Delayed Increase in Infarct Volume After Cerebral Ischemia
Correlations with Thrombolytic Treatment and Clinical Outcome

Patrizia Pantano, MD; Francesca Caramia, MD; Luigi Bozzao, MD; Christiane Dieler, MD; Rüdiger von Kummer, MD

Background and Purpose—Growing experimental evidence indicates that the development of cerebral ischemic damage is slower than previously believed. The aims of this work were (1) to study the evolution of CT hypodensity between 24 to 36 hours and 7 days in ischemic stroke patients; (2) to evaluate whether thrombolytic treatment given within 6 hours of stroke affects delayed infarction evolution; and (3) to investigate possible correlations between lesion volume changes over time and clinical outcome.

Methods—Of 620 patients included in the European Cooperative Acute Stroke Study 1 (ECASS1), we selected 450 patients whose control CT scans at day 1 (CT1) and day 7 (CT7) were available. They had been randomly divided into 2 groups: 206 patients had been treated with rtPA and 244 with placebo. CT1 and CT7 were classified according to the location of the infarct. The volume of CT hypodensity was measured using the formula $A \times B \times C/2$ for irregular volumes. The 95% confidence interval of inter- and intrarater variability was used to determine whether significant changes in lesion volume had occurred between CT1 and CT7. Clinical severity was evaluated by means of the Scandinavian Stroke Scale (SSS) at entry (SSS0) and at day 30 (SSS30).

Results—Mean lesion volumes were significantly ($P<0.0001$) higher at day 7 than at day 1 in all the subgroups of patients and particularly in patients with a subcortical lesion. Of the 450 patients studied, 287 (64%) did not show any significant change in lesion volume between CT1 and CT7, 143 (32%) showed a significant increase and the remaining 20 (4%) a significant decrease. No significant correlation was observed between treatment and lesion evolution between CT1 and CT7. Both clinical scores (SSS0 and SSS30) and degree of neurological recovery were significantly ($P<0.05$) lower in the subgroup of patients with a significant lesion volume increase than in the other 2 groups.

Conclusions—In approximately two thirds of patients, infarct size is established 24 to 36 hours after stroke onset, whereas in the remaining one third, changes in lesion volume may occur later than the first 24 to 36 hours. Many factors may be responsible for delayed infarct enlargement and for a lower degree of clinical recovery, both of which may occur despite early recombinant tissue plasminogen activator treatment. (Stroke. 1999;30:502-507.)

Key Words: cerebral infarction ■ stroke, acute ■ thrombolysis ■ tomography, x-ray computed

The target of therapeutic intervention in acute stroke is the ischemic tissue that has not yet been irreversibly damaged. In rat and cat stroke models, it has been demonstrated that it is not possible to reverse ischemic damage later than 3 hours after stroke onset.1,2 However, this time limit may be longer in phylogenetically higher species, such as primates and humans. The therapeutic window in recombinant tissue plasminogen activator (rtPA) trials, in fact, has been set to within 6 hours of the onset symptoms.3

Growing experimental evidence indicates that the development of cerebral ischemic damage is slower than previously believed. Although irreversible damage occurs relatively rapidly in the core of severe ischemia, damage in peripheral regions of less severe ischemia may develop over the course of many hours or even days.4–6 This hypothesis seems to be confirmed by positron emission tomographic studies in humans7–9 that have shown areas of preserved metabolism, low blood flow, and increased oxygen extraction, which were interpreted as ischemic penumbra, many hours after stroke. However, these penumbral areas may finally evolve into infarction, as documented by CT scans performed more than 2 weeks after stroke.

These studies therefore seem to highlight 2 fundamental points: (1) potentially salvageable ischemic tissue may be present up to 24 to 48 hours after stroke and (2) this tissue may gradually evolve into definitive necrosis in a delayed fashion.

