Presenting Pulse Pressure Predicts Thrombolytic Therapy-Related Intracranial Hemorrhage

Thrombolytic Predictive Instrument (TPI) Project Results

Harry P. Selker, MD, MSPH; Joni R. Beshansky, RN, MPH; Christopher H. Schmid, PhD; John L. Griffith, PhD; W.T. Longstreth, Jr, MD; Christopher M. O’Connor, MD; Louis R. Caplan, MD; E. Wayne Massey, MD; Ralph B. D’Agostino, PhD; Michael M. Laks, MD; Kerry L. Lee, PhD; Charles Maynard, PhD; Galen S. Wagner, MD; W. Douglas Weaver, MD; Robert M. Calif, MD

Background In selecting patients with acute myocardial infarction for thrombolytic therapy, it is important to identify patients who are at high risk for intracranial hemorrhage, for whom thrombolytic therapy is ill advised. We hypothesized that presenting pulse blood pressure, representing the "hammer" effect on cerebral vessels and the effects of age on arterial compliance, might predict thrombolysis-related intracranial hemorrhage better than systolic, diastolic, or mean arterial blood pressures.

Methods and Results Of 3483 Thrombolytic Predictive Instrument (TPI) Project subjects receiving thrombolytic therapy for acute infarction, we identified and obtained detailed clinical data on the 19 with treatment-related intracranial hemorrhages confirmed by computed tomography and on 175 matched controls. Systolic, diastolic, mean arterial, and pulse blood pressures were each significantly related to the occurrence of intracranial hemorrhage, with pulse pressure most highly related. The mean pulse pressure in patients who developed intracranial hemorrhage was 63 mm Hg, 34% higher than the 47 mm Hg mean value for those not developing hemorrhage (P=.0001). Excess pulse pressure, defined as the extent to which a patient’s pulse pressure exceeded 40 mm Hg for systolic blood pressures of at least 120 mm Hg, was even more strongly related: its mean value of 23 mm Hg for patients was 130% higher than its mean value of 10 mm Hg for controls (P<.0001). With logistic regression models to estimate the relative risks (odds ratios) for intracranial hemorrhage conferred by each form of blood pressure, the relative risk for hemorrhage was greatest for excess pulse pressure: for each 10-point pulse pressure excess, the relative risk for intracranial hemorrhage was increased by 1.85 (P=.0002; 95% confidence interval [CI], 1.34 to 2.55) by itself and 1.76 (P=.001; 95% CI, 1.26 to 2.46) when adjusted for age. In this sample, excess pulse pressure by itself predicted hemorrhage as well as systolic pressure and age together. When excess pulse pressure was combined with age to make a logistic regression model predicting intracranial hemorrhage, age contributed less to the prediction than when combined with the other blood pressure forms, even though this model predicted better than any other combination of age and pressure (receiver-operating characteristic curve area, 0.82 versus 0.77 with systolic pressure and age, 0.75 with mean arterial pressure, 0.71 with diastolic pressure, and 0.81 with both systolic and diastolic pressures).

Conclusions We found that excess pulse blood pressure predicted thrombolysis-related intracranial hemorrhage better than other forms of pretreatment blood pressure, perhaps better describing the pathophysiology of intracranial hemorrhage, including the effect of age. These findings will need confirmation in larger studies with comparable clinical detail. (Circulation. 1994;90:1657-1661.)

Key Words • pressure • hemorrhage • thrombolysis • infarction

A major concern in the use of thrombolytic therapy for treatment of acute myocardial infarction is the occurrence of intracranial hemorrhage and its devastating consequences. Because of this fear, many patients who would likely benefit are not treated.1

However, thrombolysis-related intracranial hemorrhage occurs even in seemingly appropriate candidates.2 Thus, although hemorrhagic strokes are uncommon, occurring in approximately 0.5%3-6 of treated patients, the uncertainty in knowing whether a given patient will develop this complication limits the use of this important therapy.

