End-Diastolic Velocity Increase Predicts Recanalization and Neurological Improvement in Patients With Ischemic Stroke With Proximal Arterial Occlusions Receiving Reperfusion Therapies

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Background and Purpose—It is unknown how little flow velocity improvement is necessary to achieve recanalization and clinical recovery. We sought to investigate which flow velocity parameter was associated with complete recanalization/reperfusion and neurological improvement in patients receiving reperfusion therapies.

Methods—Patients with proximal intracranial occlusions were treated with systemic or intra-arterial tissue plasminogen activator within 6 hours from symptom onset. Consecutive peak systolic and end-diastolic (EDV) velocities were measured during continuous transcranial Doppler monitoring. Recanalization was graded with Thrombolysis in Brain Ischemia grades. Neurological and functional outcomes were assessed by the National Institutes of Health Stroke Scale and modified Rankin Scale scores.

Results—Of 36 patients (mean age 57 ± 19 years, median National Institutes of Health Stroke Scale 15 points, interquartile range 9), 13 (36%) achieved complete recanalization and those had greater EDV increase during transcranial Doppler monitoring (15 ± 11 cm/s versus 6 ± 10 cm/s; P = 0.001). Peak systolic velocity increase with complete recanalization was 25 ± 11 cm/s (versus 20 ± 25 cm/s with partial recanalization/persisting occlusion; P = 0.123). Neurological improvement at 24 hours positively correlated to EDV increase (Spearman r = 0.337, P = 0.044) but not to peak systolic velocity (r = 0.197, P = 0.250). EDV increase at the end of monitoring was higher in patients with favorable functional outcome at 3 months (13 ± 13 cm/s versus 4 ± 8 cm/s; P = 0.021). After adjustment for potential confounders, including age, stroke risk factors, and baseline stroke severity, a 10-cm/s increase in EDV was independently associated with a 3-point decline in the National Institutes of Health Stroke Scale score at 24 hours from baseline (95% CI: 0 to 5; P = 0.045).

Conclusions—A modest increase in the EDV as opposed to peak systolic velocity is associated with complete recanalization/reperfusion, early neurological improvement, and favorable functional outcome. Diastolic flow augmentation may represent a novel target for development of reperfusion therapies. (Stroke. 2010;41:948-952.)

Key Words: occlusion ■ outcome ■ stroke ■ thrombectomy ■ thrombolysis

Under normal circulatory conditions, the brain receives continuous arterial blood flow supply during systole and diastole due to a low resistance in the cerebral vasculature (Figure 1). An arterial obstruction increases resistance to the incoming flow, and the end-diastolic flow becomes affected first because it is delivered at a lower arterial blood pressure than peak systole to counteract this resistance (Figure 1). The worse the pretreatment flow waveforms, the greater the clinical stroke severity and the poorer the outcomes, whereas higher flow velocities in general appear during recanalization.

Reperfusion therapies for stroke are thought to restore blood flow by induction of early recanalization as the mechanism for subsequent neurological improvement. In our previous studies, we validated the Thrombolysis in Brain Ischemia (TIBI) flow grading system and found that qualitative waveform analysis of the residual blood flow can predict complete recanalization and persistence of a proximal arterial obstruction.
occlusion in excellent agreement with angiography. Others found that absolute velocity values or velocity-derived asymmetry indices are also predictive of an acute arterial occlusion, recanalization, and recovery.

However, it remains unknown how little flow velocity improvement is necessary to achieve recanalization and subsequent neurological recovery. The importance of early reperfusion rather than late complete recanalization has been realized recently through analysis of combined systemic and intra-arterial thrombolysis angiographic data as well as MRI findings. Because the degree of recanalization and reperfusion could be discrepant, we decided to focus our analysis on those patients who achieved both early complete proximal recanalization and complete distal tissue reperfusion. In addition to good correlation with angiography to predict proximal recanalization, our TIBI system also correlates with Thrombolysis in Myocardial Infarction flow grades indicative of reperfusion. Of note, the end-diastolic velocity (EDV) is more representative of tissue reperfusion than peak systole because TIBI flow grades with positive EDV (ie, Grades 2 to 5) predict Thrombolysis in Myocardial Infarction Grades IIb to III.