Furthermore, a large amount of emerging experimental evidence points to the importance of apoptosis as a mechanism responsible for the delayed ischemic cell death of neurons.10–14 Although infarction becomes evident within a few hours and fully develops within 1 day after severe
ischemia, it appears to develop surprisingly slowly after mild ischemia, taking up to 14 days.14

In clinical studies, areas of severe ischemia may be seen by CT scan as hypodense areas within a few hours of stroke.15–19 The questions addressed in this work are whether early CT hypodensity is surrounded by less severely damaged tissue that finally evolves into infarction, whether this process develops after the first 24 to 36 hours, and whether it is affected by early reperfusion.

We investigated the evolution between day 1 and day 7 of early CT hypodense areas in a large cohort of patients recruited in the European Cooperative Acute Stroke Study 1 (ECASS1), a double-blind placebo-controlled trial on the effects of intravenous rtPA administered within 6 hours of a hemispheric ischemic stroke. Furthermore, we evaluated the effects of thrombolysis on delayed infarct enlargement and a possible correlation between lesion volume changes over time and clinical outcome.

Subjects and Methods

The patients included in this study belong to the population of the ECASS1 study.20 The ECASS1 protocol required a CT scan before randomization and further scans at 24 to 36 hours and day 7 after onset. In this multicenter trial, the CT scans were obtained according to the guidelines of the study protocol with continuous sections with 4- or 5-mm slice thickness for the skull base and 8- or 10-mm slice thickness for the cerebral hemispheres at a level of 35 to 40 Hounsfield units (HU) and at a window of 80 to 100 HU. With very few exceptions the same scanner and the same technique were used for both follow-up scans at day 1 and day 7. CT images were read by an independent committee of 3 neuroradiologists who were blinded to the assigned treatment and clinical information.

Of all 620 patients (intention-to-treat population) included in the ECASS1 study, we selected those patients whose follow-up CT scans at day 1 (24 to 36 hours: CT1) and day 7 (days 6 to 9: CT7) after stroke onset were available. Patients showing parenchymal hemorrhage (PH) at CT1, CT7, or both were also excluded for 2 main reasons: (1) it is impossible to measure the volume of ischemic lesion in these patients and (2) the clinical outcome may be affected by the hemorrhage and consecutive mass effect. Based on CT1, 86 patients were excluded: a CT was not available in 15 patients (5 patients had died) or not performed at the defined time point. Seventy-one patients showed a PH. Based on CT1, an additional 84 patients were excluded: this follow-up CT was not available in 73 patients (44 patients had died before day 7) or was performed before day 6 or after day 9. In 11 patients a PH had developed between days 1 and 7. So, altogether 170 patients (61 women, 109 men; mean age, 67±10 years) were excluded.

Thus, the population included in this analysis consisted of 450 patients, 170 of whom were women and 280 men, with a mean age of 65±12 years. They had been randomly divided into 2 groups: 206 patients had been treated with rtPA and 244 with placebo. The smaller number of patients in the rtPA group was because of a higher incidence of PH in these patients. This population includes 5 patients who were randomized but not treated and 28 patients with an ischemic lesion on the baseline CT that exceeded 33% of the middle cerebral artery (MCA) territory.

The criteria used in the analysis of CT scans have been previously reported.21 In this study, control CT scans (CT1 and C7) were classified according to the location of the infarct into 4 subgroups: “no,” “subcortical” (deep territory of the MCA without any involvement of the cerebral cortex), “cortical” (superficial territory of the MCA without any involvement of subcortical gray matter), and “mixed” (both deep and superficial MCA territories) infarcts. In the follow-up scans, the volume of the hypodense area was also automatically measured by 2 students who were not involved in the

### TABLE 1. Lesion Evolution Between CT Scans Obtained 24 to 36 Hours (CT1) and 1 Week (CT7) After Stroke in 450 Patients

<table>
<thead>
<tr>
<th>CT1</th>
<th>CT7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion (n=87)</td>
<td>80 (92%) 2 (2%) 5 (6%) ...</td>
</tr>
<tr>
<td>Subcortical (n=106)</td>
<td>1 (1%) 93 (88%) 1 (1%) 11 (10%)</td>
</tr>
<tr>
<td>Cortical (n=123)</td>
<td>1 (1%) ... 110 (89%) 12 (10%)</td>
</tr>
<tr>
<td>Mixed (n=134)</td>
<td>... 1 (1%) 2 (1%) 131 (98%)</td>
</tr>
</tbody>
</table>

ECASS1 who were blinded to all clinical information, including the treatment.

