyzing patients not taking warfarin. Inflammatory markers were significantly higher in hypertensive compared with nonhypertensive patients. Although Table 3 indicates a significantly higher mean triglyceride level in nonhypertensive compared with hypertensive patients, stratifying by race reveals nonsignificant differences in white (2.29 versus 2.40 g/L) and black (1.70 versus 1.74 g/L) patients. These differences are due to the different triglyceride levels between blacks and whites combined with a different proportion of blacks and whites in the hypertensive and nonhypertensive groups, as seen in Table 1.

Among the studied thrombogenic, lipid, and inflammatory blood variables, only d-dimer was independently associated with a history of hypertension (multivariate logistic regression model: OR = 1.38, \( P = 0.05 \)) after adjustment for the following relevant clinical covariates that entered the model at \( P < 0.05 \): age, gender, race, diabetes, pulmonary congestion, and body mass index. Levels of fibrinogen, vWF, PAI-1, hsCRP, and SAA were no longer significant.
Predictors of Outcome in Multivariate Analyses

A multivariate Cox model examining the contribution of individual blood variables to the baseline model that adjusts for age, gender, race, diabetes, pulmonary congestion, and body mass index was performed (Table 4). In patients with a history of hypertension, the only blood factor significantly predicting a greater risk of primary cardiac events is being in the highest quartile (HR: 2.22, P=0.001, g/L) of apo-A1 (HR: 2.8, P=0.005). It is important to emphasize that d-dimer also was significant in predicting primary cardiac events in nonhypertensive patients (HR=2.42, P=0.02).

Figure 2 shows Kaplan-Meier curves illustrating this observation. The risk of cardiac events in patients with d-dimer in the lower 3 quartiles was significantly less than in the highest quartile, but they were not different from each other. Abnormal levels of lipids (elevated apo-B and lowered apo-A1) were predictive for cardiac events in nonhypertensive patients but not hypertensive patients.

Discussion

Thrombogenic variables including fibrinogen, vWF, and d-dimer were higher in hypertensive than nonhypertensive patients after infarction. However, only d-dimer was significantly and independently associated with hypertension. These findings are similar to studies showing elevated levels of fibrinogen and d-dimer being associated with hypertension and end-organ damage.12,13 The association between increased thrombogenic milieu and hypertension might be related to endothelial damage but also could be related to the genetic predisposition of patients to both hypertension and end-organ damage.12,13 The association between increased thrombogenic milieu and hypertension might be related to endothelial damage but also could be related to the genetic predisposition of patients to both hypertension and enhanced thrombosis.14 In our enriched postinfarction population, vWF was higher in hypertensive patients, possibly indicating endothelial damage. However, the association between hypertension and d-dimer (the end product of the clotting and fibrinolysis system) was stronger than that of hypertension with levels of vWF.
Our patients after infarction with and without a history of hypertension had similar long-term outcomes as measured by the risk of fatal and nonfatal cardiac events. This lack of difference in outcome might be related to a significantly greater frequency of treatment with ACE inhibitors (and calcium channel blockers) in hypertensive than nonhypertensive patients. Another possibility might relate to the fact that patients in the THROMBO study were enrolled 2 months after their index myocardial infarction. This exclusion of patients who had cardiac events (nonfatal myocardial infarction or death) as well as patients who underwent revascularization procedures during the first 2 months after the index event contribute to the overall low rate of cardiac events in the studied population. Nevertheless, our study population represents a majority of patients after infarction in everyday practice, and our results seem relevant for currently treated patients.

There are limited data regarding the prognostic value of blood variables for predicting cardiac events in patients after infarction. Two studies have shown that hypertensive survivors of an acute myocardial infarction have significantly higher fibrinogen levels as compared with nonhypertensive survivors. In addition, those in the top quartile of fibrinogen levels have a 2 times greater risk of cardiac death. D-Dimer was found in our study to be similarly predictive for primary cardiac events in both hypertensive and nonhypertensive patients after infarction. This observation indicates that an enhanced thrombogenic activity contributes to cardiac events in both groups of patients.

The significant elevation in fibrinogen levels seen in the hypertensive patients in our study supports those findings seen in previous studies. However, fibrinogen failed to enter our final predictive model. This could be because the levels of fibrinogen in our patients were not as high as in other studies in which there was a significant association with cardiac events. The mean fibrinogen level in our hypertensive patients was 3.64 g/L, whereas the levels seen in studies in which fibrinogen predicted cardiac events was ≈4.42 g/L.

Another postinfarction study investigated the theory that impaired fibrinolysis plays an important role in the risk of infarction. The key factor in fibrinolysis inhibition is PAI-1, a serine protease inhibitor that binds to TPA and renders it inactive. Higher levels of PAI-1 were seen in young survivors (<45 years old) of myocardial infarctions than in control subjects, supporting the deleterious effect of elevated levels of PAI-1 and infarction. A 3-year follow-up of this study reinforced the finding that high PAI-1 levels predicted future cardiac events. In our patients after infarction, PAI-1 was only slightly higher in hypertensive than nonhypertensive patients, and it was not predictive for cardiac events in either group, possibly because of an older patient population with more advanced thrombogenic milieu.

It is worth emphasizing that abnormal levels of lipids (elevated apo-B and lowered apo-A1) were predictive for cardiac events in nonhypertensive but not in hypertensive patients. The lack of predictive value of lipids in hypertensive patients could be related to the significantly higher proportion of patients older than 60 years of age and the respectively lesser importance of lipid abnormalities in the pathogenesis of coronary events in this age group.

Limitations of this study include our classification of having a history of hypertension based on whether or not the patient ever received treatment for elevated blood pressure in the past instead of using serial blood pressure measurements. Because the original study was not focused on hypertension, multiple systematic blood pressure measurements were not recorded. Using a history of treatment for hypertension may overestimate the proportion of those classified as normoten-
sive; however, all demographic data were collected by the physician taking care of the patient, who had accurate records of the patient’s treatment history. Therefore, this study assumes that if a patient required treatment for elevated blood pressure, that patient had a history of hypertension.

An additional limitation is the finding of a lower proportion of hypertensive patients in our postinfarction study group (44%). Because hypertension is a known risk factor for cardiac events, this finding could be the result of a survival effect. Additionally, there may exist the situation whereby a patient may have been hypertensive before enrollment in the study, yet not have been diagnosed. This would lead to more hypertensive subjects being classified as nonhypertensive, resulting in differential misclassification. It is difficult to avoid such selection biases in a retrospective analysis such as this.

In comparison with previous studies that examined the relationship of thrombogenic and lipid factors to hypertension, our study has the advantage of including a large population of patients after myocardial infarction with recurrent cardiac events observed over a mean of 2 years. The atherosclerotic and thrombogenic enrichment of this population might explain the difference in results as compared with previously published studies focusing on hypertensive patients without prior coronary events.

Perspectives

Our cross-sectional analysis of 1045 patients after myocardial infarction demonstrated that elevated D-dimer is significantly associated with hypertension, and, simultaneously, D-dimer remains similarly predictive for cardiac events in hypertensive and nonhypertensive patients. In contrast, elevated apo-B and decreased apo-A1 are predictive in nonhypertensive patients, whereas they do not have predictive value in hypertensive patients. The association of elevated D-dimer with hypertension and the predictive value of D-dimer for cardiac events indicate that enhanced thrombogenic conditions in hypertensive patients after infarction may require some form of anticoagulant therapy. The results of the recent Warfarin, Aspirin, Reinfarction Study (WARIS II)24 imply that our strategy of identifying high-risk patients by using D-dimer could be applied to determine which of those patients would benefit the most from anticoagulant therapy.

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