Early Arterial Study in the Prediction of Mortality After Acute Ischemic Stroke

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Background and Purpose—The purpose of this study was to evaluate the value of the initial arterial study as a predictor of 90-day mortality in patients with acute ischemic stroke.

Methods—A total of 1220 unselected patients assessed during the first 24 hours after stroke onset were prospectively studied. Initial stroke severity was evaluated by the National Institutes of Health Stroke Scale and dichotomized in mild (National Institutes of Health Stroke Scale ≤7) and severe (National Institutes of Health Stroke Scale >7). Severe arterial stenosis (≥70%) or arterial occlusion in the symptomatic territory was determined by a Doppler study and also by additional explorations (carotid duplex, MR or CT angiography) in the first 24 hours after admission. The following variables were also analyzed: age, gender, previous functional status, smoking, hypertension, hyperlipidemia, diabetes mellitus, peripheral arterial disease, ischemic heart disease, heart failure, atrial fibrillation, previous stroke, and prior use of antithrombotic or statins. Ninety-day mortality was the end point of the study.

Results—Ninety-day mortality was 15.7%. A total of 25.5% of all deaths were in patients with mild stroke. In addition to well-known factors related to mortality (age, stroke severity, ischemic heart disease, heart failure, and previous disability), severe arterial stenosis/occlusion was the factor with the highest relationship with 90-day mortality (adjusted OR: stenosis 2.13, occlusion 4.42, both 3.36). Arterial stenosis/occlusion was a higher predictor of 90-day mortality in patients with mild (adjusted OR: 5.38) than severe stroke (adjusted OR: 3.05).

Conclusions—Severe arterial stenosis/occlusion in the early arterial study was highly related with 90-day mortality in an unselected series of patients with stroke. These data achieve special relevance in patients with initial mild stroke.

Key Words: acute stroke • Doppler • outcome

Increased mortality risk after acute ischemic stroke (AIS) has been related to several modifiable factors (initial severity, hyperthermia, hyperglycemia, blood pressure, atrial fibrillation, heart failure, and serologic markers) and other nonmodifiable risks (age, gender, prior functional status, and ethnicity).1–13 Although some authors have assessed the association between middle cerebral artery residual flow, acute arterial occlusion, or stenoocclusive disease with clinical severity or outcome in series of patients with AIS,14–17 key data in all vascular diseases such as the early arterial pathological findings have not been previously related with mortality after stroke. The aim of our study was to evaluate the influence of early arterial findings on 90-day mortality in a prospective series of unselected patients with AIS.

Patients and Methods

From January 2003 to June 2006, 1321 patients with a diagnosis of AIS fulfilling the World Health Organization criteria18 were evaluated in the emergency room of our hospital in the first 24 hours after symptom onset. Patients were included in the BasicMar database, an ongoing prospective register of patients with AIS of our hospital, which is the only public hospital serving a population of 300 000 persons in 2 districts of Barcelona City. All consecutive patients with ischemic stroke, including large and small artery lesions, were considered for the study. We excluded 101 patients because of incomplete data (83 patients attributable to an inadequate bone window for the ultrasonographic study and absence of an additional arterial study and 38 patients because of no follow up). The remaining 1220 patients constituted the definitive study cohort. All patients were evaluated at hospital admission by a neurologist who established the previous functional state based on the modified Rankin scale19 and the initial severity according to the National Institutes of Health Stroke Scale (NIHSS).20,21 All patients were initially studied by brain CT scan, performing additional new CT scans (n = 403) or brain MRI (n = 713) during the hospitalization period. Strokes were classified based on the affected vascular territory in carotid extracranial, anterior intracranial, and vertebrobasilar systems. The vascular risk factors data were obtained from the patient, families, caregivers, or prior medical records following...
the definitions recommended by the International guidelines as follows: arterial hypertension (evidence of at least 2 raised blood pressure measurements, systolic >140 mm Hg or diastolic >90 mm Hg recorded on different days before stroke onset, a physician diagnosis, or use of medication), diabetes (a physician diagnosis or use of diabetes medication), hyperlipidemia (physician diagnosis, use of medication, serum cholesterol concentration >220 mg/dL, or serum triglyceride concentration >150 mg/dL), current smoking habit, ischemic heart disease (documented history of angina pectoris or myocardial infarction), peripheral arterial disease (physician diagnosis of intermittent claudication), atrial fibrillation (documented history or diagnosis during hospitalization), heart failure (documented history), previous stroke, and previous use of anti-thrombotic or statin treatments. Additional factors recorded were age, gender, and previous disability (modified Rankin scale >1).