To calculate irregular volumes they used the following formula: \( A \times B \times C/2 \). They measured the largest diameter (A) and the perpendicular diameter (B) of the ischemic lesion and the third diameter (C) by summing up the thicknesses of the slices where the lesion was visible. Interrater tests of volume measurements provided the 95% confidence interval for lesions smaller than 50 mL (from –40% to +50%) and for lesions equal to or larger than 50 mL (±26 mL; authors’ unpublished observations). We used the 95% confidence interval to determine whether significant changes in the lesion volume had occurred between CT1 and CT7 in individual patients.

Clinical severity was evaluated by means of the Scandinavian Stroke Scale (SSS)22 at entry (SSS0) and at day 30 (SSS30). Clinical improvement and deterioration were calculated by subtracting the SSS30 from the SSS0.

For statistical evaluation we used both univariate and multivariate analysis. Univariate analysis was conducted using \( \chi^2 \) test, t test, Wilcoxon test, and linear regression. Multivariate analysis was conducted using 2-factor repeated measures ANOVA and stepwise logistic regression. Repeated measures ANOVA was used to evaluate the occurrence of significant changes either in lesion volume or in neurological status between stroke patients belonging to different subgroups. Post-hoc analysis was obtained by Wilcoxon and Fisher’s protected least significant difference (PLSD) tests. Stepwise logistic regression was used in order to evaluate the independent association of clinical and CT variables with the clinical outcome.

Results

Lesion Evolution From 6 Hours to 7 Days

The baseline CT scan (CT0) showed no hypodensity in 255 (57%) of the 450 patients, an area of early hypodensity in 190 (42%), and was not readable in the remaining 5 patients.

CT1 showed no lesion in 87 (19%) patients and an area of hypodensity in the remaining 363 (81%). The hypodensity area was subcortical in 106 patients (62 of them with a normal CT1), cortical in 123 (69 of them with a normal CT1), and mixed in 134 (37 of them with a normal CT1).

Table 1 shows the evolution of CT lesions between day 1 and day 7. Eighty of the 87 patients with no lesion at CT1 had a normal CT scan at day 7, whereas 7 patients developed CT hypodensity between day 1 and day 7. In 2 patients no lesion was observed at CT7, despite the presence of hypodensity at CT1. In 23 patients lesions described as “cortical” or “subcortical” at CT1 were classified as “mixed” at CT7.

Two-way repeated measures ANOVA (“infarct site”× “lesion volume”) showed that both factors were significant (df=3; F=128.8; P=0.0001 and df=1; F=98.9; P=0.0001, respectively). Moreover, the interaction between the 2 factors was highly significant (df=3; F=25; P=0.0001), indicating that lesion volume changes occurring between CT1 and CT7.
were significantly different among subgroups (Table 2). Post hoc analysis revealed that in all subgroups the mean lesion volumes at CT₇ were significantly greater than at CT₁ (P=0.0001, Wilcoxon test). The percent changes in lesion volume between CT₁ and CT₇ were significantly higher in subcortical patients than in the other groups (P<0.05, Fisher’s PLSD), whereas no significant differences were observed in lesion volume percent changes between the cortical and mixed groups.

Of the 450 patients we studied, 287 did not show any significant change in lesion volume between CT₁ and CT₇, 143 showed a significant increase (see the Figure) and the remaining 20 a significant decrease. The number of patients showing or not showing significant changes in lesion volume between day 1 and day 7 was significantly different in the 4 subgroups (χ²=49.06; P=0.0001; Table 3).

