Urgent Therapy for Acute Stroke
Effects of a Stroke Trial on Untreated Patients

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Background and Purpose As part of the recruitment efforts for the National Institutes of Health Tissue Plasminogen Activator Pilot Study, public education and awareness campaigns were conducted to encourage early hospital arrival. We evaluated the change in arrival times during the course of the study for all stroke patients, including those who were not entered into study.

Methods Data were gathered on all patients presenting within 24 hours of stroke onset to all of the study hospitals. Coincident with the start of the study, educational and promotional programs, which stressed signs and symptoms of stroke and the need to call 911, were presented to physicians, paramedical personnel, and the public. The study was divided into four quarters to analyze differences in time to hospital arrival and use of 911.

Results Of 2099 patients screened, time data were available on 1116. During the course of the study, the mean time from symptom onset to hospital arrival declined significantly (3.2 hours versus 1.5 hours). Patients arrived for treatment sooner at community hospitals than at university/teaching hospitals. The use of 911 increased from 39% in the first quartile of the study to 60% in the fourth quartile. This was a consistent finding in all study sites. Increased use of 911 was seen almost exclusively in patients with nonhemorrhagic stroke.

Conclusions Times from stroke onset to hospital arrival decreased significantly during the course of the National Institutes of Health Tissue Plasminogen Activator Pilot Study. Significantly increased use of 911 was the likely major explanation for the shortened arrival times. The decrease in arrival times may be a consequence of the public and professional education programs conducted at all study sites. (Stroke. 1994;25:2132-2137.)

Key Words • clinical trials • emergency medical services • health education

Ischemic stroke is an acute disease in which the early pathophysiological changes are dynamic. Once arterial occlusion occurs, there is a limited amount of time for selected interventions to be effective in salvaging brain tissue.1,2 There is increasing evidence that this window of opportunity probably exists for less than 4 to 6 hours after stroke onset, indicating the necessity for rapid patient assessment and evaluation for interventional treatment.2-5 One of the key elements for rapid assessment is early patient access of the healthcare delivery system.

The necessity for early patient evaluation and treatment also exists in patients with acute myocardial infarction (AMI).2-6 The procedures surrounding the process of salvaging heart tissue have been divided into three phases.7 Phase 1 is recognition of the signs and symptoms of AMI and the necessity for action. Phase 2 is emergency care that takes place after the decision to seek medical care has occurred but before the patient has arrived at the hospital. Phase 3 is the appropriate emergency care that should occur after arrival at the hospital or emergency center.

These same phases can be applied to emergency stroke evaluation and treatment. However, compared with the data available regarding emergency care of patients with AMI, appropriate information regarding stroke patients is almost nonexistent. Few studies have critically evaluated the time intervals from stroke onset to hospital arrival.10-12 Little data are available on why patients delay and on the most efficient ways to access the healthcare system.

We evaluated patient arrival times to the hospital as part of the National Institutes of Health (NIH) Tissue Plasminogen Activator (TPA) Pilot Study and showed that more than 50% of patients present to the hospital within 3 hours of stroke onset.13 As part of the recruitment efforts for that study, we conducted an extensive public education and awareness campaign to encourage early hospital arrival after stroke. We evaluated the change in arrival times during the course of the study for all stroke patients in the study locale, including those who were not entered into the study.

Subjects and Methods

Hospital medical records were screened at all participating centers (University of Cincinnati, University of Virginia, Cornell University) between February 1987 and August 1989. Data were gathered only on patients presenting within 24 hours of stroke onset. Information obtained from the patient, the patient's family, or most commonly from the medical record was gathered as part of the NIH TPA Pilot Study. Patients were eligible to receive TPA if they met the inclusion criteria and had no exclusions. Demographic data and information related to ictal events were gathered by study nurses on all patients presenting to the study hospitals within 24 hours of stroke onset whether or not they participated in the study. The data were collected retrospectively on a monthly basis within 30 to 60 days of stroke onset. Three of the hospitals were university hospitals, and nine were community hospitals with or without university affiliation. Of the community hospitals,
two were classified as "teaching hospitals" because they support a range of postgraduate training programs.

