



## Discover Generics

Cost-Effective CT & MRI Contrast Agents



[VIEW CATALOG](#)

# AJNR

This information is current as of September 15, 2025.

### **Safety and Efficacy of Endovascular Sonolysis Using the EkoSonic Endovascular System in Patients with Acute Stroke**

M. Kuliha, M. Roubec, T. Jonszta, J. Krajca, D. Czerny, A. Krajina, K. Langová, R. Herzig, V. Procházka and D. Skoloudík

*AJNR Am J Neuroradiol* 2013, 34 (7) 1401-1406

doi: <https://doi.org/10.3174/ajnr.A3416>

<http://www.ajnr.org/content/34/7/1401>

# Safety and Efficacy of Endovascular Sonolysis Using the EkoSonic Endovascular System in Patients with Acute Stroke

M. Kuliha, M. Roubec, T. Jonszta, J. Krajča, D. Czerny, A. Krajina, K. Langová, R. Herzig, V. Procházka, and D. Školoudík



## ABSTRACT

**BACKGROUND AND PURPOSE:** Sonolysis is a new therapeutic procedure for arterial recanalization. The aim of this study was to confirm the safety and efficacy of endovascular sonolysis by using the EkoSonic Endovascular System in subjects with acute ischemic stroke.

**MATERIALS AND METHODS:** Patients with acute ischemic stroke with occlusion of the middle cerebral artery or basilar artery were enrolled consecutively in this prospective study. The control group (44 MCA and 12 BA occlusions) was selected from historical controls. EkoSonic Endovascular System was started within 8 hours after stroke onset. The NIHSS score at hospital admission, after 24 hours, and at 7 days; arterial recanalization; early neurologic improvement; symptomatic intracerebral hemorrhage; and favorable 3-month clinical outcome defined as a modified Rankin Scale score of 0–2 were evaluated by statistical means.

**RESULTS:** Fourteen patients (10 men; mean age,  $65.1 \pm 11.2$  years; median NIHSS score, 16.5) underwent EkoSonic endovascular sonolysis. Arterial recanalization after endovascular treatment was achieved in 6 of 7 (85.7%) patients with MCA occlusion (4 complete recanalizations) and in all 7 (100%) patients with BA occlusion (6 complete recanalizations). No (0%) symptomatic intracerebral hemorrhage or periprocedural complications occurred. Seven (50%) patients were independent at 3 months (median mRS score, 2). Early neurologic improvement and favorable clinical outcome were significantly more frequent in patients with MCA occlusion undergoing EkoSonic endovascular sonolysis than in controls (100% and 71.4% versus 4.6% and 13.6% of patients;  $P = .0001$  and  $P = .003$ , respectively). Three-month mortality was significantly lower in patients with BA occlusion undergoing EkoSonic endovascular sonolysis than in controls (0% versus 66.7% patients,  $P = .013$ ).

**CONCLUSIONS:** In this small study, EkoSonic endovascular sonolysis allowed safe and potentially effective revascularization in patients experiencing acute ischemic stroke.

**ABBREVIATIONS:** BA = basilar artery; cPTAS = combined percutaneous transluminal angioplasty and stenting; mRS = modified Rankin Scale; IAT = intra-arterial thrombolysis; TICl = Thrombolysis in Cerebral Ischemia

Acute occlusion of cervical or intracranial arteries is the most common cause of ischemic stroke. Detection of arterial occlusion during the first 6 hours after the onset of ischemic stroke is possible in  $\leq 70\%$  of patients.<sup>1–4</sup> Clinical studies have shown that the prognosis of patients with occlusion of the intracranial arteries

in the acute phase of ischemic stroke is worse compared with patients without occlusion of a major intracranial artery.<sup>5</sup> One of the most important prognostic factors in patients with occlusion of the intracranial arteries is the time to recanalization.<sup>6–9</sup>

Data from a meta-analysis of 53 clinical trials (2066 patients) suggest that early recanalization is present in only 24.1% of patients without specific treatment (spontaneous recanalization), 46.2% of patients treated with intravenous thrombolysis, 63.2% of patients treated with intra-arterial thrombolysis, 67.5% of patients treated with combined IV thrombolysis–IAT, and in  $\leq 83.6\%$  of patients treated by mechanical methods.<sup>5</sup>

The options for acceleration of recanalization of intracranial

Received May 24, 2012; accepted after revision September 22.