Relationship Between Treatment and CT Lesion Evolution Between Day 1 and Day 7
Of 450 patients, 206 had been treated with rtPA and 244 with placebo. No significant differences were observed in the distribution of patients treated with either rtPA or placebo according to the lesion site: the ratio between treated and untreated patients was 48/39 in the “no lesion” group, 51/55 in the “subcortical” group, 55/68 in the “cortical” group, and 52/82 in the “mixed” group.

No significant relationship was observed between treatment and lesion evolution between CT₁ and CT₇ (Table 4), there being no significant difference in the frequency distribution of patients with or without a significant increase in lesion volume between the placebo and the rtPA group (χ²=3.32; NS). The percent changes in lesion volume were not different between the 2 groups either.

Of the 143 patients presenting a significant delayed volume increase, 57 (40%) had received rtPA and 86 (60%) placebo.

Relationship Between CT Findings and Clinical Outcome
On average there was a significant improvement in the neurological status as assessed by the Scandinavian Scale in 433 patients (in 17 patients SSS at entry was not available). SSS improved from 29.4±11 at entry to 41.5±16 at day 30 (SSS₃₀; P=0.0001, Wilcoxon test).

Two-factor repeated measures ANOVA showed that there was a significant effect of both subgroup (“no significant changes,” “significant increase,” and “significant decrease” in lesion volume between CT₁ and CT₇; df=2, F=40.2, P=0.0001), repeated SSS (at entry and at 1 month; df=1, F=429.7, P=0.0001), and a significant interaction between subgroup and SSS (df=2, F=19, P=0.0001; Table 5). Post hoc analysis showed that SSS₀ in the subgroup of patients with a significant lesion volume increase were significantly (P<0.05; Fisher’s PLSD) lower than in the other 2 groups. No differences in either SSS₀ or SSS₃₀ were observed between patients with no significant changes and those with a significant decrease in lesion volume. Differ-

### Table 2. Changes in Lesion Volume Between CT Scans Obtained 24 to 36 Hours (CT₁) and 1 Week (CT₇) After Stroke in 450 Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>CT₁ (cm³)</th>
<th>CT₇ (cm³)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion (n=87)</td>
<td>0</td>
<td>0.773±6*</td>
<td>9.2±29*</td>
</tr>
<tr>
<td>Subcortical (n=106)</td>
<td>9.3±9</td>
<td>17.6±28†</td>
<td>131.6±50†</td>
</tr>
<tr>
<td>Cortical (n=123)</td>
<td>42.1±37</td>
<td>49.47†</td>
<td>30.8±112</td>
</tr>
<tr>
<td>Mixed (n=134)</td>
<td>82.9±54</td>
<td>112.75†</td>
<td>45.1±66</td>
</tr>
</tbody>
</table>

Significant effect of subgroup (df=3, F=128.8, P=0.0001) and lesion volume (df=1, F=98.9, P=0.0001) and significant interaction between the 2 factors (df=3, F=25, P=0.0001) by 2-factor repeated measures ANOVA.

*Significantly different from volume at CT₁ (P<0.0001, post hoc by Wilcoxon test).
†Significantly different from volume at CT₁ (P<0.0001, Wilcoxon test).
‡Significantly different from the other groups (P<0.05, Fisher’s PLSD).

### Table 3. Significant Changes in Lesion Volume Between CT Scans Obtained 24 to 36 Hours (CT₁) and 1 Week (CT₇) After Stroke in 450 Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No Significant Changes</th>
<th>Significant Increase</th>
<th>Significant Decrease</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lesion (n=87)*</td>
<td>80 (92%)</td>
<td>7 (8%)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Subcortical (n=106)</td>
<td>59 (56%)</td>
<td>39 (37%)</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>Cortical (n=123)</td>
<td>81 (66%)</td>
<td>33 (27%)</td>
<td>9 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mixed (n=134)</td>
<td>67 (50%)</td>
<td>64 (48%)</td>
<td>3 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

*In the “no lesion” group all patients showing an area of hypodensity at CT₁ not seen at CT₁ were considered to have a significant change in lesion volume. χ²=49.06, P=0.0001.

