Hypertension as a Risk Factor for Spontaneous Intracerebral Hemorrhage

THOMAS BROTT, M.D., KAREN THALINGER, M.D. AND VICKI HERTZBERG, PH.D.

SUMMARY To better define the etiologic importance of hypertension for spontaneous intracerebral hemorrhage, hospital records were studied for all patients sustaining intracerebral hemorrhage during 1982 in the Cincinnati metropolitan area. Hypertension pre-dating the hemorrhage was present in 45% (69 of 154), as determined by history. A more inclusive definition of hypertension, combining those with a positive history with those found to have left ventricular hypertrophy by electrocardiogram or cardiomegaly by chest radiography, applied in 56% (87 of 154). The cases were compared to controls with and without hypertension derived from the NHANES II study of blood pressure (n = 16,204) to determine relative risk. For the presence of hypertension by history, the relative risk of intracerebral hemorrhage was 3.9 (95% confidence interval, 2.7 to 5.7). For the inclusive definition of hypertension, the relative risk was 5.4 (3.7 to 7.9). Relative risk was also determined for hypertension in blacks (= 4.4), age > 70 (= 7), prior cerebral infarction ( = 22), and diabetes ( = 3).

We conclude that the term "hypertensive hemorrhage" should be used very selectively, particularly in whites, and propose that hypertension be viewed as one of several important risk factors for spontaneous intracerebral hemorrhage.

THE TERM HYPERTENSIVE INTRACEREBRAL HEMORRHAGE is firmly imbedded in the medical literature.""3 When the characteristic high density lesion is seen in the computed tomographic scan (CT) critical differential diagnosis in the setting of acute stroke is too often truncated. Hypertension is quickly assumed to be causal, if present on the admission exam or if detected by history.

We have been impressed at the bedside that an adequate history of hypertension is often lacking in patients with spontaneous intracerebral hemorrhage. When an adequate history for hypertension is established, other disorders of potential etiologic importance may be identified but are seldom given serious consideration. In prior studies of intracerebral hemorrhage, the blood pressure measurements (BP) were often those obtained during the acute event,""5 or they were not provided.6 Potential risk factors such as prior cerebral infarction or diabetes mellitus, were infrequently documented.7 In 2 large studies of intracerebral hemorrhage in which criteria for the definition of hypertension were carefully specified, the results differed sharply regarding the importance of hypertension in pathogenesis,8,9

A prospective epidemiologic study of intracerebral hemorrhage and potential risk factors is impractical. A ten-year study would require follow-up of approximately one million subjects to obtain 100 or more index cases. A longer study would require fewer subjects but would overlap too many changes in diagnosis and therapy. Therefore, we conducted a retrospective study of spontaneous intracerebral hemorrhage in a very large heterogeneous population to define more clearly the relative importance of hypertension and other selected stroke risk factors in the pathogenesis of this condition.

Methods

Patients

The medical records of all adults with the diagnosis of spontaneous intracerebral hemorrhage were reviewed for the year 1982 in the Cincinnati, Ohio metropolitan area (1.4 million). The records were obtained from the area's 16 general hospitals by the medical record technicians; records with the ICD-9 CM codes of 431 and 432.9 were retrieved while records with other codes were excluded (e.g. code 430 — subarachnoid hemorrhage). Each record was then reviewed by a board certified neurologist, and 58 clinical variables were defined for each patient (e.g. age, sex, race, coexistent diseases, medications, etc.). Intracerebral hemorrhage (ICH) was recorded only when confirmed by CT scan. Patients with clinically diagnosed trauma, aneurysmal subarachnoid hemorrhage, or hemorrhagic infarction were excluded, as were patients under the age of 20. Patients who were without the clinical diagnosis of subarachnoid hemorrhage but who had sudden headache and blood limited to the subarachnoid space by CT were excluded.

Hypertension was recorded if the pre-hemorrhage blood pressure (BP) was documented to be >140 mm Hg systolic or >90 mm Hg diastolic, if the patient was previously hypertensive in the physician notes, or if the patient was taking anti-hypertensive...
medications (these criteria were designed to be relatively inclusive). Left ventricular hypertrophy (LVH) was recorded when documented in the electrocardiogram (EKG) report. Cardiomegaly was recorded when reported in the chest radiograph consultation.

When documented in the medical record, the following were recorded: prior cerebral infarction, prior ICH, diabetes mellitus, prior myocardial infarction, prior congestive heart failure, chronic obstructive pulmonary disease, blood dyscrasias, and prior and ongoing use of anti-coagulants. Sufficient documentation of aspirin use was not consistently present in the records.

