Blood Pressure and Functional Recovery in Acute Ischemic Stroke

A. Chamorro, MD; N. Vila, MD; C. Ascaso, PhD; E. Elices, MD; W. Schonewille, MD; R. Blanc, MD

Background and Purpose—The relevance of elevated blood pressure in acute ischemic stroke and its most appropriate management are unresolved. We aimed to evaluate the rate of functional recovery with relation to early blood pressure management in patients with ischemic stroke.

Methods—Four hundred eighty-one consecutive ischemic stroke patients were admitted to the Neurology Service within 20.9 ± 10.5 hours of symptoms onset as part of the Barcelona Downtown Stroke Registry, including 235 patients who received oral antihypertensive agents within <24 hours after stroke onset. Demographic, clinical (Mathew scale), and CT scan findings were collected prospectively. Mean arterial pressure (MAP) was recorded before hospital arrival and at 7 AM on days 1, 2, and 7 of hospitalization. The primary end point was complete functional recovery at day 7 defined as a score of 0 to 1 on the modified Rankin scale.

Results—Two hundred fifty-two patients achieved complete recovery on day 7. Using logistic regression, independent predictors of complete recovery included mild impairment at stroke presentation, lack of history of hypertension, and absence of brain edema on CT scan. Also, a 20% to 30% drop in MAP on day 2 after stroke onset almost tripled the odds of full recovery (odds ratio, 2.9; 95% CI, 1.3 to 6.3). MAP tended to normalize after stroke in all subjects, more rapidly if hypotensive agents were administered. Brain edema was also less frequent in patients with a greater drop in blood pressure. Despite the fact that a drop in MAP >30% from baseline was observed in 49 patients, this preceded worsening stroke in only 4 patients. Conversely, worsening stroke occurred in 51 patients despite stable blood pressure.

Conclusions—These results suggest that complete recovery in ischemic stroke is facilitated by a moderate blood pressure reduction when brain edema develops, most likely as the result of a more adequate cerebral perfusion pressure. Conversely, stroke worsening due to pharmacological hypoperfusion is exceptional. (Stroke. 1998;29:1850-1853.)

Key Words: cerebrovascular disorders ■ blood pressure ■ stroke therapy

A transient elevation of arterial blood pressure is observed frequently in patients with acute ischemic stroke4–4 as the result of mental stress,5,6 central mechanisms,7 neuroendocrine factors,8,9 alcohol intake before stroke,10 or the topography of the infarct.11 Frequently, elevated blood pressure declines spontaneously after stroke without intervening medications.12 However, it remains unresolved whether post-stroke hypertension represents a pathophysiological response to maintain or enhance perfusion of reversibly damaged cerebrum or is a marker of the severity of stroke and the risk of further clinical progression.13–15 Based on clinical studies of the autoregulation of the cerebral blood flow in humans and animals, and current concepts concerning the pathophysiology of focal brain ischemia, most authorities discourage the use of antihypertensive drugs in acute stroke patients because these agents may reduce the pressure-dependent cerebral blood flow to the ischemic penumbra and increase cerebral damage.16–23 Conversely, it has also been argued that post-stroke hypertension could be deleterious and facilitate edema formation in the ischemic tissue.24,25 However, these conflicting opinions have not received adequate testing in a large series of acute stroke patients. Rather, the available clinical data are restricted to a few case reports that include patients with ischemic and hemorrhagic stroke.5,10–12 In a large series of ischemic stroke patients, we analyzed the rate of functional recovery in relation to prehospital and in-hospital blood pressure values. The risk of stroke worsening as the result of early blood pressure lowering was also addressed.

Subjects and Methods

From July 1992 to January 1997 we admitted 481 ischemic stroke patients to the Neurology Service less than 48 hours from the time of symptom onset. Of those, 235 patients received oral antihypertensive agents before admission to the Neurology Service, either during hospital transportation or at the emergency room. At hospital admission, baseline characteristics of patients, main work-up findings, in-hospital events, and treatment regimes were collected prospectively by stroke neurologists as part of the Downtown Barcelona Stroke Registry.26 In addition, written records provided by the emergency medical systems and emergency room (ER) personnel were reviewed retrospectively to assess prehospital blood pressure values and determine whether antihypertensive agents had been