### Table 4. Relationship Between Treatment and Lesion Evolution Between CT Scans Obtained 24 to 36 Hours (CT₁) and 1 Week (CT₇) After Stroke in 450 Patients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No Significant Changes</th>
<th>Significant Increase</th>
<th>Significant Decrease</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>rtPA (n=206)</td>
<td>138 (67%)</td>
<td>57 (28%)</td>
<td>11 (5%)</td>
<td>57.6±349</td>
</tr>
<tr>
<td>Placebo (n=244)</td>
<td>149 (61%)</td>
<td>86 (35%)</td>
<td>9 (4%)</td>
<td>51.0±140</td>
</tr>
</tbody>
</table>

Two transverse CT images obtained 3.25 hours (CT₀), 30 hours (CT₁), and 8 days (CT₇) after stroke onset. CT₀ was normal. CT₁ showed a subcortical area of hypodensity involving the internal capsule, lentiform nucleus, and white matter (volume=62.4 cm³). CT₇ showed a dramatic enlargement of hypodensity that extended to the cerebral cortex (volume=246 cm³).
TABLE 5. Relationship Between Significant Changes in Lesion Volume (CT₁−CT₇) and Neurological Status (SSS₀−SSS₃₀)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>SSS₀</th>
<th>SSS₃₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>No changes (n=276)</td>
<td>31.6±9.9</td>
<td>46.0±14.2</td>
</tr>
<tr>
<td>Lesion volume increase (n=138)</td>
<td>24.8±11.5</td>
<td>32.1±17.0</td>
</tr>
<tr>
<td>Lesion volume decrease (n=19)</td>
<td>30.9±11.1</td>
<td>52.2±13.1</td>
</tr>
</tbody>
</table>

Significant effect of subgroup (df=2; F=40.2, P=0.0001) and repeated SSS (df=1, F=429.7, P=0.0001) and significant interaction between subgroup and SSS (df=2, F=19, P=0.0001) by 2-factor repeated measures ANOVA.

ences between SSS₀ and SSS₃₀ were significant (P<0.05) between groups: 7.3±12.4 in patients with a significant lesion volume increase, 14.4±12.5 in patients with no lesion changes, and 20.3±14.1 in patients with a significant lesion volume decrease.

The difference in lesion volume (CT₇ minus CT₁) and the difference in SSS (SSS₃₀ minus SSS₀) were significantly correlated (r=0.399, P=0.0001).

Outcome was good in 292 patients and poor in 151 (outcome data were not available in the remaining 7 patients). Among 6 CT variables, ie, the presence or absence of early hypodensity at CT₀, the volume of the lesion at CT₁ and CT₇, the site of the lesion (no, subcortical, cortical, or mixed) at CT₁ and CT₇, and the changes in lesion volume between CT₁ and CT₇, we found that the variable most significantly correlated with clinical outcome was the lesion volume at CT₇ (P<0.001), followed by the percent change in lesion volume between CT₁ and CT₇ (P<0.01), whereas the other variables were not significantly correlated.

Discussion

Substantial changes were observed in CT scans between the first few hours and the next 24 to 36 hours, indicating that this is the time during which parenchymal damage matures toward definitive necrosis. In our study no area of hypodensity was evident within 6 hours of stroke in more than half of the patients. After 24 to 36 hours the percentage of patients showing no parenchymal hypodensity dropped to approximately 20%.

However, 24 to 36 hours after stroke the size of the lesion does not appear to be definitive: mean volumes were significantly higher at day 7 than at day 1 in all the subgroups of patients, and particularly in those with a subcortical lesion.