Endovascular thrombolytic treatment with recombinant tissue-type plasminogen activator was administrated based on the European Medicines Evaluation Agency Criteria (SITS-MOST criteria) in the first 3 hours after stroke onset. All baseline data were registered at hospital admission blind to the 90-day patient’s outcome. We assessed the 90-day mortality by inhospital mortality and postdischarge control. Patients failing the postdischarge control (n=187) were evaluated by telephone interviews or by medical reports.

Arterial Study

Early arterial findings were determined based on the results of an immediate intra- and extracranial Doppler study (DS) of the supraaortic arteries (Multi-Dop-Portable Doppler System-DWL) performed routinely in all patients in our center in the first 12 hours after admission (mean, 3.72 hours [SD, 4.98]) by a trained neurologist in ultrasonographic techniques. The DS results were interpreted following previous established criteria for arterial stenosis or occlusion. We defined as pathologic the early detection of any intra- or extracranial severe arterial stenosis (?70%) or intra- or extracranial arterial occlusion in the symptomatic arterial territory. An additional neurovascular exploration (carotid duplex, MR or CT angiography) was performed at discharge (mean, 5.04 hours [SD, 7.23]; range, 0 to 18) in selected patients (n=297) by availability, clinical interest, or inadequate ultrasonographic study. If any discordance with the DS was found, the results of the carotid duplex, MR or CT angiography were used in the study. We also performed additional explorations (n=503) during the hospitalization period in patients with arterial stenosis to confirm the initial DS results (n=240) and in those with normal DS with strokes of unknown cause and in the vertebrobasilar territory. These explorations were used as validity controls of the DS. Although the transcranial Doppler is a reliable method to detect intracranial arterial stenosis, we used dichotomization in nonpathologic or pathologic stenosis/occlusion to reduce false-negative results and to increase the sensibility of the results and the interobserver correlation and with other radiological neurovascular explorations.

Statistical Analysis

\( t \) test for parametric and the Mann-Whitney U test for nonparametric variables were used to evaluate differences in continuous variables and the \( \chi^2 \) test for those in proportions. The logistic regression models were performed introducing age and initial severity as continuous variables. We included in the regression model those variables that reached a significant association (\( P<0.1 \)) in the univariate analysis. Although the low number of patients with thrombolytic treatment did not allow an accurate analysis, this factor was also introduced in all regression models attributable to its demonstrated efficacy in stroke outcome. The regression analysis was performed by forward method and variables were cross-tabulated to assess multicollinearity. Adjusted ORs with 95% CIs were calculated by logistic regression model. Statistical significance was determined at a \( \alpha \) level of 0.05. Attributable to the relationship found between initial stroke severity, mortality and arterial occlusion, a second analysis was performed after categorization according to the initial stroke severity following previously described criteria in mild (NIHSS \( \leq 7 \)) and severe (NIHSS >7). Finally, we obtained the adjusted OR for each arterial territory. Statistical analyses were performed with the SPSS 12 software package.

Ethics

The information in the study was collected from the prospective clinical protocols of our hospital, which fulfilled the local ethical guidelines. Therefore, patients signed no specific informed consent. Patients did not experience any delay of therapeutic interventions attributable to the performance of the present study.