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prescribed. Because physicians involved in the early care of patients were not part of the stroke team, antihypertensive agents were prescribed according to the physicians’ particular understanding of poststroke hypertension. These agents included diuretics (n=42), calcium channel blockers (n=44), angiotensin-converting enzyme inhibitors (n=70), beta-blockers (n=7), or some combination of the above (n=72). None of the hypotensive agents given to the patients was investigational; therefore, informed consent was not required. Neurological impairment was measured at baseline and on day 7 after stroke onset using the Mathew Stroke Scale27 (normal=100), whose specific value has been established.28 According to this ordinal scale, moderate-to-severe stroke at baseline indicated a score ≤74, mild stroke indicated a score >74, and worsening stroke indicated a Mathew score at hospital discharge lower than at baseline. Routine blood tests, chest x-rays, electrocardiography, and a brain CT scan were performed on all patients on hospital arrival. Additional diagnostic tests were performed as appropriate to document the causes of stroke, which were classified as lacunar (n=67), cardioembolic (n=190), and undetermined (n=153), according to the clinical and radiological criteria used by the Stroke Data Bank.29 Before death or hospital discharge, a second brain CT scan was performed to outline the topography and size of the infarct and assess the development of brain edema, which was defined as the presence of midline shift or displacement of the ventricles. None of the patients included in the study received thrombolytic agents, intravenous antihypertensive therapy, or investigational drugs. Antipatelet agents were given to 199 patients, and fractionated or unfractionated heparin was given to 282. Functional status was measured on day 7 using the modified Rankin Scale by investigators blind to the use of oral antihypertensive agents. A score of 0 to 1 indicated complete recovery, and a score of 2 to 6 indicated incomplete recovery or death.

History of arterial hypertension was defined in subjects who were taking hypotensive drugs regularly before the index event. History of diabetes, coronary heart disease, smoking, or hyperlipidemia were defined according to standard criteria. In-hospital blood pressure was measured by nursing staff using a calibrated sphygmomanometer with the patients in a supine position; disappearance of the Korotkoff phase-5 sound was defined as diastolic blood pressure. Baseline blood pressure referred to values obtained during hospital transportation or at the ER. Mean arterial pressure (MAP), defined as

\[
\text{MAP} = \frac{(\text{diastolic blood pressure}) + \frac{1}{3}(\text{systolic blood pressure} - \text{diastolic blood pressure})}{2}
\]

was also recorded at 7 AM on days 1, 2, and 7 of hospitalization. Drop in MAP on days 1, 2, and 7 was calculated according to the formula \([\text{(Follow-up MAP)} - \text{(baseline MAP)}] / \text{(baseline MAP)}\times100\). A drop in MAP of >30% from baseline values was defined as significant blood pressure reduction.

**Table 1. Main Characteristics of the Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (246)</th>
<th>Yes (235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>796 (32)</td>
<td>796 (32)</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.1 (11.3)</td>
<td>72.1 (11.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>120 (25)</td>
<td>120 (25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>289 (60)</td>
<td>289 (60)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>63 (13)</td>
<td>63 (13)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>109 (23)</td>
<td>109 (23)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>106 (22)</td>
<td>106 (22)</td>
</tr>
<tr>
<td>Smoking</td>
<td>104 (22)</td>
<td>104 (22)</td>
</tr>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>153 (32)</td>
<td>153 (32)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>71 (15)</td>
<td>71 (15)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>190 (39)</td>
<td>190 (39)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>67 (14)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>Diurnal/nocturnal stroke onset</td>
<td>271/210 (56/44)</td>
<td>271/210 (56/44)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>12.0 (6.6)</td>
<td>12.0 (6.6)</td>
</tr>
<tr>
<td>Baseline impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild stroke</td>
<td>156 (32)</td>
<td>156 (32)</td>
</tr>
<tr>
<td>Moderate-severe stroke</td>
<td>325 (68)</td>
<td>325 (68)</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean (SD), noncontinuous data as numbers (%).