To surmount this problem, studies are needed to inform clinicians of the best predictors of thrombolysis-related intracranial hemorrhage to avoid using thrombolytic therapy on high-risk patients. Because the incidence of thrombolysis-related intracranial hemorrhage is so low and because the predictive power for intracranial hemorrhage of each of the standard variables collected in clinical trials is relatively low, to identify key predictors, it is necessary to pool subjects from multiple clinical trials and extract data beyond those originally collected as part of routine thrombolytic therapy trials.
This is an aim of the Thrombolytic Predictive Instrument (TPI) Project, a collaborative study by investigators from a number of thrombolytic therapy clinical trials.

Methods

TPI Database
The TPI Database is made up of the original data from 12 clinical trials and registries: the Western Washington Intracoronary Streptokinase Trial (250 patients); Western Washington Intravenous Streptokinase Trial (368 patients); Western Washington t-PA Study (160 patients); Myocardial Infarction Triage and Intervention (MITI) Project registry data (533 patients); the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trials (TAMI 1: 368 patients, TAMI 2: 147 patients, TAMI 3: 175 patients, TAMI UK: 102 patients, TAMI 5: 577 patients); the Multicenter Acute Ischemic Heart Disease Predictive Instrument Trial (396 patients); the Boston City Hospital Predictive Instrument Trial (57 patients); and the Duke (Coronary Care Unit) Databank (1773 patients). For this study we used the 3483 patients receiving thrombolytic therapy with inclusion criteria for use of thrombolytic therapy of age of 57 years and systolic blood pressure of ≤190 mm Hg.

Study Subjects and Data Collection
In addition to the originally collected clinical trial data, to get detailed additional information that might provide clues as to the key risk factors for thrombolyisis-related stroke, we performed detailed medical record reviews at 35 hospitals for all thrombolyisis-treated patients with a stroke (59) and for 215 randomly selected control subjects who were selected based on the following rationale. To maximize the statistical power of the analysis of the limited number of stroke patients, control subjects were matched to patients on a 4:1 basis. Because quality of care or other practice differences at different hospitals might relate to the likelihood of thrombolyisis-related stroke, for each stroke patient, four control subjects were randomly selected from the same hospital. When all cases were reviewed by the Stroke Review Committee, a number of patients designated as having a stroke in their original study were found not to have had intracranial hemorrhages and thus were eliminated. For a small number of patients, there were not four control subjects available at the same hospital, resulting in 215 control subjects rather than the projected 236 (4×59). Because fewer than half of the initial cases had confirmed intracranial hemorrhages by the Stroke Review Committee (see “Results”), the final ratio of control subjects to patients was still greater than 4:1.

A specially trained and experienced nurse-reviewer or non-nurse-reviewer retrieved records at each site, including computed tomography (CT), magnetic resonance imaging (MRI), and other key test reports using a data collection form and manual developed to ensure uniform data collection. The form contained items on patient history, including stroke, head trauma, headache, and seizures; initial and subsequent vital signs; laboratory results (eg, protrombin time); blood products given; and medication changes (eg, heparin discontinued) before neurological changes.

Stroke Review Committee
An independent Stroke Review Committee consisting of neurologists with special clinical and research expertise in both stroke and the use of thrombolytic therapy evaluated each case to verify the presence of a stroke and then to classify it as hemorrhagic or nonhemorrhagic, based on a stroke confirmation form developed by the committee before case review.

For each study subject, each Stroke Review Committee member received a copy of the completed case report form and copies of reports from a CT scan, MRI, echocardiogram, and autopsy, as well as medical records containing the initial history and physical examination, neurology consultation, and discharge summary.

Pulse Pressure Definitions
Pulse pressure was calculated as systolic blood pressure minus diastolic blood pressure as determined on initial presentation. Our a priori hypothesis was that elevated pulse pressure would relate to the occurrence of intracranial hemorrhage, and particularly excess pulse pressure defined as the extent to which a patient’s pulse pressure exceeded 40 mm Hg (corresponding to the pulse pressure associated with a “normal” blood pressure of 120/80 mm Hg) for patients with systolic blood pressure of >120 mm Hg. For example, for a blood pressure of 150/100 mm Hg, the pulse pressure of 50 mm Hg would represent an excess pulse pressure of 10 mm Hg. The excess pulse pressure was considered 0 for patients with systolic pressures of <120 mm Hg to avoid counting the wide pulse pressure of hypotension, as in a patient with a blood pressure of 70/0 mm Hg. To create a smooth transition to the full counting of the excess pulse pressure effect for patients with systolic pressures of >120 mm Hg, between systolic pressures of 120 and 125 mm Hg, the excess pulse pressure was multiplied by the factor [(systolic pressure minus 120)/5]. Thus, the excess pulse pressures for the respective systolic blood pressures were multiplied by the following values: for ≤120 mm Hg, 0; for 121 mm Hg, 0.2; for 122 mm Hg, 0.4; for 123 mm Hg, 0.6; for 124 mm Hg, 0.8; and for ≥125 mm Hg, 1.0.

