The Relation of Blood Pressure to Stroke Prognosis

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The relation between blood pressure before stroke and survival after the event, was examined in the Manitoba study cohort of 3983 men. The last recorded blood pressure before the first stroke and the change in blood pressure from a measurement 5 years earlier were used. Increasing magnitude of systolic blood pressure and its 5-year changes were associated with worsening prognosis. The same association was less apparent for diastolic blood pressure and was not found for 5-year change in diastolic pressure. After adjusting for the effect of age at stroke and previous evidence of ischemic heart disease in multivariate analysis, systolic blood pressure and its 5-year change were each significant predictors of short-term (30 days) mortality. Considering all these factors as well as diastolic blood pressure, systolic blood pressure was the best predictor of short-term mortality. Thus, high blood pressure and large positive 5-year change in systolic blood pressure before stroke occurrence are significant predictors of a poor prognosis.

“In acute disease it is not quite safe to prognosticate death or recovery.”

Hippocrates

Methods

The details of this study have been reported previously (12-15). In summary, the cohort consists of 3983 healthy men who were found fit for pilot training in World War II. After release from the service some continued to fly, but the majority found different occupations and are in all strata of society. From 1946 to 1948, contact was re-established with the postwar survivors, and on 1 July 1948 the population was sealed. The mean age at entry was 30.8 years. Medical information and examinations provided evidence that they were without clinical manifestations of cerebrovascular disease at entry. Since then, they have been followed by annual mail contact and periodic medical examination of at first 5 and later 3 years. Annual contact has been lost with only one person.

CASE SELECTION

The criteria used for the diagnosis of cerebrovascular disease (see appendix) are similar to those used by the coronary drug project (16), because this cohort is not a community-based one wherein all stroke patients might undergo a standard investigation. For the present analysis, only cases of stroke were considered and not cases with only intermittent cerebral ischemic attacks. Each of the 52 stroke cases that occurred during the 26-year observation period (15) fulfilled the criteria for inclusion in this analysis, namely: [1] at least two blood-pressure measurements before the first stroke, one closest to and within 5 years of the stroke and a second, 5 years (no less than 3 or more than 7 years) earlier; and [2] at least 1 year of follow-up. A 5-year interval between blood pressures was selected, because longer intervals have a weaker association with the incidence of cerebrovascular disease (14). The mean age at the stroke was 56.3 ± 1.4 years (± 1 SEM). The first blood-pressure measurement was 1.3 ± 0.2 years before the stroke and the second was 5.0 ± 0.1 years before the first.

Men for whom antihypertensive medications had been prescribed were included in the analysis because [1] they comprised less than one third (15/52) of the group; [2] compliance with long-term medications is often poor especially in middle-aged men; and [3] their compliance was not assessed. Information about those prescribed such therapy is provided when relevant.

The distribution of stroke cases according to the period in which they occurred is as follows: 1 July 1948 to 30 June 1954, four cases; 1954 to 1959, two cases; 1959 to 1964, 12 cases; 1964 to 1969, 13 cases; and 1969 to 1974, 21 cases.

Reports from physicians, hospitals, death certificates, relatives, or executors of the estate, and whenever possible, autopsy, comprise the data used to ascertain the cause of death. A death was said to be due to stroke if it occurred shortly after the event. There were 23 deaths within 5 years of the first stroke and of these 20 were due to or attributable to stroke, one to ischemic heart disease, one to dissecting hematoma of aorta, and one uncertain case. Of the 20 stroke deaths, nine had autopsies; six of these had cerebral hemorrhage and three had cerebral infarction.

Data Analysis

The life-table method of Cutler and Ederer (17) was used because it has several advantages, including the calculation of

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"lost to follow-up," which incorporate cases of death not due to cerebrovascular disease. Thus, the survival rate that would pertain if stroke were the only cause of deaths can be calculated. Several variables were assessed for their ability to differentiate subgroups with differing survival. These were age, systolic and diastolic blood pressure, 5-year blood pressure change, and ischemic heart disease. The criteria for and the 26-year incidence of ischemic heart disease have been presented in detail previously (12).

Because of the interrelation of these variables and the need to examine the influence of blood pressure after adjusting for the other variables, multivariate statistical methods were used. The multiple logistic function model was selected because it has become widely used in cardiovascular epidemiology and, as pointed out by others (18), its results are similar to the multiple linear regression model but it has the advantage of yielding estimates of risk that can be interpreted as probabilities.