From the Comprehensive Stroke Center (M.K., M.R., D.Š., T.J., J.K., D.C., V.P.), Department of Neurology, Faculty of Medicine, Ostrava University and University Hospital Ostrava, Ostrava, Czech Republic; Comprehensive Stroke Center (M.K., R.H., D.Š.), Department of Neurology, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic; Comprehensive Stroke Center, Department of Radiology (A.K.), Faculty of Medicine, Charles University and University Hospital Hradec Králové, Hradec Králové, Czech Republic; and Department of Biophysics (K.L.), Faculty of Medicine and Dentistry, Institute of Molecular and Translational Medicine, Palacký University, Olomouc, Czech Republic.

This work was supported by grants from the Internal Grant Agency of the Ministry of Health of the Czech Republic (numbers NT/11386-5/2010 and NT/11046-6/2010) and by grant number CZ.1.05/2.1.00/010030.

Please address correspondence to David Školoudík, MD, PhD, FESO, Comprehensive Stroke Center, Department of Neurology, University Hospital Ostrava 17, listopadu 1790 CZ–708 52 Ostrava, Czech Republic; e-mail: skoloudik@hotmail.com

Indicates open access to non-subscribers at [www.ajnr.org](http://www.ajnr.org)

<http://dx.doi.org/10.3174/ajnr.A3416>

artery occlusion are the following: IV thrombolysis, IAT, or combined thrombolysis; mechanical recanalization by using several mechanical devices for thrombectomy and/or stent placement; and remote or local sonolysis.<sup>10–24</sup> Endovascular sonolysis can be used to accelerate and achieve recanalization of intracranial arterial occlusion.<sup>22–24</sup>

The aim of the present study was to confirm the safety and efficacy of endovascular sonolysis by using the EkoSonic Endovascular System (EKOS, Bothell, Washington) in patients with acute ischemic stroke with occlusion of the middle cerebral artery or basilar artery within 8 hours after stroke onset.

## MATERIALS AND METHODS

### Patients

Consecutive patients who fulfilled the following inclusion criteria between August 2009 and September 2011 were recruited into this prospective case control study: acute ischemic stroke due to occlusion of the MCA or BA detected by using CTA; presenting with an NIHSS score of 4–25 on hospital admission; contraindicated for IV thrombolysis or with persistent artery occlusion 60 minutes after IV thrombolysis commencement; 18–80 years of age; and start of therapy within 8 hours of symptom onset. Patients with a modified Rankin Scale score of >1 before stroke onset, intracranial hemorrhage, or brain tumor detected by using CT were excluded from the study. The control group was selected from consecutive historical controls fulfilling the same inclusion and exclusion criteria, hospitalized between July 2006 and January 2008 (ie, before the era of mechanical recanalization at the stroke center in which the study was performed).

### Diagnostics

On hospital admission, physical examination, blood samples, electrocardiography, chest radiography, and standard neurologic evaluation by a certified neurologist using the NIHSS were undertaken. These tests were followed by CT of the brain and CTA of the cervical and brain arteries. Duplex sonography of the cervical portion of the carotid and vertebral arteries and transcranial color-coded duplex sonography were performed before and 60 minutes after IV thrombolysis commencement.

Neurologic and physical examinations were repeated after 24 hours, at 7 days, and at 90 days. Early neurologic improvement was defined as an NIHSS score of zero or 1 at 24 hours after treatment or a decrease of  $\geq 4$  points in the NIHSS score 24 hours after treatment. The mRS was used for the evaluation of clinical outcome 90 days after ischemic stroke onset with a favorable clinical outcome defined as mRS 0–2. Intracranial bleeding detected in the control brain CT 24 hours after therapy onset was recorded. Intracranial bleeding with worsening of neurologic symptoms ( $\geq 4$  points in the NIHSS) was classified as “symptomatic intracerebral hemorrhage.”<sup>25</sup>

### Treatment

Patients were treated at a comprehensive stroke center with 24/7 accessibility to IV thrombolysis and endovascular interventions, and they underwent standard treatment.<sup>26</sup> All patients who fulfilled the Safe Implementation of Thrombolysis in Stroke-Moni-