Statistical Analysis
To compare the characteristics of patients with intracranial hemorrhage versus those without, we used two-tailed t tests and χ2 tests with no continuity correction. Logistic regression analyses were used to construct multivariable models using PROC LOGISTIC in SAS, and receiver-operating characteristic (ROC) curve areas were derived from the c-statistic given in the SAS output, which is equivalent to the use of the Wilcoxon statistic. Odds ratios and 95% confidence intervals (CIs) for the model variables were based on the parameter estimates and asymptotic standard errors. P values were based on the asymptotic normal distribution of the Wald statistic (the ratio of the parameter estimate to its standard error).

Results
Patient and Stroke Characteristics
After a thorough search of the 3483 patients who were receiving thrombolytic therapy among the 4911 TPI Project subjects, medical records and CT confirmation were obtained on 58 of 59 thrombolytic therapy-treated subjects designated as having had a stroke in their original study’s database. Of these, 9 were found by review of additional data to not have had a stroke. Of the 49 confirmed strokes, representing 1.4% of thrombolytic-treated patients, 24 were identified as intracranial hemorrhage and 25 as ischemic. Four of the 24 hemorrhages were excluded from our analysis because these patients had suffered some form of previous head injury and probably should not have received thrombolytic therapy; 1 was excluded due to unavailability of the medical record (however, an intracranial hemorrhage was confirmed by the radiology department’s CT scan report). Of the remaining 19 intracranial hemorrhages, 16 (84%) were classified as parenchymal hemorrhages, 2 (11%) as subarachnoid hemorrhages, and 1 (5%) as a subdural hematoma. The data analyzed in this report relate to these 19 intracranial hemorrhages. Of the 215 control subjects, 41 would have not qualified for use of
TABLE 1. Characteristics of Patients With Thrombolysis-Related Intracranial Hemorrhage and Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=19)</th>
<th>Control Subjects (n=175)</th>
<th>P</th>
<th>Absolute Difference</th>
<th>Percent Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±8.2</td>
<td>57±10</td>
<td>.006</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>68</td>
<td>79</td>
<td>.3</td>
<td>−11</td>
<td>−13</td>
</tr>
<tr>
<td>History of hypertension, %</td>
<td>42</td>
<td>35</td>
<td>.5</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>58</td>
<td>6</td>
<td>&lt;.0001</td>
<td>52</td>
<td>914</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>154±26</td>
<td>134±25</td>
<td>.001</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>91±16</td>
<td>87±17</td>
<td>.3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>63±16</td>
<td>47±16</td>
<td>.0001</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Excess pulse pressure, mm Hg</td>
<td>23±16</td>
<td>10±12</td>
<td>&lt;.0001</td>
<td>13</td>
<td>130</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>122±21</td>
<td>110±20</td>
<td>.01</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

The mean age of the patients with intracranial hemorrhage, 64 years, was 7 years greater than the control subjects’ mean age of 57 years (P=.006), whereas the two groups were similar in their being predominantly male (NS) and just more than one third had a history of hypertension (NS) (Table 1). The mortality rate for patients with intracranial hemorrhage was 58% compared with 6% for control subjects (P<.0001).

Blood Pressure and Intracranial Hemorrhage

As shown in Table 1, patients with intracranial hemorrhage had higher initial blood pressure by all measures at hospital presentation (pretreatment and prein- tracranial hemorrhage) than those without hemorrhage. Their mean systolic blood pressure was 20 mm Hg (15%) higher (P=.001), diastolic pressure was 4 mm Hg (5%) higher (P=.3), mean arterial pressure was 12 mm Hg (11%) higher (P=.01), and pulse pressure was 16 mm Hg (34%) higher (P=.0001). Their excess pulse pressure (as defined in “Methods”) was 13 mm Hg (130%) higher (P<.0001) than those without intracranial hemorrhages.