Emergency room records as well as the physician history notes were inspected to ascertain symptoms, signs, and outcome. Location of the hemorrhage was estimated from the CT scan reports and autopsy results. Location was subdivided into 7 categories: lobar, putaminal, thalamoganglionic, intraventricular only, thalamic, pontine, and cerebellar.

Symptoms upon admission included the following: change in mental status (82 per cent), headache (63 per cent), vomiting (22 per cent), and seizures (14 per cent). Common signs were coma (36 per cent), lethargy or confusion (36 per cent), hemiparesis (29 per cent), hemiplegia (25 per cent), quadriplegia (23 per cent), and eye deviation (13 per cent). Overall mortality was 49 per cent.

Controls

The National Health and Nutrition Examination Survey (NHANES) of 17,854 Americans during the years 1971-1974 was used to obtain samples of Americans age 45-74 without hypertension (n = 4123) and with hypertension (n = 2224), where hypertension was defined as a single BP determination of systolic BP >= 160 mm Hg or diastolic BP >= 95 mm Hg. Similar samples were derived for blacks using the decade-by-decade prevalence rates for hypertension determined by history, hypertension and/or LVH and/or cardiomegaly. Sufficient documentation of aspirin use was not consistently present in the records.

Prevalence figures for other diseases were used to derive samples of adults with and without prior cerebral infarction, samples with and without diabetes, and samples with and without coronary artery disease.

Analysis

The samples obtained were used for calculation of relative risk point estimates and the associated 95 per cent logit confidence intervals. For example, the relative risk of hypertension for intracerebral hemorrhage was calculated as follows:

\[
\text{Relative risk} = \frac{\# \text{ cases with hypertension}}{\# \text{ cases without hypertension}} \times \frac{\# \text{ controls without hypertension}}{\# \text{ controls with hypertension}}
\]

In addition, the Mantel-Haenszel procedure for stratified data was applied to investigate the relationship between intracerebral hemorrhage and hypertension while controlling for age. Attributable risk was calculated for hypertension determined by history, hypertension and/or LVH, and cardiomegaly, prior cerebral infarction, diabetes, and coronary artery disease. It was not possible to employ multiple logistic regression analysis since a multivariate breakdown of many of the potential risk factors such as diabetes or prior cerebral infarction is not available. Incidence rates with and without age adjustment were determined.

Results

Intracerebral Hemorrhage and Hypertension

In the year 1982, 154 patients from the Greater Cincinnati area population of 1.4 million presented with spontaneous intracerebral hemorrhage. By race and sex, the incidence rate was 17.5 per 100,000 for blacks, 13.5 for whites, 15.1 for all females, and 12.6 for all males. Hypertension pre-dating the hemorrhage was present in 69 patients (45 per cent). Pre-hemorrhage hypertension could also have been present in the 18 additional patients (12 per cent) who had cardiomegaly by chest radiograph or left ventricular hypertrophy by EKG but who had no history of hypertension (table 1). No suggestion of hypertension by history, EKG, or chest radiograph criteria could be found in 67 of the 154 patients with hemorrhage (44 per cent).

Upon admission for the hemorrhage, 24 of these patients without evidence of pre-morbid hypertension had either systolic pressure > 160 mm Hg or diastolic > 90 mm Hg (16 per cent). These were added to the hypertension-HVH-cardiomegaly group, hypertension pre-dating hemorrhage would be overcounted as involving 111 of 154 (72 per cent). Twenty-nine of the 69 patients with a history of hypertension had a systolic BP > 160 mm Hg and/or a diastolic BP > 90 mm Hg upon admission.

Whites were less often hypertensive by history than blacks: 52 of 131 (40 per cent) vs. 17 of 23 (74 per cent) p < 0.003. Whites were also less often hypertensive by inclusive criteria (history + LVH + cardiomegaly): 68 of 131 (52 per cent) vs. 19 of 23 (83 per cent), p < 0.006.

The relative risk of hypertension for intracerebral hemorrhage was 3.9 (95 per cent confidence interval, 2.7 to 5.7) indicating that adults age 45 to 74 with hypertension have 3.9 times the risk for hemorrhage
compared to those without hypertension. For the presence of hypertension by history and/or LVH and/or cardiomegaly, the relative risk was 5.4 (3.7 to 7.9). For blacks with a history of hypertension, the relative risk was 13.3 (3.0 to 58.5). Using the earlier 1971-1974 population data for hypertension prevalence figures (i.e., NHANES I instead of NHANES II), the relative risk of hypertension for intracerebral hemorrhage was 2.0 (1.9 to 4.0).