In the Combined Lysis Of Thrombus in Brain ischemia using 2 MHz transcranial Ultrasound and Systemic T-PA (CLOTBUST) trial, we observed early complete recanalization on transcranial Doppler (TCD) coupled with dramatic neurological improvement suggesting that early recanalization can lead to substantial tissue reperfusion as evident from complete or nearly complete clinical recovery. We therefore sought to investigate which flow velocity parameter changes during treatment were independently associated with early complete recanalization and neurological improvement in patients receiving reperfusion therapies.

Subjects and Methods

Patients enrolled in a recent Phase II sonothrombolysis trial (Transcranial Ultrasound in Clinical SONothrombolysis [TUCSON]) had to have evidence of a proximal arterial occlusion such as the middle cerebral artery, terminal internal carotid artery, tandem internal carotid artery/middle cerebral artery, or the top-of-the-basilar/P1 posterior cerebral artery segments. All subjects had ultrasound evidence of the pretreatment proximal arterial occlusions such as abnormal 0 to 3 TIBI flow grades. In addition, all spectral waveforms were continuously captured and digitally stored using latest-generation digital TCD (Multigon, Yonkers, NY, and Spence Technologies, Seattle, Wash). Further details of the TUCSON trial protocol can be found elsewhere. Since completion of the TUCSON trial, our collaborative group continued similar digital TCD data acquisition during combined intravenous–intra-arterial or primary intra-arterial reperfusion therapy with tissue plasminogen activator within 6 hours from symptom onset. All subjects signed informed consent and TCD study protocols were approved by Institutional Review Boards at all participating institutions.

Digital data capturing permitted sampling peak systolic velocities (PSV) and EDV at the site of intracranial occlusions in real time. The baseline pretreatment values, the highest velocities detected at any time during, and final values at the end of the 90 minutes monitoring were selected. After waveforms were optimized to minimize the background noise and avoid aliasing, manual measurements were made by experienced sonographers (G.T. and M.R.) who were unaware of clinical outcomes.

Pretreatment stroke severity was assessed using the National Institutes of Health Stroke Scale Score (NIHSS) score by clinical investigators certified in the NIHSS. Continuous TCD monitoring for 90 minutes after tissue plasminogen activator bolus provided consecutive PSV and EDV measurements. Complete recanalization was defined as TIBI 5 (normal) waveform or Arterial Occlusive Lesions III score on catheter angiograms. Complete reperfusion was defined as TIBI Grade 5 low-resistance flow (pulsatility index recovery to values at <30% difference from the nonaffected side) or Thrombolysis in Myocardial Infarction III flow on catheter angiograms. Neurological and functional outcomes were assessed by the NIHSS scores and modified Rankin Scale scores, respectively. Neurological improvement was defined as any decrease in the NIHSS score (ie, by ≥1 points) at 24 hours compared with baseline. Favorable functional outcomes at 3 months were defined as modified Rankin Scale scores 0 to 2. All NIHSS and modified Rankin Scale scores were obtained by clinical investigators unaware of the purposes of this analysis.

Statistical Analyses

Statistical comparisons were performed between patients with complete recanalization and patients with partial recanalization/persisting occlusion using the χ² test, Fisher exact test, unpaired t test, and Mann-Whitney U test as indicated for dichotomous or continuous variables. The potential association between TCD parameters and the degree of neurological improvement was evaluated using Spearman correlation coefficient (r) and multiple linear regression models. Simple and multiple linear regression analyses were performed to assess which factors are associated independently with improvement (decline) in NIHSS score at 24 hours from baseline. Baseline characteristics and ultrasound parameters were selected as independent variables; NIHSS score decline was the dependent variable. The NIHSS score decline data were entered as continuous values in the model. The PSV and EDV data were also entered as continuous independent variables in the model. In the initial simple regression analysis, a threshold of P<0.1 was used to identify candidate variables for inclusion in the final model (because of the risk of Type II error attributable to low statistical power in such an analysis). The multiple regression analyses were performed using the backward procedure and repeated using a forward selection procedure. Statistical significance was achieved with a 2-tailed value of P<0.05. The associations between NIHSS score decline and the other variables are presented by means of linear regression coefficients with their corresponding 95% CIs. In multiple regression, a given regression coefficient indicates how much the predicted value of the dependent variable (NIHSS score decline) changes each time the respective variable increases by 1 U holding the values of all other variables in the regression equation constant. Finally, the significant independent variables selected by the multiple regression models were ranked...
Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>57 ± 19</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>58%</td>
</tr>
<tr>
<td>Baseline NIHSS score (median, interquartile range)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>69%</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>39%</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>31%</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>25%</td>
</tr>
<tr>
<td>Intrar-arterial thrombolysis (%)</td>
<td>64%</td>
</tr>
</tbody>
</table>