The educational programs began coincident with the start of the study in February 1987. The centers developed their own programs for educating emergency department medical staff and nursing staff. These included informational mailings, in-service training programs, and personal visits by study investigators. Educational lectures were given to the medical staff at many of the hospitals concerning the early evaluation and management of stroke patients. More importantly, educational programs were also conducted for the paramedics and prehospital care providers in the different locales. Programs for the paramedics stressed rapid assessment and transport of stroke patients with early notification of the study hospitals.

Promotional programs to the public were conducted by a multimedia approach with public service announcements and interviews on radio, television, and newspaper. The content of the messages was centered on the signs and symptoms of stroke and the need to call 911 if these signs and symptoms occurred.

Definitions of time intervals were established before data collection. The time of stroke onset was defined as the time when symptoms of stroke first occurred. If the patient was not able to give accurate information, the stroke was considered to start when the patient was last known to be asymptomatic. When the time of stroke onset was thought to be within 24 hours but could not be accurately assigned (eg, patient awakened with neurological deficits), this variable was labeled "unknown." The time of hospital arrival was the time noted on the emergency department record if the patient presented to the emergency department or the time of hospital admission if the patient was not seen in the emergency department. If the patient was transferred from another hospital, the time of emergency department arrival at the first hospital was used.

The time of first medical contact was defined as the first time at which medical assistance was requested. The categories included were 911, study hospital, another hospital, personal physician, and other. The 911 category for first medical contact referred to use of emergency medical services (EMS) as the first contact with medical professionals. EMS transport to the hospital by basic versus advanced emergency medical technicians was not differentiated.

Addition of Study Hospitals

When the study commenced, there were four university/teaching hospitals enrolling patients. By the end of the study, there were five university/teaching hospitals and seven community hospitals. The fifth university/teaching hospital was entered in the first quartile of the study, and subsequent hospital additions were all community hospitals. No community hospitals were entering patients in the first quartile. Two community hospitals were added in the second quartile, 3 in the third quartile, and 2 in the fourth quartile.

Data Analysis

The primary outcome variable, time elapsed from stroke onset to hospital arrival, was not normally distributed. A log transformation was performed, and the resulting variable was found to be normally distributed. All statistical tests on time from stroke onset to hospital arrival used this transformed variable. ANOVA was used to evaluate factors influencing time from onset to arrival. Potentially predictive factors were entered singly into ANOVAs with a liberal (P < .05) significance level as a cut point for inclusion in further analysis. Factors found significant in these ANOVAs were entered together into a main effects ANOVA with a significance level of P < .05 for the overall model. Tests for interaction effects and post hoc means comparisons were performed when appropriate. Logistic regression analyses were used to evaluate factors related to change during the course of the study and factors related to use of 911. Differences of P < .05 were considered statistically significant.

### Results

#### Sample Description

A total of 2099 patients were initially screened for the study. All patients presented to the participating institutions within 24 hours of stroke onset. Of these, 151 were found to have been admitted to a hospital before the stroke occurred and were excluded from further analysis. The remaining 1948 patients are described in Table 1. Of the 1948 patients screened, definitive time data regarding time of symptom onset were only present in 1116. Only 74 patients (3.5% of those screened) received TPA.

Table 2 shows characteristics of the stroke episodes included in the final sample. Table 2 also shows the time from stroke onset in the 1116 evaluable patients from whom accurate times were available. Thirty-nine percent of evaluable patients (22% of total patients) arrived within 90 minutes of stroke onset. By 6 hours, 77% of the evaluable patients had arrived at the hospital (44% of total).