Results

We analyzed 1220 patients with AIS. The demographic and vascular risk factors are detailed in Table 1. A total of 1064 strokes (87.2%) were in the carotid territory and 156 (12.8%) in the vertebrobasilar territory. Patients excluded from the study (n=101) compared with those included were older (77.84 years [SD, 11.11]; \( P=0.001 \)), but without other significant differences for the initial stroke severity (median NIHSS 5; \( P=0.583 \)), mortality rate (12 of 83 [14.4%]) or vascular risk factors.

Mortality and Stroke Severity

The hospitalization length period was 9.95 days (SD, 12.06). The rate of 90-day mortality was 15.7% (192 patients). Inhospital mortality was 12.1% (148 cases). Patients who died were older than those who survived (mean, 80.73 years [8.9] versus 72.99 years [12], \( P<0.001 \)). The causes of mortality were neurological in 59 patients (32 cases of intracranial hypertension/brain edema and 27 cases of brain stem stroke/recurrences or hemorrhagic transformation) and noneurological in 133 patients, classified in 98 cases of respiratory etiology (pneumonia/bronchoaspiration, 89 cases; pulmonary thromboembolism, 3 cases; respiratory insufficiency, 6 cases); heart causes, 10 cases (heart failure, 3 cases; sudden death or heart ischemic event, 7 cases); systemic malignancies, 9 cases; sepsis, 2 cases; digestive hemorrhages, 2 cases; and other etiologies or undetermined causes, 12 cases. The presence of pathological arterial study was asso-
TABLE 2. Factors Related with 90-Day Mortality*

<table>
<thead>
<tr>
<th></th>
<th>Univariate Analysis OR (95% CI)</th>
<th>Multivariate Analysis OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.07 (1.05–1.09)</td>
<td>1.06 (1.04–1.09)</td>
</tr>
<tr>
<td>Initial stroke severity</td>
<td>1.21 (1.19–1.24)</td>
<td>1.17 (1.14–1.21)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.79 (0.6–1)</td>
<td>1.97 (1.2–2.9)</td>
</tr>
<tr>
<td>Previous disability</td>
<td>3.29 (2.4–4.6)</td>
<td>3.87 (2.4–6.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.84 (0.6–1.2)</td>
<td>0.72 (0.5–0.9)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.33 (0.9–1.9)</td>
<td>1.19 (0.9–1.6)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.67 (0.5–0.9)</td>
<td>0.60 (0.4–0.8)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.49 (0.3–0.7)</td>
<td>0.46 (0.3–0.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.64 (1.2–2.4)</td>
<td>1.64 (1.2–2.7)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.71 (1.2–2.5)</td>
<td>1.71 (1.2–2.5)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1.1 (0.7–1.8)</td>
<td>1.1 (0.7–1.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.29 (2.4–4.5)</td>
<td>3.29 (2.4–4.5)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.32 (1.5–3.6)</td>
<td>2.04 (1.3–3.1)</td>
</tr>
<tr>
<td>Antithrombotic pretreatment</td>
<td>1.65 (1.2–2.2)</td>
<td>1.65 (1.2–2.2)</td>
</tr>
<tr>
<td>Statin pretreatment</td>
<td>0.85 (0.5–1.3)</td>
<td>0.85 (0.5–1.3)</td>
</tr>
<tr>
<td>Thrombolytic treatment</td>
<td>1.01 (0.4–2.3)</td>
<td>1.01 (0.4–2.3)</td>
</tr>
<tr>
<td>Arterial stenosis/occlusion</td>
<td>4.67 (3.4–6.4)</td>
<td>4.67 (3.4–6.4)</td>
</tr>
</tbody>
</table>

*Adjusted OR with P<0.05 in the multivariate analysis.