To avoid any methodological bias due to the fact that the lesion area at day 7 is more easily outlined from the apparently normal tissue than at day 1, we calculated the 95% confidence interval of volume measurements, which takes into account of interrater variability. This analysis showed that although changes in lesion volume were considered as not significant in almost two thirds of the cases (287 of 450 patients), a significant volume increase between day 1 and day 7 was evident in almost one third of the cases (143 of 450 patients). Interestingly, in 20 patients the lesion volume significantly decreased.

The temporal profile of parenchymal damage following an ischemic event until the final size of infarction is reached is still unknown. Many studies have addressed the issue of early CT signs of infarction within 6 to 8 hours of stroke and their ability to predict the subsequent infarct location.

Few studies have focused their attention on lesion volume changes in the first week, and those that have were conducted on a small number of stroke patients. No study has yet systematically evaluated the evolution of ischemic lesions in the first week in a large cohort of stroke patients.

The increase in CT lesion size we observed up to 1 week following the acute ischemic event supports the hypothesis of delayed neuronal death after ischemia. This observation raises questions about the pathophysiological mechanism underlying this event.

The hypodensity measured at 24 to 36 hours may correspond to the part of the tissue in which, following severe ischemia, cytotoxic edema has already developed. The areas that are apparently normal at 24 to 36 hours and hypodense at 7 days may represent a delayed transition toward infarction, due to a less severe degree of ischemia. Because the evolution from ischemic penumbra to necrosis has been classically linked to 2 main factors, ie, time and severity of ischemia, the areas above a given threshold of blood supply may evolve into infarction in a longer period of time, if reperfusion, collateral circulation, or both are ineffective. A cortical extension of early isolated hypodensity of the lentiform nucleus has been observed in patients with acute ischemic stroke between 6 and 24 hours.

Although some studies have reported a gradual expansion of the infarct core into the penumbra until the latter disappeared after a few hours, others support the concept of the ischemic penumbra as a dynamic process that gradually spreads over a longer period of time from the center of ischemia to the neighboring tissue.

Human studies seem to confirm the delayed evolution of penumbral areas. In stroke patients, Heiss and colleagues showed that areas of increased oxygen extraction were present at the border zone of the ischemic core up to 48 hours after stroke and deteriorated in the following 2 weeks. In a correlative positron emission tomography–CT study, Marchal et al found substantial volumes of tissue with metabolic characteristics of ischemic penumbra in 8 stroke patients, up to 17 hours after stroke onset, that eventually evolved into infarction.

After the first hours following the onset of ischemia, a variety of cellular and molecular events triggered by the ischemic insult contribute to the maturation of tissue damage.

Recently, a large amount of evidence has emerged from experimental studies that neuronal death after transient ischemia may be caused by 2 different mechanisms: necrosis within the ischemic core and apoptosis at the borders of the infarct volume. This latter process can develop in a surprisingly delayed fashion, ie, between 3 days and 2 weeks.

There is no evidence that apoptosis contributes to ischemic damage in humans. However, we cannot exclude the possibility that apoptosis caused the progression of infarct volume we observed up to 1 week following the ischemic insult. Besides these molecular mechanisms, substantial changes may also play a role. Ischemic edema may increase intracranial pressure and thus reduce the perfusion pressure, affecting...
above all vessels with exhausted perfusion reserve. Direct compression of microvessels may contribute to the expansion of tissue volume with critical low perfusion. Reperfusion after spontaneous or induced recanalization may enhance edema or supply cytotoxic agents to the ischemic tissue. A decrease in arterial blood pressure could further increase the volume of critical perfused brain tissue. Secondary arterial occlusions by repeated embolism, an increase in size of a thrombus, and fragmentation of thrombi with distal migration could also cause secondary enlargement of the ischemic tissue damage.

Our analysis also addressed the question of whether early treatment with rtPA can limit or prevent this delayed infarction evolution.