#### Factors Predicting Time to Hospital Arrival

The following potential predictors of time from stroke onset to hospital arrival were entered into exploratory ANOVAs: age group, research community, type of hospital, stroke type, type of first medical contact (dichotomized by 911 versus other), sex, hour of day, race, patient location at time of stroke, and quartile of study. Quartile of the study was computed by dividing patient admissions over time into four chronological groups of equal number. The outcome variable, time from onset to hospital arrival, was log-normalized for this analysis. In a preliminary screening ANOVA, all factors except race, sex, and type of stroke were signif-
TABLE 2. Characteristics of the Stroke Episode

<table>
<thead>
<tr>
<th>Stroke-Related Variables</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>313</td>
<td>16</td>
</tr>
<tr>
<td>Nonhemorrhagic</td>
<td>1602</td>
<td>82</td>
</tr>
<tr>
<td>Patient's location when stroke occurred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>1862</td>
<td>85</td>
</tr>
<tr>
<td>Work</td>
<td>141</td>
<td>7</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>102</td>
<td>5</td>
</tr>
<tr>
<td>Hour of day when stroke occurred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midnight to 6 AM</td>
<td>135</td>
<td>7</td>
</tr>
<tr>
<td>6 AM to noon</td>
<td>459</td>
<td>24</td>
</tr>
<tr>
<td>Noon to 6 PM</td>
<td>431</td>
<td>22</td>
</tr>
<tr>
<td>6 PM to midnight</td>
<td>268</td>
<td>14</td>
</tr>
<tr>
<td>Unknown or not recorded</td>
<td>655</td>
<td>34</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Type of first medical contact</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMS (911)</td>
<td>885</td>
<td>45</td>
</tr>
<tr>
<td>Study hospital</td>
<td>591</td>
<td>30</td>
</tr>
<tr>
<td>Personal physician</td>
<td>196</td>
<td>10</td>
</tr>
<tr>
<td>Another hospital</td>
<td>144</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>Time from stroke onset to ED arrival, h*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1.5</td>
<td>432</td>
<td>38</td>
</tr>
<tr>
<td>1.5-3</td>
<td>223</td>
<td>20</td>
</tr>
<tr>
<td>3-4.5</td>
<td>112</td>
<td>10</td>
</tr>
<tr>
<td>4.5-6</td>
<td>93</td>
<td>8</td>
</tr>
<tr>
<td>6-24</td>
<td>256</td>
<td>23</td>
</tr>
</tbody>
</table>

EMR indicates emergency medical services; ED, emergency department. Percentages may not total 100% because of missing data.

*In 1116 evaluable patients from whom accurate times were available.

significant at P<.2; they were then entered into a final ANOVA with selected interaction terms tested. Significant terms in the final ANOVA model are shown in Table 3.

Post hoc tests (P<.01) were conducted on all significant main effect factors to describe the nature of the differences observed. These are depicted as median times to hospital arrival in Fig 1. Type of first medical contact was the factor most strongly related to early arrival at the hospital after stroke (Fig 1A). Patients using 911 arrived, on average, significantly more quickly (P<.0001) than other patients whose time of stroke was recorded between midnight and 6 AM (Fig 1E; P<.0056). There is, of course, difficulty in determining stroke onset when a patient awakens with a stroke. If stroke occurred during sleep, we assumed the stroke onset time to be immediately after the last time at which the patient was known to be asymptomatic (ie, at bedtime).

The significant interaction effect, shown in Fig 2, suggests that time from symptom onset to hospital arrival changed significantly during the course of the study and differentially in the three research communities studied. Across all sites, the first one quarter of patients screened had mean time to hospital arrival of 194 minutes (3.2 hours); subsequent quartiles showed a linear decrease to 167 minutes (2.8 hours), 121 minutes (2 hours), and finally 90 minutes (1.5 hours) during the last one quarter of the study (P<.032). However, as shown in Fig 2, while time to hospital arrival declined linearly at the University of Virginia and Cornell, there was an increase in time to arrival in Cincinnati for the second quartile of patients screened.

Factors Related to Change During the Course of the Study

As shown above, the time from symptom onset to hospital arrival declined significantly during the course of the study. To determine what other factors related to this decline, logistic regression analysis was performed to predict differences during the course of the study among possible explanatory variables including time of day, day of the week, age group, sex, race, type of first medical contact, patient's location when stroke occurred, type of stroke (hemorrhagic or nonhemorrhagic), type of hospital (teaching/university or community), and research community.