Multivariable logistic regression showed age and blood pressure to be most highly predictive of intracranial hemorrhage. To compare the predictive power of the different measures of blood pressure a priori considered to be potentially important, we tested the blood pressure variables and age in a series of logistic regressions, the final one of which is in Table 2 and is illustrated in the Figure. In these models, age has a linear effect, truncated at age 35 (only 2 study subjects were less than age 35).

By itself, increasing age had a strong correlation with an increased risk of thrombolysis-related intracranial hemorrhage. In a logistic regression using age as its only variable, a 10-year increase in age corresponds to an increased odds ratio for intracranial hemorrhage of 2.08 (P=.008). This age effect did not diminish when taking into account systolic, diastolic, or mean arterial blood pressure as an added variable in the logistic regression [odds ratios for age, respectively, in combination with each of these three variables in two-variable logistic regressions, 2.15 (P=.008), 2.27 (P=.005), and 2.25 (P=.005)]. However, when excess pulse pressure is taken into account as a variable in a two-variable model or indirectly by including a variable each for systolic and diastolic pressures in a three-variable model, the effect of age is weaker and the odds ratio for a 10-year age increase drops below 2.0 [respectively, 1.84 (P=.03) and 1.90 (P=.03)].

Nevertheless, both these models predict intracranial hemorrhage better than the others, as demonstrated by their respective ROC curve areas of 0.82 and 0.81, reflecting excellent predictive performance. The former, which is more attractive because of its form and slightly better performance, is in Table 2. By comparison, the ROC areas for the other models with age and blood pressure ranged from 0.71 to 0.77. The model with excess pulse pressure, which predicts best, shows that adjusted for age, the odds ratio associated with a 10 mm Hg increase in excess pulse pressure is 1.76 (95% CI, 1.26 to 2.46). The decreased importance of age in this model indicates that excess pulse pressure indeed explains part of the effect of age. In fact, by itself in a one-variable logistic regression, excess pulse pressure provides a model with an ROC area of 0.77, ie, predicting intracranial hemorrhage, as well or better than any other single measure of blood pressure in combination with age. In this model, by itself, a 10 mm Hg increase in

TABLE 2. Logistic Regression Model Predicting Thrombolysis-Related Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Estimate</th>
<th>95% CI*</th>
<th>Odds Ratio for 10-year Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.0621</td>
<td>1.06</td>
<td>1.01–1.12</td>
<td>1.84</td>
</tr>
<tr>
<td>Excess pulse pressure†</td>
<td>.0551</td>
<td>1.06</td>
<td>1.02–1.09</td>
<td>1.76</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.†Systolic blood pressure minus diastolic blood pressure.
excess pulse pressure confers an increased relative risk for stroke of 1.85 (95% CI, 1.34 to 2.55).

Discussion

Thrombolytic therapy is potentially life saving for patients with acute myocardial infarction but should be avoided in those at high risk for thrombolysis-related intracranial hemorrhage. Therefore, it is important for clinicians to be able to accurately estimate a patient’s risk for thrombolysis-related intracranial hemorrhage, to discern for whom thrombolytic therapy might be ill advised.1

The relatively rare occurrence of thrombolytic therapy-related intracranial hemorrhage and the resultant paucity of detailed information about study subjects with this complication have hampered identification of predictors that would provide the clinician and patient with an accurate estimate of risk. To date, the factors found to be associated with thrombolysis-related intracranial hemorrhage include increasing age over 65 years, female gender, history of diabetes mellitus, history of prior stroke, prior ongoing oral anticoagulant use, tissue-type plasminogen activator dose of 150 mg, body weight of less than 70 kg, and hypertension at admission.2,6,10-14 The incidence of thrombolysis-related intracranial hemorrhage in the TPI Database was 0.7%, representing half of the total stroke incidence of 1.4%, which is consistent with other large studies.3-6,11,12 The remaining half of the strokes were ischemic, a recognized complication of myocardial infarction. This study did not address the issue of thrombolysis increasing or decreasing the frequency of brain infarction. Its univariate and multivariable analyses did confirm the findings of other studies10,11,14 that increasing age and blood pressure were most strongly predictive of thrombolysis-related intracranial hemorrhage.