The attributable risk of hypertension for intracerebral hemorrhage indicates that proportion by which spontaneous intracerebral hemorrhage could be decreased, if hypertension were eliminated from the population. In Cincinnati, the attributable risk of hypertension by history was 0.49 (0.36 to 0.59). In other words, eliminating hypertension from the population, using an inclusive definition of hypertension, would decrease the incidence of intracerebral hemorrhage by 49%.

The presence of hypertension did not reliably predict location of the hemorrhage (table 2). Twenty-four of 51 patients with deep hemispheric lesions had hypertension by history (47 per cent) while 30 of 73 with lobar lesions had hypertension by history (41 per cent). Eleven of the 16 patients with pontine or cerebellar lesions had hypertension by history (69 per cent).

Fifty-five of the hemorrhage cases were without known cause (36 per cent); mortality in this group was 53 per cent (vs. 49 per cent for all 154 cases).

**Other Conditions Associated with Intracerebral Hemorrhage**

Other potentially important conditions associated with the hemorrhage are listed in table 3. The coexistence of hypertension by history is also noted. Of the 154 patients with intracerebral hemorrhage, 91 (59 per cent) had at least one of these conditions. Only 39 of the 154 patients had a history of hypertension while having none of these conditions (25 per cent); 49 had a history of hypertension or LVH or cardiomegaly while having none of these conditions (32 per cent).

The relative risk conferred by each of these associated conditions for intracerebral hemorrhage was determined where possible and is listed in table 4. Prior stroke was the disorder most strongly associated with subsequent intracerebral hemorrhage (relative risk of 22). The relative risk of anti-coagulant therapy could not be determined as adequate prevalence data are not available for its use.

Advancing age positively correlated with increasing incidence of hemorrhage (fig 1). Incidence roughly doubled with each advancing decade until age ≥80, after which the incidence became 25 times greater than that of the total population and 7 times greater than that of the preceding decade. Using the 1980 U.S. Census and our data, we calculated a relative risk of 7 for adults older than age 70 compared to those 70 and younger.

**Discussion**

This study of a very large and representative population indicates an association of hypertension to spontaneous intracerebral hemorrhage that is weaker and less specific than implied by the term "hypertensive hemor-

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**Table 1** Intracerebral Hemorrhage and Hypertension, by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>2* 8 12 29 31 42 30 154*</td>
</tr>
<tr>
<td>30-39</td>
<td>1 2 4 14 20 21 7 69 (45)</td>
</tr>
<tr>
<td>40-49</td>
<td>1 2 5 15 20 28 16 87 (56)</td>
</tr>
<tr>
<td>50-59</td>
<td>1 3 4 16 20 25 12 81 (53)</td>
</tr>
</tbody>
</table>

*The sum for each column does not equal the number of cases per decade as the rows are not mutually exclusive; in addition, 43 patients did not fall into any of the above hypertension categories.

†LVH = left ventricular hypertrophy by electrocardiographic criteria.

‡CMEG = cardiomegaly by chest radiographic criteria.

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**Table 2** Intracerebral Hemorrhage Location and Hypertension*

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of cases</th>
<th>No. with coexistent hypertension (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar</td>
<td>73</td>
<td>30 (41)</td>
</tr>
<tr>
<td>Putamenal</td>
<td>36</td>
<td>19 (52)</td>
</tr>
<tr>
<td>Thalamoganglionic</td>
<td>14</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Intraventricular only</td>
<td>14</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>11</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Pontine</td>
<td>5</td>
<td>3 (60)</td>
</tr>
<tr>
<td>Thalamic only</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>69 (45)</td>
</tr>
</tbody>
</table>

*As defined by history.
rhage." Recognizing the limitations of the medical records, we made every effort to avoid undercounting hypertension in the hemorrhage group, and included those patients on diuretics as well as other drugs commonly but not exclusively used for blood pressure control. We created a separate, inclusive category of hypertension, possibly over-counting hypertension by adding patients with LVH by EKG, or cardiomegaly by chest radiograph. Nonetheless, the relative risk of hypertension (3.9) and that for the inclusive definition for hypertension (5.4) do not approach the relative risk of smoking for lung cancer death (20 to 30). The Cincinnati attributable risk data indicate that elimination of smoking for lung cancer death (10) or that of heavy hypertension (5.4) do not approach the relative risk of hypertension (3.9) and that for the inclusive definition for hypertension (5.4) do not approach the relative risk of smoking for lung cancer death (10) or that of heavy smoking for lung cancer death (20 to 30). The Cincinnati attributable risk data indicate that elimination of hypertension from the population would eventually result in reduction of intracerebral hemorrhage by 40 to 50 per cent, indicating 50 per cent or more of the cases of spontaneous intracerebral hemorrhage may be unrelated to hypertension.