**Table 2. Baseline Traits According to Antihypertensive Therapy**

<table>
<thead>
<tr>
<th>Trait</th>
<th>No (246)</th>
<th>Yes (235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay to medical care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS, min</td>
<td>46 (28)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>ER, min</td>
<td>358 (433)</td>
<td>364 (363)</td>
</tr>
<tr>
<td>Ward, h</td>
<td>20.9 (10.5)</td>
<td>21.2 (13.0)</td>
</tr>
<tr>
<td>Baseline Mathew Stroke Scale</td>
<td>67.7 (17.3)</td>
<td>66.6 (17.3)</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS*</td>
<td>102.5 (16.5)</td>
<td>122.8 (21.4)</td>
</tr>
<tr>
<td>ER*</td>
<td>109.7 (15.4)</td>
<td>122.1 (19.0)</td>
</tr>
<tr>
<td>Ward, day 1*</td>
<td>102.7 (14.0)</td>
<td>111.7 (18.2)</td>
</tr>
</tbody>
</table>

*P<0.0001; Data are mean (SD). Student t test and Mann-Whitney test as appropriate. EMS indicates emergency medical systems and ER, emergency room.

**Statistical analysis**

The chi-square test, Student t test, and Mann-Whitney U test were used as appropriate. Bonferroni correction for multiple comparisons of continuous variables was used if an overall difference was found. ANCOVA was used to adjust for unbalanced baseline MAP values when estimating the effect of several factors on drop in blood pressure. Functional recovery was evaluated using logistic regression analysis entering into the model variables with a P value <0.10 on univariate analysis and forcing into the model the time from baseline to follow-up blood pressure measurements. The level of significance was set at 0.05.

**Results**

**Characteristics of the Population and Blood Pressure Course**

The main features of the patients studied are described in Table 1. As expected, patients who received antihypertensive therapy had a higher prevalence of arterial hypertension (77% versus 44%; P<0.0001) and higher blood pressure values than untreated patients. However, as shown in Table 2, the delay to medical attention, and the initial severity of stroke symptoms, did not differ between treated and untreated patients.

Time from baseline MAP measurement to the 7 AM day 1 measurement was 959±629 minutes for patients with mild stroke on admission and 856±631 minutes for those with moderate-to-severe stroke on admission (nonsignificant differences). Overall, there was a tendency toward progressive reduction in MAP over time. Probably due to the phenomenon of the regression toward the mean,30 the decline was greater in patients with higher baseline values. Yet, after adjusting for unbalanced baseline values, patients who received antihypertensive agents had a greater drop in MAP after admission than untreated patients. The differences were statistically significant on day 2 after stroke onset.
(14.1\pm 15.3\% vs. 10.3\pm 5.4\%; P<0.05). On the contrary, the relative blood pressure drop observed on day 1 between treated and untreated patients (7.2\pm 16.3 vs. 5.2\pm 14.3) did not reach statistical significance, possibly because the medication had been administered orally.

Predictors of Functional Recovery

Two hundred fifty-two (52\%) patients had a Rankin score of 0 to 1 on day 7. In univariate analysis, factors associated with complete recovery included younger age, lacunar stroke, baseline Mathew score \( \geq 74 \), absence of history of hypertension, lack of brain edema on CT scan, and higher MAP at baseline. Further, post-hoc analysis also showed that 20\% to 30\% drops in MAP on days 2 and 7, respectively, were associated with complete recovery. Using logistic regression analysis, a Mathew score \( \geq 74 \), lack of hypertension, absence of edema on CT scan, and a 20\% to 30\% drop in MAP on day 2 remained associated with complete recovery, as shown in Table 3. On the contrary, variables that did not remain in the model included stroke type and age. Additionally, when MAP decline on day 2 was replaced in the model by MAP decline on day 1 or 7, these variables did not remain in the regression model.

Clinical Worsening and Blood Pressure Course

The potential association between edema formation, stroke worsening, and blood pressure changes over time was also tested. Worsening stroke occurred in 31 of 235 (13.1\%) patients treated with antihypertensive drugs, and in 24 of 246 (9.7\%) untreated patients (nonsignificant differences). Overall, 49 patients (10\%) experienced a drop in MAP \( >30\% \) from baseline values, including 18 patients who did not receive hypotensive agents. However, only 4 patients (0.8\%) sustained worsening symptoms in association with a drop in MAP \( >30\% \). At follow-up 110 (23\%) patients developed brain edema, and this CT finding was associated with a smaller MAP decline over time than in patients without brain edema. On day 2, the drop in blood pressure was 8.6\pm 16.0\% in patients with edema, compared with 13.3\pm 15.5\%, in those without edema (\( P<0.01 \)); on day 7, the figures observed in both radiological groups were 15.1\pm 15.9\% and 19.0\pm 14.8\% (\( P<0.01 \)), respectively.