The efficacy of early rtPA administration in reducing infarct size is documented in various animal stroke models. In humans, the benefit of rtPA treatment on clinical outcome is well documented, whereas studies on the effect of rtPA treatment on the final volume of parenchymal damage are less exhaustive. Ringelstein et al reported a marginally significant correlation between size of infarction at CT and recanalization within 24 hours in 17 stroke patients. Fiorelli et al analyzed cortical extension at 24 hours of early isolated hypoattenuation of the lentiform nucleus in 88 patients from the ECASS1 cohort. They found that size of cortical extension was significantly lower in patients receiving rtPA than in the placebo group.

In our study, 57 (40%) of the 143 patients showing infarct enlargement between 24 to 36 hours and 7 days had received rtPA treatment within 6 hours.

Two hypotheses may explain the delayed lesion enlargement that may occur despite early rtPA treatment.

On one hand, reperfusion might be ineffective in tissue in which neurons have already undergone irreversible cell alterations. The apparent integrity at CT scan is compatible with ultrastructural changes, such as those seen in apoptosis, but less likely with cytotoxic edema preceding necrosis. In rats, neurons showing apoptotic changes, such as fragmentation of DNA, have been found 3 hours after ischemia, and in 1 study even earlier.

On the other hand, rtPA administration may fail to reperfuse a part of the ischemic tissue. Grotta and Alexandrov have found reperfusion after 24 hours to be greater in patients given rtPA than in patients given placebo. However, Heiss and colleagues reported various degrees of reperfusion after thrombolysis, with one third of patients showing no reperfusion in more than half of the ischemic territory.

These findings, along with experimental data, reinforce the hypothesis that the combination of neuroprotective drugs and thrombolytic therapy may limit the final volume of infarction.

The third point we addressed in this study is whether the CT evolution of the ischemic lesion has a clinical correlate, particularly in terms of neurological outcome.

In our study, the group of patients with a significantly delayed volume increase initially had a more severe neurological deficit and a lower degree of neurological improvement at 1 month. These data suggest that the initial neurological deficit corresponds to initial infarction and brain tissue at risk of subsequent delayed infarction. The damage to the tissue around the ischemic core that progresses over time and causes a significant enlargement of the infarction is likely to explain the minimal clinical recovery in these patients.

Finally, an unexpected result was the significant reduction in hypoattenuation between 24 to 36 hours and 7 days. Early hypoattenuation is generally considered a sign of irreversible injury, because it is due to cytotoxic edema.

In our study, of 20 patients with a significant lesion volume decrease, only 2 had an apparent resolution at day 7 of the area of hypoattenuation seen at CT. The resolution of early CT hypoattenuation was described in 1 patient who received intra-arterial thrombolysis. A fogging effect caused by extravasation of proteins, blood cells, or both through a disrupted blood-brain barrier may explain this finding. Alternatively, regression of vasogenic edema between CT and CT might also explain a lesion volume decrease. However, the greater neurological improvement at 1 month observed in this subgroup of patients is intriguing and deserves further investigation.

In conclusion, this study indicates that infarct development after ischemia in humans is heterogeneous and unpredictable. Although the infarct size is established at 24 to 36 hours after stroke onset in approximately two thirds of patients, changes in lesion volume may occur later than 24 to 36 hours in the remaining third. More frequently, the infarct volume significantly increases over time, through a significant volume decrease may be observed in a minority of cases. Many factors may be involved in this delayed infarct enlargement, which may occur despite early rtPA treatment and result in a lower degree of clinical recovery. CT technique may help increase our knowledge of the mechanisms of cerebral ischemia. However, further investigations aimed at investigating functional and morphological characteristics of peri-infarcted tissue over time will help to shed light on some of the numerous points that are still unclear.

Acknowledgments

The authors thank all of the ECASS investigators who were involved in the clinical trial and contributed to the data collection, and Dr Costantino Iadecola for his helpful comments on experimental ischemia.

References


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