Results

Continuous digital velocity recordings were available in 36 patients (mean age 57 ± 19 years, median pretreatment NIHSS 15, interquartile range 9). Baseline characteristics of the study population are shown in Table 1. The location of proximal arterial occlusions was as follows: M1/M2 middle cerebral artery (64% (n=23)), internal carotid artery (28% (n=10)), and top-of-the-basilar/P1 posterior cerebral artery (8% (n=3)). The median pretreatment TIBI score was 1 (interquartile range 2). A total of 15 (42%) patients had a pretreatment TIBI score of 0 to 1, whereas the remaining 21 (58%) had a pretreatment TIBI score of 2 to 3.

According to the absolute value of their standardized effect quantified by the standardized regression coefficient (β). A standardized regression coefficient is defined as a regression coefficient that has the effect of the measurement scale removed so that the size of the coefficient can be interpreted; it is computed by multiplying the regression coefficient by the ratio of the SD (SDx) of the independent variable to the SD (SDy) of the dependent variable (β=regression coefficient×SDx/SDy). All covariates included in the final models were tested for interactions with each other. Because the tolerance values for each covariate were >0.5, no corrections for the collinearity of data or multiple testing were necessary. Statistical significance was achieved with a 2-tailed value of P<0.05. The Statistical Package for Social Science (Version 11.5 for Windows; SPSS Inc, Chicago, Ill) was used for statistical analyses.

Table 2. Improvement in TIBI Grades and NIHSS Scores During TCD Monitoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment TIBI 0–1 (n=15)</th>
<th>Pretreatment TIBI 2–3 (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment NIHSS score</td>
<td>22 ± 9</td>
<td>13 ± 6</td>
</tr>
<tr>
<td>NIHSS at the end of monitoring</td>
<td>21 ± 6</td>
<td>12 ± 9</td>
</tr>
</tbody>
</table>

Neurological improvement at 24 hours was positively correlated to EDV increase (Spearman correlation coefficient r=0.337, P=0.044) but was not related to PSV increase (r=0.197, P=0.250). EDV increase at the end of TCD monitoring was higher (P=0.021) in patients with favorable functional outcome at 3 months (13±13 cm/s versus 4±2 cm/s; or 102%±95% versus 62%±155% from baseline). No difference was noted in PSV increases (P=0.422) between patients with favorable and unfavorable 3-month functional outcome (29±30 cm/s versus 18±17 cm/s; or 97%±109% versus 52%±51% from baseline P=0.422). After adjustment for potential confounders, including age, stroke risk factors, and baseline stroke severity, EDV increase was linearly and positively associated with NIHSS score decline at 24 hours from baseline (standardized linear regression coefficient β=0.337; P=0.045). More specifically, a 1-cm/s increase in EDV was independently associated with a 0.26-point (unstandardized linear regression coefficient) decline in NIHSS score at 24 hours (95% CI: 0.01 to 0.56), whereas a 10-cm/s increase in EDV was independently associated with a 3-point (unstandardized linear regression coefficient) decline in the NIHSS score at 24 hours from baseline (95% CI: 0 to 5; P=0.045).

Discussion

Our study showed that a modest absolute increase in the EDV as opposed to PSV is associated with complete recanalization/reperfusion, early neurological improvement, and favorable functional outcome. It provides a closer look at the components of arterial blood supply that are relevant to the early improvement of the residual flow and reperfusion process for the ischemic brain.