The parameters of the logistic function were estimated using the discriminant method (19). Because of differences in the range of values for each variable, a direct comparison of the logistic function coefficients is not appropriate to ascertain their relative predictive strength. Thus, each variable was standardized by its respective population standard deviation: standardized coefficients (logistic function coefficient times population standard deviation) (15). To ascertain the predictive strength of blood pressure, the "standardized relative risk" was calculated (20). It is the approximate relative risk corresponding to a change in blood pressure by an amount equal to the population standard deviation.

Because varying lengths of follow-up after stroke are a potential source of bias in the survivorship analysis (21), all persons under observation in a specific time period were examined. Short-term survival was defined as death occurring within 1 month after stroke, in order to be consistent with other studies (1, 4, 5). The smaller number of later deaths precluded meaningful analysis of long-term prognosis as a separate group. Deaths within 30 days were, with one exception, a result of the stroke.

Results

The survival curves for men classified according to their age at stroke are shown in Figure 1, left. The well-recognized association of worsening survival with increasing age was evident. Considering the blood pressure closest to the stroke shows that the highest value of systolic blood pressure was associated with the lowest curve of survival (Figure 1, center). Decreasing blood pressure levels were associated with progressively better survival. The same association of decreasing survival with increasing blood pressure levels was seen for diastolic pressure (Figure 1, right), but it is much less apparent compared with systolic pressure.

The survival for men classified according to the magnitude and direction of 5-year blood pressure change is shown in Figures 2, left and center, for systolic and diastolic blood pressure respectively. For systolic blood pressure the worst prognosis was found for those with the largest positive changes, whereas the moderate changes showed a better survival. The pattern of increasing mortality with increasing level of change was not seen for diastolic blood pressure.

Another factor, the presence of ischemic heart disease before stroke, resulted in an unfavourable prognosis (Figure 2, right).

Some details of the clinical and blood pressure status of the men who died within 30 days of their stroke are shown in Table 1. Comparing them with men who survived, there was no significant difference in mean age (57.3 ± 2.9 years versus 55.0 ± 1.5 years) or in the proportion that were known to have been prescribed antihy-
pertensive medications (28% versus 25%). For men who died within 30 days of their stroke, there was an increased proportion (36%) with previous ischemic heart disease compared with the survivors (13%) and a significantly (p < 0.05) larger systolic blood pressure (Figure 3). Although the mean values for diastolic and change in systolic pressure are not different, the pattern of decreasing survival with increasing values of each of these blood pressures was found as in Figures 1, right, and 2, left.

In multivariate analysis, systolic blood pressure, its 5-year change, and previous ischemic heart disease were each significantly associated with short-term mortality (Table 2). Systolic blood pressure was the most strongly associated with mortality, as it had the largest standardized coefficient and relative risk. The relative risk for systolic blood pressure of 8.6 means that for men whose pressure differs by one standard deviation unit and yet have similar values for all other variables, a 8.6 times greater short-term mortality would be expected in the men with the higher blood pressure levels. The relative risk for change in systolic blood pressure is less than one. This should not be interpreted as an indicator of lower risk, because it is the result of the negative sign of the logistic coefficient for change. Change in systolic blood pressure significantly (p < 0.05) (X² = 3.96) improves the prediction of short-term mortality as seen by comparing the likelihood ratio statistic for the logistic function with and without change.

The substitution of diastolic and its 5-year change for systolic blood pressure and its 5-year change in multivariate analysis markedly decreased the significance of the blood pressure in the prediction of short-term mortality.

The relative risk for diastolic blood pressure was 2.8 and the 5-year diastolic blood pressure change was not significant at 5%.

Discussion

Cerebrovascular disease is one of the leading causes of death in many countries. It is often responsible for severe disability in survivors and may become a larger problem with a greater proportion of the population reaching advancing age. Thus, identifying persons at high risk for morbidity and mortality from the disease is important and is the initial step in its prevention.

Although there is little doubt that elevated blood pressure is a predictor of stroke occurrence (22-26), the evidence for its ability to predict survivorship after the onset of stroke is less clear (1-10). This may in part be due to variations between studies in their criteria for elevated blood pressures and variations in length of time blood pressure is measured after admission for the acute event. Prospectively acquired blood pressure data before the occurrence of stroke minimizes these sources of variability and avoids the problem of the influence of recent stroke on blood pressure. To our knowledge this has not received much attention in prospective cardiovascular studies. Using this kind of data in the Manitoba study showed that the higher the blood pressure, mainly systolic, before the stroke, the worse the mortality when it occurred.