Discussion

The present study assessed the rate of early complete neurological recovery in consecutive acute ischemic stroke patients in which blood pressure was recorded before hospital arrival, at the ER, and during the first days of hospital admission. Stroke outcome was measured in consecutive patients evaluating clinical, radiological, hemodynamic, and therapeutic variables that included the administration of hypotensive agents before admission to the Neurology Service. Moreover, because we controlled the time elapsed from baseline to follow-up blood pressure measurements, we ruled out an association between stroke outcome and differential change in MAP due to time differences between outcome groups. We confirmed the natural tendency of arterial blood pressure to decrease after stroke onset, although the most relevant finding of the study was that patients with a moderate drop in blood pressure on day 2 after stroke (20\% to 30\% from baseline values) almost tripled the odds of full recovery compared with patients whose blood pressure did not decline. Conversely, stroke recovery was unrelated to baseline blood pressure values or the course attained by blood pressure during the first day after stroke. Although patients who received hypertensive agents had a greater blood pressure decline than untreated patients, these differences only reached statistical significance during the second day after stroke. It is likely that an earlier blood pressure drop was not achieved because the medication was administered orally. Therefore, we cannot exclude the possibility that a more rapid blood pressure reduction might have increased ischemic damage, as suggested by others. Nevertheless, the lower incidence of brain edema and the better outcome observed in patients who sustained a moderate drop in blood pressure on day 2 suggested that these patients benefited from a more propitious cerebral perfusion pressure at the time that brain edema becomes clinically significant after ischemic stroke. Finally, the clinical effects of blood pressure lowering did not include a significant risk of stroke worsening associated with pharmacologically mediated hypoperfusion.

The prognostic significance of poststroke hypertension is undetermined in part by the fact that most previous studies grouped together patients with ischemic and hemorrhagic stroke, despite the fact that the clinical effects of elevated blood pressure might differ between the two conditions. Carlberg and colleagues found admission blood pressure to be unrelated to clinical outcome except in patients with impaired conscious levels, in whom increased blood pressure was associated with a worse prognosis. Others found very high blood pressure on admission to be associated with a greater stroke mortality. Conversely, Allen reported that higher systolic blood pressure on admission indicated a good outcome, and Jørgensen and colleagues found an inverse relationship between high systolic pressure and the risk of further progression. Moreover, the value of pharmacological hypotension has not been addressed specifically in acute stroke trials, although some indirect data and a few case reports warn against excessive blood pressure lowering in stroke patients. Thus, the Intravenous Nimodipine West European Stroke Trial study had to be terminated prematurely because of unexpected safety problems involving hemodynamic effects of the intravenous administration of nimodipine to ischemic stroke patients. It is likely that the clinical repercussion of blood pressure lowering in acute stroke depends greatly on the rate at which normotension is achieved, in addition to the manifold effects that different
antihypertensive agents might have on cerebral blood flow, autoregulation, and intracranial pressure.  

Several limitations of the study deserve explanation. Allocation to hypotensive medication was not randomized but depended on unselected criteria. It could be argued that physicians’ decisions were somehow influenced by the rate of recovery shown by patients’ prior admission into the Neurology Service. However, we found no baseline differences in stroke severity or delay to treatment between treated and untreated patients. Furthermore, the rate of functional recovery was assessed using multivariate analysis that controlled the effect of confounders, including the delay to first blood pressure recording. Our results suggest that the theoretical risks of blood pressure lowering do not have a clinical correlate in most acute ischemic stroke patients. In addition, we found that <1% of the studied population worsened in relation to the use of hypotensive medication. On the contrary, other factors, such as previous history of hypertension, the formation of brain edema, or the initial severity of stroke, predicted the rate of recovery.

In summary, these results illustrate that despite current recommendations for acute stroke management, many stroke patients receive hypotensive medications before they are admitted into neurological centers. Our data also indicate that both the rate of early stroke recovery and the incidence of brain edema is associated with an earlier normalization of blood pressure after the symptoms’ onset. Caution is warranted, however, because the study did not include patients treated with intravenous hypotensive agents. Therefore, we cannot exclude that an overzealous blood pressure reduction at an earlier phase after stroke onset might have produced opposing clinical results. Nevertheless, we believe that the “wait and see” attitude currently recommended to most acute ischemic stroke patients with elevated blood pressure deserves reconsideration in a randomized study. Better knowledge of the effect of blood pressure in acute ischemic stroke could result in more effective therapeutic strategies, including a safer use of thrombolytic and antithrombotic agents.

References

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