Our study parallels previous findings that the higher the velocity on the affected side, the greater the chance of lesser occlusion burden and faster recovery from stroke. The appearance and improvement of EDV during treatment indicates that low resistance flow to the brain can be re-established because the waveform pulsatility reflects both the proximal and distal circulatory conditions, that is, resistance at the site of an arterial occlusion as well in the vasculature and tissues distal to it. The worst case scenario is the absent or even reversed diastolic flow that was shown to predict the most severe ischemic brain damage. The best case scenario is EDV recovery to 25% to 50% of PSV values during the same cardiac cycle in the affected vessel with <30% difference to the contralateral side that indicates
complete recanalization and low resistance reperfusion.\textsuperscript{1,4,5} In our study, an early and modest EDV improvement was a favorable prognostic sign. This, perhaps, was observed because the relative increase from baseline EDV was disproportionately greater than that of PSV, and the brain regained more continuous flow during this initially most compromised phase of the cardiac cycle. Although it is somewhat counterintuitive, we hypothesize that greater recovery of EDV indicates that the ischemic brain still maintains its low resistance and recanalization/reperfusion will likely occur into noncongested arterial branches and microcirculation, that is, without a “no reflow” phenomenon or distal embolic debris (that could account for discrepancies between proximal recanalization and lack of tissue reperfusion).\textsuperscript{16} This hypothesis is in line with data from coronary artery bypass grafting literature, in which the pattern of transmitral flow during diastolic filling has been documented as an independent outcome predictor. More specifically, patients with a restrictive transmirtal flow pattern have a higher risk of mortality and recurrent cardiac events after coronary artery bypass grafting.\textsuperscript{22}

Our study suggests a new target for acute reperfusion therapies by demonstration that even a very modest absolute increase in the diastolic velocity (in the range of 10 cm/s) can lead to significant neurological (3-point or more decrease in baseline NIHSS score at 24 hours after stroke onset) and functional improvement if achieved early. Our data underscore the significance of the end-diastolic flow (and likely systemic parameters that it depends on) for early brain reperfusion. Perhaps, future studies of acute blood pressure management or blood flow augmentation should consider monitoring EDV responses to blood pressure manipulations, particularly in patients with persisting arterial occlusions.

Our study has limitations because it is an exploratory analysis with relatively few patients. Moreover, continuous blood pressure monitoring was not performed during catheter angiography. Furthermore, velocity should not be equated with flow.\textsuperscript{23} However, velocity changes over short periods of time and at steady angles of insonation can reflect relative increases in blood flow,\textsuperscript{24,25} thus explaining the correlation with recanalization and neurological recovery. In addition, given the limited sample of patients, we were unable to...
evaluate the association between EDV increase and favorable functional outcome on the 3-month modified Rankin Scale score using multivariate logistic regression models and adjusting for potential confounders. Therefore, the present preliminary findings may serve only for hypothesis generation and need further confirmation by independent investigators. Indeed, we plan to prospectively validate the current observations in the CLOTBUST-PRO multicenter study including a large sample (n=480) of patients treated with systemic or intra-arterial thrombolysis and continuously monitored with TCD over 2 hours after tissue plasminogen activator bolus.26

In conclusion, a modest absolute increase in the EDV as opposed to PSV is associated with complete recanalization, early neurological improvement, and favorable functional outcome. Diastolic flow augmentation may represent a novel target for development of reperfusion therapies.

Disclosures
A.V.A. was the Principal Investigator of the CLOTBUST trial, study director of the TUCSON trial, serves on the speaker bureau of Genentech, Inc, and develops novel technologies under his patent on ultrasound enhanced thrombolysis for stroke. G.T. received a fellowship grant from the Neurology Department, Eginition Hospital, University of Athens School of Medicine, Athens, Greece. M.R. received a fellowship grant from the Instituto de Recerca Hospital Vall d’Hebron, Barcelona, Spain. C.A.M. was the Principal Investigator of the TUCSON trial. A.W.A. serves on the speaker bureau for Genentech, Inc.

References
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