The presence of ischemic heart disease before the occurrence of stroke increased the mortality during the acute event. This association has been reported by others (2, 3, 6) although there is some disagreement (9). In the present study, heart disease was defined before the stroke.

![Figure 2 Left](image-url) Survivorship after stroke in groups classified according to 5-year change in systolic blood pressure. Number of persons lost to follow-up were for change in systolic blood pressure ≤ −20 mm Hg, none; change in systolic blood pressure −19 to 1 mm Hg, one at 3 to 4 years, one at 4 to 5 years; change in systolic blood pressure 0 to −19 mm Hg, one at 2 to 3 years; for change in systolic blood pressure ≥ 20 mm Hg, two at 1 year and one at 3 to 4 years. **Center.** Survivorship after stroke in groups classified according to 5-year change in diastolic blood pressure. Number of persons lost to follow-up includes for change in diastolic blood pressure ≤ 0 mm Hg, one at 1 to 2 years; for 0 to 9 mm Hg and 10 to 19 mm Hg, one each at 0 to 1 year. **Right.** Survivorship after stroke classified according to presence or absence of ischemic heart disease (IHD) before stroke. Lost to follow-up includes for no IHD group, two at 0 to 1 year and for IHD group, one at 1 to 2 years.
Table 1. Clinical and Blood Pressure Data on Those Dying Within 30 Days of Stroke

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at Stroke (years)</th>
<th>Last Blood Pressure* SBP/DBP</th>
<th>5-Year Blood Pressure Change* SBP/DBP</th>
<th>Previous IHD†</th>
<th>Antihypertensive Treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>240/130</td>
<td>110/40</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>210/110</td>
<td>80/30</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>230/130</td>
<td>60/10</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>240/110</td>
<td>40/0</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>170/100</td>
<td>40/15</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>185/90</td>
<td>28/20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>180/100</td>
<td>26/12</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>230/130</td>
<td>20/10</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>165/110</td>
<td>15/16</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>150/85</td>
<td>15/10</td>
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</tr>
<tr>
<td>11</td>
<td>49</td>
<td>130/80</td>
<td>10/10</td>
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<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>51</td>
<td>120/80</td>
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<tr>
<td>13</td>
<td>58</td>
<td>174/96</td>
<td>-16/6</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>14</td>
<td>55</td>
<td>150/95</td>
<td>-34/25</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Mean ± 1 SEM: 57.3 ± 2.9 181.9 ± 10.9/103.3 ± 4.7 27.3 ± 10.2 14.0 ± 4.6

* SBP = systolic blood pressure, DBP = diastolic blood pressure.
† IHD = ischemic heart disease.

This avoids the problem of diagnosing heart disease by the electrocardiogram on admission for stroke (1, 6, 27, 28). The relation between increased stroke mortality and ischemic heart disease may or may not be causal. Possible causation of physiologic mechanisms for this relation in-
clude the inability of myocardium in persons with ischemic heart disease to maintain a cerebral perfusion pressure sufficient to prevent the death of cells on the border of the infarct, that might be salvaged if sufficient blood flow could be maintained. Thus a larger stroke occurs with its attendant higher mortality. Another possibility is that the cardiac arrhythmias associated with stroke (29, 30) are more lethal in the presence of pre-existing heart disease. These suggestions raise the possibility that pharmacologic therapy directed at the heart might improve the survival of stroke patients.

The association of an unfavorable short-term prognosis with large positive 5-year changes in systolic blood pressure can be supported by Farmer, Gifford, and Hines (31), who noted that a shorter duration of known hypertension, and thus presumably a greater rate of change to hypertensive levels, was associated with a higher mortality, the majority of which was due to stroke. We have previously observed (14) that blood-pressure change can identify those at high risk for the development of cerebrovascular disease. Change in systolic blood pressure may be an indicator of an already damaged vasculature or it may play a pathophysiologic role in damage to the cerebral vasculature or in production of cerebral atherosclerosis leading to stroke. A decline in blood pressure was observed in three men who died shortly after their stroke. This may reflect one end of the distribution of blood pressure change or represent the unexplained fall in blood pressure that occurs in the last 2 years of life reported by Evans (32) and found before fatal myocardial infarction (13).