TABLE 3. Factors Independently Associated With 90-Day Mortality in the Multivariate Analysis Classified in Mild and Severe Stroke Dichotomizing the Initial NIHSS in 7 Points*

<table>
<thead>
<tr>
<th></th>
<th>Initial Mild Stroke (NIHSS ≤7)</th>
<th>Initial Severe Stroke (NIHSS &gt;7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.05 (1.02–1.09)</td>
<td>1.05 (1.03–1.08)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.52 (0.3–1)</td>
<td>0.52 (0.3–1)</td>
</tr>
<tr>
<td>Previous disability</td>
<td>2.02 (1–4.1)</td>
<td>1.80 (1–3.2)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.31 (0.1–0.6)</td>
<td>0.31 (0.1–0.6)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3.07 (1.5–6.3)</td>
<td>3.07 (1.5–6.3)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.46 (1.2–5.1)</td>
<td>2.46 (1.2–5.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.44 (1.2–4.8)</td>
<td>2.44 (1.2–4.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.80 (1.6–9.1)</td>
<td>3.80 (1.6–9.1)</td>
</tr>
<tr>
<td>Thrombolytic treatment</td>
<td>0.35 (0.1–0.9)</td>
<td>0.35 (0.1–0.9)</td>
</tr>
<tr>
<td>Arterial stenosis/occlusion</td>
<td>5.38 (2.7–10.5)</td>
<td>5.38 (2.7–10.5)</td>
</tr>
</tbody>
</table>

*Adjusted OR (95% CI) with P<0.05.

Factors Associated With 90-Day Mortality

Variables associated with 90-day mortality were age, initial stroke severity, prior modified Rankin scale ≥1, ischemic heart disease, heart failure, thrombolytic treatment as protector, and arterial stenosis/occlusion, the latter factor having the highest OR (Table 2). When arterial occlusion and severe stenosis were analyzed separately in the multivariate analysis, both severe stenosis (P<0.007; adjusted OR, 2.13; 95% CI, 1.2 to 3.7) and arterial occlusion (P<0.001; adjusted OR, 4.42; 95% CI, 2.6 to 7.6) were independently associated with 90-day mortality. An additional regression model introducing the detailed arterial stenosis/occlusion data classified based on the affected arterial territory and adjusted by confounders showed an independent association with 90-day mortality for all territories: carotid (P<0.008; adjusted OR, 2.3; 95% CI, 1.5 to 3.7), intracranial (P<0.001; adjusted OR, 2.19; 95% CI, 1.4 to 3.5), and vertebrobasilar (P<0.001; adjusted OR, 2.3; 95% CI, 1.4 to 3.5).

In the second part of the study, we analyzed the repercussion of the early arterial study results in patients classified based on the initial severity in mild and severe strokes dichotomizing the NIHSS in 7 points. In patients with mild stroke, 90-day mortality was independently associated with female gender, prior modified Rankin scale >1, absence of hyperlipidemia, heart ischemic disease, previous stroke, atrial fibrillation, arterial stenosis/occlusion, and age (Table 3). In patients with severe stroke, 90-day mortality was independently associated with previous modified Rankin scale >1, heart failure, thrombolytic treatment, arterial stenosis/occlusion, and age (Table 3). The influence of arterial stenosis/occlusion on 90-day mortality was higher in patients with initial mild strokes than in severe stokes (Table 3).

Arterial Study

The early arterial study showed a severe arterial stenosis or occlusion in 359 patients (29.4%) who were classified based on the arterial territory in carotid artery (138 patients [38.4%]), intracranial anterior artery (204 patients [56.8%]), and vertebrobasilar system (45 patients [12.5%]). A tandem pattern was found in 28 patients. The initial DS and other additional neurovascular explorations performed in 297 patients in the first hours after admission had a correlation between both explorations of 92.5% for the detection of any arterial pathology. The concordance between the initial DS and other additional explorations performed during the hospitalization period (n=503) was 93%. Patients with a pathological arterial study compared with those with a normal study had more initial severity: median 8 (interquartile range, 3 to 18) versus 3 (interquartile range, 2 to 7; P<0.001).