The overall model significantly related to quartile of the study (P<.0001). When maximum likelihood estimates for individual predictors were examined, significant effects were found for race (P<.04), location at time of stroke (P<.05), type of hospital (P<.0001), and use of 911 for first medical contact (P<.0001).

The distribution of race differed primarily in the first and second quartiles of the study. On average across the study's time span, the sample included in these analyses averaged 75% white and 22% black. However, the first quartile included relatively few black patients (16% of the sample for that quarter) and more white patients (81%), while in the second quartile there were relatively more black patients (30%) and fewer white patients (67%) enrolled.

The proportion of patients screened at community hospitals changed drastically as the study progressed. No
community hospitals were screening patients in the first quartile. In the second quartile, 2 of 7 study hospitals were community hospitals and accounted for 2 patients. By the third quartile, 50 patients (19% of the third quartile sample) were screened at community hospitals (5 of 10 study hospitals), and in the fourth quartile 98 patients, or 38% of the sample in that quartile, came from community hospitals (7 of 12 study hospitals).

The patient’s location at time of stroke showed one minor change across the span of the study. Across the entire study span, approximately 9% of patients in these analyses were at work when stroke occurred, and approximately 85% were at home. However, in the fourth quartile a greater than usual proportion of patients were at work (14%) rather than at home (80%).

Although there was a significant change in the time from symptom onset to hospital arrival during the course of the study, the time from symptom onset to first medical contact did not change significantly during the study. There was a trend toward decreasing time from symptom onset to first medical contact, but standard deviations were great.

When type of first medical contact was dichotomized into use of the emergency medical system (911) versus all others, major changes were seen in use of 911 across the time span of the study. For the study as a whole, 911 served as the first medical contact 45% of the time. However, Fig 3 shows that use of 911 increased across the study, from 39% of contacts in the first quartile to 60% in the fourth quartile. This represents a 55% increase in use of 911 from the start of the study to its completion. Other factors related to 911 use are explored below.
Other Factors Related to Use of 911

To determine the factors related to the likelihood of 911 contact when stroke occurred, logistic regression was performed, predicting dichotomized type of first medical contact (911 versus all others) by simultaneously evaluating the same set of variables as those for the quartile analysis above. The overall model fit was significant (P<.0001). Significant individual predictors of 911 use included age, race, sex, research community, hospital type, and stroke type.

Age was found to be marginally related to use of 911 (P<.006), with patients aged younger than 55 years using 911 approximately 40% of the time, whereas this sample as a whole used 911 approximately 49% of the time. Race was also found to be significantly related to 911 use (P<.005), with black patients using 911 slightly more (55% of the time) and patients of "other" (not black or white) races using 911 less (26% of the time) than the overall rate of 49% in the sample being analyzed. Differences in 911 use by sex (P<.04) resulted from slightly greater use of EMS by men (53%) compared with women (47%) in this sample.

There were major differences in 911 use among the three research communities involved in the study (P<.0001). Whereas 57% of patients in the Cincinnati area registered 911 as their first medical contact, only 42% of those at Cornell and 44% of University of Virginia area patients had contact with 911. Proportion of 911 use also differed significantly, although perhaps not meaningfully, according to whether patients were eventually treated at community hospitals or at university/teaching hospitals (P<.04). Whereas 50% of those presenting at community hospitals recorded EMS/911 as first medical contact, the percentage at university/teaching hospitals was only slightly lower (48%).

Interestingly, use of 911 was unrelated to the time of day when stroke occurred, the day of the week, or the patient’s location at the time of stroke. However, the type of stroke influenced the probability of 911 use (P<.0001); 58% of hemorrhagic strokes had a first medical contact through the 911 system, and 47% of patients with nonhemorrhagic strokes made contact with 911 services.