The stronger association of systolic compared with diastolic blood pressure in predicting stroke survivorship is similar to their respective roles in predicting stroke occurrence (15, 33). The failure of age to be a significant predictor in multivariate analysis does not mean that it is unimportant, but rather that its effect may be accounted for by the other variables (34), especially blood pressure. It is possible that the small effect of age may in part be
due to the "young" age at onset of stroke in this cohort compared with the age group where strokes are usually seen. However, the community study of Bergen (35) supports the contention that at high systolic blood-pressure levels mortality was related to blood pressure and not to age.

Several cautions are relevant. Although there is concern that no cardiovascular epidemiologic study is representative of the general population (36), it must be remembered that the Manitoba study cohort is a highly selected one. Secondly, the favorable long-term prognosis observed here, although it is supported by other studies (37), should be interpreted with caution in the present study because of the relatively small number of survivors of the acute event available in whom to adequately evaluate long-term prognosis. Thirdly, the number of stroke cases is relatively small, 52 men, and the age at the stroke was relatively "young," 56 years. Thus, additional data are needed from a larger number of elderly stroke victims.

The most important factors determining short-term prognosis after stroke are undoubtedly those present at the time of its occurrence such as the presence, depth, and duration of unconsciousness, papillary abnormalities, conjugate deviation of the eyes, signs of meningeal irritation, bilateral extensor plantar responses, pyrexia, and stentorophonous breathing of Cheyne-Stokes respiration (10, 38). These are in part dependent on the size and location of the damaged area, which is in turn a function of the extent, severity, and site of cerebral atherosclerosis. Thus, one possible explanation for the importance of blood pressure in identifying those with a poor prognosis is that elevated blood pressure is associated with more extensive or severe cerebral vascular damage or atherosclerosis (39, 40).

The use of prospective blood-pressure data focuses attention on the importance of blood pressure and its long-term changes to assess the prognosis of stroke. Thus, an elevated blood pressure before the event not only predicts stroke occurrence (14, 15, 21-26), but also predicts a greater likelihood of death.

Appendix

DIAGNOSTIC CRITERIA FOR STROKE

**Definite:**

I. One or more of the following symptoms and signs.
   a) Carotid-cerebral arterial system: weakness or numbness in the contralateral limbs (arm, left or both), homonymous or monocular visual loss, dysphasia or agnosia.
   b) Vertebral-basilar arterial system: weakness or numbness of one or more limbs, episodes of vertigo and nausea, numbness of the face—particularly about the mouth, diplopia, dysphagia, dysarthria, homonymous hemianopia, ataxia, nystagmus, or altered consciousness.

II. The above symptoms or signs for more than 24 h.

III. Objective neurologic deficits are present.

Events due to another known cause, for example, trauma were excluded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standardized Coefficient</th>
<th>Standardized Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>-0.0428</td>
<td>-0.4332</td>
<td>0.65</td>
</tr>
<tr>
<td>SBP</td>
<td>0.0579</td>
<td>2.1538</td>
<td>8.58</td>
</tr>
<tr>
<td>Change SBP</td>
<td>-0.0388</td>
<td>-1.2118</td>
<td>0.30</td>
</tr>
<tr>
<td>Previous IHD (0, 1)</td>
<td>2.6125</td>
<td>1.0396</td>
<td>2.83</td>
</tr>
<tr>
<td>Intercept</td>
<td>-8.0896</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Standardized coefficient is the coefficient times population standard deviation of the factor.

# Probable: Stroke, when one or more of the above signs or symptoms were present but were equivocal and persisted for more than 24 h, and equivocal neurologic deficits or residuals were present.

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**References**

15. RABKIN SW, MATTHEWSON FA, TATE RB: Predicting risk of ischemic


30. ESTANOL BV, MARIN OSM: Cardiac arrhythmias and sudden death in subarachnoid hemorrhage. Stroke 6:382-386, 1975


32. EVANS PH: Relation of long-standing blood pressure levels to atherosclerosis. Lancet 1:514-519, 1965


34. GORDON T: Hazards in the use of the logistic function with special reference to data from prospective cardiovascular studies. J Chronic Dis 27:97-102, 1974


40. SOLBERG LA, McGABRY PA: Cerebral atherosclerosis in persons with selected diseases. Lab Invest 18:613-619, 1968