We propose that the term "hypertensive hemorrhage" be used very selectively, and propose that hypertension be viewed as an important risk factor for spontaneous intracerebral hemorrhage.

These results differ from the recently published epidemiologic study of Furlan, Whisnant and Elveback in which 89 per cent of cases involved prehemorrhage hypertension. However, they studied the years 1945-1976 and noted a decrease in both the frequency and severity of pre-morbid hypertension in the later years of the study. They also noted that elderly victims of hemorrhage were less often hypertensive than younger patients. The population studied was overwhelmingly white and not representative of the United States. Diagnostic criteria were unavoidably biased toward detection of primarily massive hemorrhages as only 4 of the 142 case were diagnosed by CT scan; their group mortality was 92 per cent compared with the Cincinnati mortality of 49 per cent. Other studies have shown a frequency of hypertension ranging from 59 per cent to 90 per cent. These studies were not population based, usually did not explicitly detail criteria for determining the presence or absence of hypertension, and did not explicitly distinguish preadmission hypertension from admission hypertension. Admission hypertension most likely reflects altered hemodynamics due to the intracerebral mass effect and/or acute changes in catecholamines. McCormick and Rosenfield defined pre-ictal blood pressures in their post mortem series of 144 intracerebral hemorrhages (20 patients with ruptured aneurysms included), and also considered those with heart weights ≥400 gms as hypertensive. Nonetheless, only 58 patients were hypertensive (40 per cent) and 21 of these patients had other causes for the

**Table 3** Spontaneous Intracerebral Hemorrhages: Causes and Associated Conditions

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>No. of cases (%)</th>
<th>No. with coexistent hypertension†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>21 (14)</td>
<td>11</td>
</tr>
<tr>
<td>Prior cerebral infarction, not on anti-coagulant</td>
<td>21 (14)</td>
<td>8</td>
</tr>
<tr>
<td>Coronary artery disease not on anti-coagulant</td>
<td>17 (11)</td>
<td>7</td>
</tr>
<tr>
<td>Anti-coagulant</td>
<td>13 (8)</td>
<td>9</td>
</tr>
<tr>
<td>Cerebral metastasis</td>
<td>7 (4)</td>
<td>2</td>
</tr>
<tr>
<td>Prior cerebral hemorrhage</td>
<td>5 (4)</td>
<td>1</td>
</tr>
<tr>
<td>Primary cerebral neoplasm</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>91 (59)</td>
<td>38</td>
</tr>
</tbody>
</table>

*The categories are not mutually exclusive.
†As defined by history.

**Table 4** Selected Risk Factors for Spontaneous Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Relative risk</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid hypertension</td>
<td>3.9</td>
<td>2.7, 5.7</td>
</tr>
<tr>
<td>Premorbid hypertension and/or LVH*</td>
<td>5.4</td>
<td>3.7, 7.9</td>
</tr>
<tr>
<td>and/or CMEG†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cerebral infarction, not on anti-coagulant</td>
<td>21.9</td>
<td>13.7, 34.8</td>
</tr>
<tr>
<td>Prior cerebral infarction on anti-coagulant</td>
<td>25.4</td>
<td>16.6, 38.7</td>
</tr>
<tr>
<td>Coronary artery disease not on anti-coagulant</td>
<td>8.2</td>
<td>5.2, 12.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.9</td>
<td>1.7, 4.9</td>
</tr>
</tbody>
</table>

*LVH = left ventricular hypertrophy by electrocardiographic criteria.
†CMEG = cardiomegaly by chest radiographic criteria.

FIGURE 1. Incidence of spontaneous intracerebral hemorrhage by age. The number of cases for each decade are provided in table 1. The incidence for those age 80 or older is 25 times higher than that for the total population.
hemorrhage, resulting in hypertension as being causal in only 37 of 144 (26 per cent). 

Advancing age may be as important as hypertension in regard to the risk of spontaneous intracerebral hemorrhage. The Cincinnati data reveal a consistent decade to decade rise in hemorrhage incidence (fig. 1). Those older than 70 had 7 times the risk of those 70 and under. Those age 80 and older had 25 times the risk of the total population. These age risks could not be explained by co-existent hypertension, diabetes, coronary artery disease, or prior cerebral infarction. The Rochester population study also showed a rising incidence of hemorrhage with age; 12 per cent of the hemorrhages occurring in the 1945–1960 period involved patients aged 75 and older while 37 per cent of those occurring in the 1961–1976 period involved that elderly group. 