Discussion

Animal studies suggest that neurological deficits induced by arterial occlusion may be at least partially reversible for several hours after onset of stroke. The therapeutic window in humans may be only 3 to 4 hours, necessitating aggressive early stroke intervention and treatment. In the past, few stroke trials have emphasized early treatment; consequently, few have shown beneficial effects from treatment. If benefits are to be derived from early treatment, patients must be available for treatment shortly after the onset of stroke. Although the need for early patient evaluation is becoming more readily recognized, only one previous study has evaluated efforts to increase early arrival. This is in stark contrast to AMI, which has been the subject of numerous studies evaluating the reasons for delays in treatment.

To fulfill our study requirement for early patient entry in the NIH TPA Pilot Study, the investigators used different educational and public information forums to publicize the study and the need for early treatment of stroke.

Our results indicate that the time from stroke onset to hospital arrival changed significantly during the course of the NIH TPA Pilot Study. There are several possible explanations for this finding. We did not characterize stroke severity in screened patients, and it is possible that the change in arrival times after stroke onset may in some way be related to stroke severity. This is unlikely in that the number of patients with brain hemorrhage did not change significantly during the course of the study. We have also demonstrated previously that patients with hemorrhagic stroke did not arrive at the hospital earlier than those with nonhemorrhagic stroke presenting during the first 24 hours.

Some of the improvement in arrival times does relate to the use of community hospitals for patient enrollment. The finding of shorter times from stroke onset to hospital arrival in patients presenting to community hospitals has not been described previously but was quite dramatic in our study. Although the addition of community hospitals may have contributed to shorter arrival times in the Cincinnati community, the decrease in arrival times was also significant for Cornell patients, in which case no community hospitals were used.

The greatest single reason for early arrival during the course of the study appeared to be increased use of 911. Although the percentage of patients arriving early increased significantly by the end of the study, the time from stroke onset to first medical contact did not. It would appear that patients did not seek medical contact
sooner but did change their choice of whom to contact. While the increased use of 911 was presumably the result of public education efforts, it is possible that 911 use increased in all groups of patients and not just in those with stroke. This is unlikely in that the increase in 911 use that we observed was almost exclusively seen in patients with nonhemorrhagic stroke. A previous study by Alberts et al\textsuperscript{11} also showed that although public education efforts did not shorten arrival times for patients with hemorrhagic stroke, patients with ischemic stroke did arrive earlier. They postulated that the urgency for seeking medical care with hemorrhagic stroke was already maximized by the severity of symptoms and would not be further increased by public education. The increasing use of 911 during the course of this stroke therapy trial was encouraging in absolute terms (40\% in first quartile, 60\% in fourth quartile), and the change was statistically significant. Nonetheless, the results also show the need for ongoing emphasis of 911 systems. More than one of every three stroke patients were initially evaluated and transported through other, slower pathways in the Final quartile of the trial.

The finding that 77\% of evaluable patients (44\% of total) arrived within 6 hours of stroke onset is surprising. One of the few studies evaluating arrival to the hospital after stroke showed that only 42\% of patients arrived within 24 hours of stroke onset.\textsuperscript{10} A follow-up study by the same author found that this percentage increased to 86\% after a public and professional education campaign.\textsuperscript{11} In our study, data were only collected on patients presenting within 24 hours of stroke onset. Therefore, the total number of stroke patients in our population is underrepresented to some degree. However, even if one assumes that only 80\% of patients present within 24 hours as demonstrated by Alberts et al,\textsuperscript{11} and that all of the patients for whom accurate times of stroke onset were not available presented later than 6 hours, a minimum of 35\% of stroke patients presented within 6 hours of symptom onset.

Conclusions

During the course of the NIH TPA Pilot Study, the time from stroke onset to hospital arrival showed a significant decrease at all the study sites. Significantly increased use of 911 was the likely major explanation for the shortened arrival times. The decrease in arrival times was seen primarily in patients with nonhemorrhagic stroke and may be a consequence of the public and professional education and information programs conducted at all the study sites. Community hospitals may be ideal sites for acute stroke studies because patient arrival times are significantly shorter than those at university/teaching hospitals.

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/11/2132