Discussion

The neurosonology in the Acute Ischemic Stroke study has recently showed the relevance of the ultra-early DS in predicting outcome at 90 days after moderate to severe hemispheric AIS. Previous studies of early arterial status were focused on the relationship between acute arterial occlusion and stroke clinical outcome, and a recent study has also showed an association of stenoocclusive...
disease with stroke recurrence and clinical outcome. Because the relationship between a pathological early arterial study and 90-day mortality has not been previously demonstrated, the aim of our study was to evaluate this relationship in an unselected series of patients with AIS. We have systematically used DS in the early evaluation of all symptomatic patients independently of the clinical severity or the infarct localization. Our finding of severe arterial stenosis or occlusion as the factor with the highest association with 90-day mortality reflects the importance of an early arterial study for the selection of patients with a higher risk of death. We have also found that, in addition to acute complete occlusion, severe arterial stenosis is related with 90-day mortality with an adjusted OR of 2.13 for stenosis and 4.42 for arterial occlusion.

The 90-day mortality rate of patients with AIS was 15.7% in our study, a similar value found in previous reports. In addition to the arterial study, age, initial stroke severity, prestroke functional situation, heart ischemic disease, heart failure, and atrial fibrillation were factors associated with mortality as previously reported. We also found differences in mortality after stroke according to gender as well as a protective effect of hypercholesterolemia and thrombolytic therapy.

Several and heterogeneous mechanisms may be involved in the increased mortality found in patients with a pathological arterial study. The presence of early arterial pathological findings was related in the univariate analysis to both neurological and nonneurological deaths, although the impact was higher for the former. This may suggest a relationship with a higher risk of increased damage in the involved vascular territory. Patients with a pathological arterial study may have more widespread atherosclerosis disease and greater arterial stiffness leading to dysfunction of the vasoregulatory mechanisms that can be related to a higher risk of poor neurological evolution and increased mortality risk. The analysis by different arterial territories showed that the highest association with mortality was found in patients with arterial stenosis/occlusion in the vertebrobasilar system. This finding agrees with previous reports showing that posterior territory has a higher risk of mortality, probably in relation to the involvement of vital structures such as respiratory or cardiac centers.

We reanalyzed the multivariable model classifying patients in initial mild and severe stroke attributable to the high association of stroke severity and a pathological arterial study with 90-day mortality. Both groups had an independent association between arterial stenosis/occlusion and 90-day mortality, although the highest OR was found in patients with initial mild strokes (Table 3). This result may suggest that the repercussion of arterial disorders may be lower in patients with an initial severe stroke and higher disability in contrast to patients with mild stroke who may have a higher risk of neurological deterioration or recurrences and a higher subsequent mortality. Moreover, the high death rate observed in patients with initial minor stroke was noteworthy and reflects an unresolved problem in the clinical care of these patients.

Some limitations of our study should be emphasized. Although the previous functional status was introduced in the statistical analysis, the advanced age of patients who died could suggest a higher comorbidity in these cases. Attributable to the difficulty to perform routinely an immediate neurovascular evaluation in all consecutive patients attended in the emergency room of our hospital, we used DS, an accessible and portable tool that can be performed by the same neurologist who attends the patients. However, DS has lower sensibility to evaluate the arterial tree than other explorations such as an angiographic study. Nevertheless, this limitation may be superimposed to the simplicity of DS to evaluate the arterial status. In addition, to reduce false-negative results, we used criteria to define pathological/nonpathological study that increases the sensibility of the results providing a higher correlation with other radiological neurovascular explorations. Other limitations of our study were the absence of assessment of recanalization and reocclusion and of modifiable factors influenced by medical care differences such as initial temperature, blood pressure, or blood glucose levels.

In summary, we found that patients with an early pathological arterial study represent a group with a high risk of mortality. Our results emphasize the necessity to perform an early arterial study in all patients with stroke. New studies are necessary in the evaluation of specific medical attention and the role that urgent revascularization strategies might play to improve the outcome of these patients.

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Disclosures

None.

References

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