Given that age and systolic blood pressure have been the most consistently found risk factors for thrombolysis-related intracranial hemorrhage, we hypothesized that pulse blood pressure would be a particularly important risk factor, representing the effect of age in reducing arterial wall compliance and the pressure “hammer” on cerebral vessels, under the circumstances of thrombolysis-enhanced risk of bleeding. Furthermore, we hypothesized that excess pulse pressure, the extent to which pulse pressure exceeds the “normal” 40 mm Hg for blood pressure of >120 mm Hg, would be particularly important. Indeed, of the physiological measures of blood pressure, pulse pressure, especially excess pulse pressure, was most strongly related to the development of a thrombolysis-related intracranial hemorrhage; compared with control subjects, patients with hemorrhages had a mean pulse pressure that was 34% higher and a mean excess pulse pressure that was 130% higher (Table 1).

Multivariable logistic regression models predicting thrombolysis-related intracranial hemorrhage confirmed the predictive superiority of excess pulse pressure over the other measures of blood pressures. A 10 mm Hg increase in excess pulse pressure conferred an increased relative risk for hemorrhage of 1.85 (P = .0002; 95% CI, 1.34 to 2.55); thus, the 13 mm Hg greater mean excess pulse pressure among patients compared with control subjects represents a 2.3-fold greater risk of intracranial hemorrhage. When both systolic and diastolic blood pressures were included in the model, the ROC area was 0.81, quite close to the value for excess pulse pressure. It is likely that the exact shape of the relation among systolic and diastolic blood pressure and stroke can be refitted in larger data sets, but these data demonstrate that both systolic and diastolic blood pressures and the relationship between the two must be considered to make the best prediction of risk.

The multivariable models also confirmed that excess pulse pressure captures some of the risk for stroke related to advancing age. Excess pulse pressure by itself predicted intracranial hemorrhage as well as systolic pressure and age together when systolic pressure was combined with age to make a predictive model. Moreover, in combination with excess pulse pressure, age contributed less to prediction than when combined with any other blood pressure form, despite the fact that this model predicted intracranial hemorrhage better (with an ROC area of 0.82, reflecting excellent performance) than any other combination of age and blood pressure. These results, illustrated in the Figure, support the hypothesis that the excess pulse pressure reflects the propensity to intracranial hemorrhage due to the combined pathophysiologic effects of age, increased blood pressure, and reduced arterial compliance.

A limitation of this study is its reliance on a relatively small number of cases. From a thorough search of study and medical record data on the 3483 patients receiving thrombolytic therapy in the TPI Database, we were able to definitively confirm intracranial hemorrhage in 24 patients (and ischemic stroke in 25 patients). This study’s overall 1.4% incidence of stroke among thrombolysis-treated patients, including the 0.7% incidence of intracranial hemorrhages studied in detail, are consistent with the findings of others.11,14 Indeed, although the number of intracranial hemorrhages in this study is relatively small, it is among the largest groups of thrombolytic therapy-related intracranial hemorrhages reported and, we believe, the largest group reported with the uniform degree of clinical confirmation described herein. Nevertheless, this study’s results need confirmation by other and larger studies. Moreover, larger studies should allow study of differences in stroke rates related to the use of specific agents. If the importance of pulse pressure is so confirmed, it would deserve consid-
eration in pathophysiological models of intracranial hemorrhage.

Intracranial hemorrhage related to thrombolytic therapy can be devastating, as demonstrated by a hospital mortality rate of 58%, nearly 10 times that of matched control subjects. Therefore, the ability to more accurately predict the occurrence of this complication, to make more informed trade-offs in real-time clinical practice, is potentially valuable. For this purpose, excess pulse blood pressure, particularly its combination with age, as represented by our predictive model, holds promise. Indeed, the predictive performance of this simple model has potential use in the clinical setting.7

Acknowledgments

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