**Table 1: Thrombolysis in Cerebral Ischemia criteria<sup>28</sup>**

| TICI Flow Grade | Characteristics                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| Grade 0         | No perfusion                                                                          |
| Grade I         | Perfusion past the initial occlusion, but no distal branch filling                    |
| Grade IIa       | Partial perfusion with incomplete distal filling of <50% of the expected territory    |
| Grade IIb       | Partial perfusion with incomplete distal filling of 50%–99% of the expected territory |
| Grade IIc       | Near-complete perfusion, but with delay in contrast runoff                            |
| Grade III       | Full perfusion with normal filling of distal branches in a normal hemodynamic fashion |

toring Study criteria for IV thrombolysis were treated by using rtPA (0.9 mg/kg) within 4.5 hours after ischemic stroke onset.<sup>26,27</sup>

Anticoagulation therapy (oral, subcutaneous, or intravenous) and oral administration of acetylsalicylic acid or other antiplatelet agents were used as standard treatment for patients 24 hours after ischemic stroke onset according to guidelines set by the European Stroke Organization.<sup>26</sup>

### Endovascular Treatment

For vessel occlusion, verification was confirmed in all patients by using 4-vessel diagnostic DSA (Innova 4100; GE Healthcare, Milwaukee, Wisconsin). After intra-arterial administration of heparin (total dose, 50 IU/kg) and placement of the EkoSonic Endovascular catheter within the occluded segment of the artery, the insonation with pulsed high-frequency (2.05–2.35 MHz) and low-power (400 mW/cm<sup>2</sup>) sonographic waves and local administration of rtPA directly into the thrombus were started simultaneously. Patients without contraindication to thrombolysis treatment received rtPA (15 mg/h). The maximum calculated total dosage was  $\leq 20$  mg of rtPA, and the endovascular sonolysis was  $\leq 60$  minutes.

In the case of partial recanalization or early reocclusion after endovascular sonolysis, patients had additional treatment with angioplasty and stent implantation (Enterprise; Cordis Neurovascular, Miami Lakes, Florida or Wingspan; Boston Scientific, Natick, Massachusetts). In all patients with stent implantation, 500 mg of acetylsalicylic acid was administered intravenously at the end of the endovascular procedure. Subsequently, within the next 2 hours, 150 mg of oral clopidogrel followed by 6-week dual oral antiplatelet therapy (100 mg acetylsalicylic acid daily and 75 mg clopidogrel daily) was used in all patients with cPTAS, as an instituted therapy regimen. Repeated diagnostic angiography of the treated region was undertaken to assess the recanalization grade according to Thrombolysis in Cerebral Ischemia criteria (Table 1).<sup>28</sup>

### Evaluation of Recanalization

The efficacy of recanalization was evaluated at the end of the endovascular procedure by using TICI criteria. Final recanalization status, TICI IIa or IIb, was considered “partial recanalization” and final status, TICI IIc or III, was “complete recanalization.” An experienced independent radiologist (A.K.), blinded to the study protocol, evaluated all findings before definitive assessment of the diagnosis.