Additional risk factors for intracerebral hemorrhage were prior cerebral infarction (relative risk = 22), diabetes (relative risk = 3), coronary artery disease (relative risk = 18), and anticoagulants. The relationships of these disorders to hemorrhage has been noted previously. 

In the Rochester population study, 13 per cent of patients had a history of prior stroke, 11 per cent had prior TIA, 34 per cent had a prior clinical myocardial infarction, and 23 per cent were on anticoagulants. We agree with the authors' conclusion that the primary vascular abnormality in intracerebral hemorrhage must relate to the interplay of at least several variables in addition to hypertension.

Blacks had a significantly higher incidence of intracerebral hemorrhage than whites, being 17.5 per 100,000 versus 13.5. However, the blacks were younger (mean age 58 versus 67 for whites) and were more often hypertensive (74 per cent versus 40 per cent). The risk of ICH for hypertensive blacks was 4.4 times that for normotensive blacks. The implications of these racial differences are unclear. Gorelick, et al, have recently noted more diffuse and severe intracranial arterial disease among blacks compared to whites, in a study of arteriograms done for cerebral symptoms. 

The pathophysiology of intracerebral hemorrhage might differ in the younger, more often hypertensive blacks when compared to whites. Our data did not reveal significant racial differences in mortality or other potential risk factors.

The pathologic anatomy of the vascular defects underlying intracerebral hemorrhage continue to be elusive and controversial. Micro-aneurysms, fibrinoid arteritis, and plasmatic arterionecrosis have been described. Further pathologic studies have documented the increasing incidence of cerebral amyloid angiopathy with age and its etiologic importance within the framework of an aging population and better long term management of hypertension. In one large pathologic series where 54 specimens were adequate for analysis, the etiology was more often amyloid angiopathy (n = 6) than hypertensive vasculopathy (n = 4); however, a specific anatomic etiology could be found in only 26 per cent of the specimens. In our series, the hemorrhages in the elderly were not more likely to be superficially located, as might be expected with amyloid angiopathy. 

This study has several unavoidable limitations. Ascertainment of cases was imperfect, though superior to ascertainment in the pre-CT era when smaller hemorrhages were difficult to detect (whether deep or lobar). The threshold for the performance of brain CT was and is probably low enough so as not to result in the inadvertent exclusion of rapidly moribund patients with large hemorrhages nor of alert patients with subtle focal deficits resulting from small hemorrhages.

The medical records were often incomplete with respect to past medical history and to medication history. Details of the history in relation to hypertension were rarely provided. An undetermined number of truly hypertensive patients were likely not identified as such and might not have had LVH or cardiomegaly by chest radiograph. In the NHANES II study, 40 per cent of the adults ages 25–74 found to be hypertensive had not been previously diagnosed as hypertensive by a physician; however, we would expect the percentage of undiagnosed hypertension to be lower for our population of patients with intracerebral hemorrhage as these patients were older (mean age 66) and so more likely to have encountered physician assessment on a recurring basis. In addition, our determination of relative risk excluded in the control group those patients taking anti-hypertensive medication who were not measured to be hypertensive (34% of those taking anti-hypertensive medication), and this exclusion increased the estimated relative risk of hypertension for intracerebral hemorrhage. The other epidemiologic surveys and estimates used for risk factor calculation, though the best available, were not current or had significant methodologic weaknesses. As a result, one or more of the associated conditions could have been underestimated in our population, and perhaps overestimated in the control surveys (relative to true 1985 prevalence). 

The CT scan reports were often difficult to interpret, particularly with respect to location: the 14 cases of intraventricular-only hemorrhage suggest that some cases of aneurysmal hemorrhage were unintentionally included; the lobar location may have been overestimated; and we may not have been able to accurately exclude hemorrhagic infarction. The large number of lobar hemorrhages could have biased the study against the etiologic importance hypertension. Premorbid hypertension was more common in patients with intracerebral hemorrhage located in areas thought typical for "hypertensive" hemorrhage (i.e. thalamus, putamen, pons, and cerebellum), compared to patients with lobar intracerebral hemorrhage: 35 of 67 patients with classic locations were hypertensive while 30 of 73 patients with lobar hemorrhage were hypertensive. This difference was not statistically significant, however.

These sources of potential error are unlikely to have altered the risk estimates sufficiently to negate the major conclusions presented. The pathogenesis of spontaneous intracerebral hemorrhage is likely heterogeneous and complex. The relative importance of hypertension...
compared to age and other markers of vascular disease remains to be defined. In studies of intracerebral hemorrhage and other forms of stroke, care must be exercised regarding variables common in the unaf-

Acknowledgments

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