**Table 2: Demographic data of the study group**

|                                            | EKOS<br>MCA   | Control<br>MCA | P    | EKOS<br>BA    | Control<br>BA | P    |
|--------------------------------------------|---------------|----------------|------|---------------|---------------|------|
| No. of subjects                            | 7             | 44             | —    | 7             | 12            | —    |
| Age (mean) (yr)                            | 69.1 ± 11.4   | 68.7 ± 11.2    | <.05 | 61.0 ± 9.4    | 68.9 ± 12.9   | <.05 |
| Males (No.) (%)                            | 5 (71.4%)     | 22 (50.0%)     | <.05 | 5 (71.4%)     | 9 (75.0%)     | <.05 |
| Arterial hypertension (No.) (%)            | 7 (100%)      | 33 (75.0%)     | <.05 | 4 (57.1%)     | 9 (75.0%)     | <.05 |
| Diabetes mellitus (No.) (%)                | 2 (28.6%)     | 8 (18.2%)      | <.05 | 1 (14.3%)     | 3 (25.0%)     | <.05 |
| Hyperlipidemia (No.) (%)                   | 2 (28.6%)     | 9 (20.5%)      | <.05 | 2 (28.6%)     | 5 (41.7%)     | <.05 |
| Atrial fibrillation (No.) (%)              | 2 (28.6%)     | 19 (43.2%)     | <.05 | 2 (28.6%)     | 4 (33.3%)     | <.05 |
| Smoking (No.) (%)                          | 2 (28.6%)     | 8 (18.2%)      | <.05 | 1 (14.3%)     | 2 (25.0%)     | <.05 |
| Heavy alcohol consumption (No.) (%)        | 0 (0%)        | 1 (2.3%)       | <.05 | 0 (0%)        | 0 (0%)        | <.05 |
| ICA/VA stenosis >50% (No.) (%)             | 1/0 (14.3/0%) | 7/0 (15.9/0%)  | <.05 | 0/3 (0/42.3%) | 0/4 (0/33.3%) | <.05 |
| Left hemisphere (No.) (%)                  | 3 (42.9%)     | 25 (56.8%)     | <.05 | —             | —             | —    |
| Use of acetylsalicylic acid (No.) (%)      | 2 (28.6%)     | 15 (34.1%)     | <.05 | 2 (28.6%)     | 4 (33.3%)     | <.05 |
| Stroke in medical history (No.) (%)        | 1 (14.3%)     | 7 (15.9%)      | <.05 | 1 (14.3%)     | 3 (25.0%)     | <.05 |
| Myocardial infarction in history (No.) (%) | 1 (14.3%)     | 8 (18.2%)      | <.05 | 1 (14.3%)     | 2 (16.7%)     | <.05 |
| IV thrombolysis (No.) (%)                  | 3 (42.9%)     | 26 (59.1%)     | <.05 | 2 (28.6%)     | 6 (50.0%)     | <.05 |
| IAT (No.) (%)                              | 6 (85.7%)     | 0 (0%)         | —    | 7 (100%)      | 0 (0%)        | —    |
| cPTAS (No.) (%)                            | 3 (42.9%)     | 0 (0%)         | —    | 5 (71.4%)     | 0 (0%)        | —    |

**Note:**—VA indicates vertebral artery; EKOS, EkoSonic Endovascular System.

**Table 3: Recanalization at the end of use of the EkoSonic Endovascular System in patients with MCA and BA occlusion and procedural data**

|                                            | MCA          | BA           | All          |
|--------------------------------------------|--------------|--------------|--------------|
| Complete MCA recanalization (TICI IIc-III) | 4 (57.1%)    | 6 (85.7%)    | 10 (71.4%)   |
| Partial MCA recanalization (TICI IIa-IIb)  | 2 (28.6%)    | 1 (14.3%)    | 3 (21.4%)    |
| No recanalization (TICI 0-I)               | 1 (14.3%)    | 0 (0%)       | 1 (7.1%)     |
| Time from onset to admission (mean) (min)  | 139.3 ± 76.6 | 171.4 ± 76.4 | 155.4 ± 78.1 |
| Time from onset to EKOS start (mean) (min) | 163.6 ± 75.5 | 210.7 ± 78.6 | 187.1 ± 80.6 |
| Length of procedure (mean) (min)           | 67.1 ± 11.4  | 57.9 ± 9.4   | 62.5 ± 28.0  |

**Note:**—EKOS indicates EkoSonic Endovascular System.

### Statistical Analyses

Kolmogorov-Smirnov and Shapiro-Wilk methods were used for testing the fit of the parameters calculated to a normal distribution. Data with a normal distribution are reported as the mean ± SD. All parameters that did not fit a normal distribution are presented as median and interquartile ranges; the Mann-Whitney *U* test and Fischer exact test were used for comparisons of groups. Statistical analyses were performed by using the Statistical Package for the Social Sciences software, Version 14.0 (SPSS, Chicago, Illinois). *P* < .05 was considered significant.

### Approval of the Study Protocol by the Ethics Committee

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008). The ethics committee of the stroke center in which the study was performed approved the study. All patients signed informed consent forms for treatment. Independent witnesses verified the signatures if there were technical problems.

### RESULTS

Fourteen patients (10 men; range, 47–80 years of age; mean, 65.1 ± 11.2 years) with acute ischemic stroke due to MCA or BA occlusion were enrolled in this prospective study. Five patients fulfilling the criteria for IV thrombolysis started receiving rtPA within 4.5 hours after ischemic stroke onset. The control group comprised 44 patients with acute ischemic stroke with MCA occlusion and 12 patients with BA occlusion (demographic data are shown in Table 2). Median NIHSS scores on hospital admission did not differ significantly between treatment and control groups

(MCA: 15 versus 15.5; BA: 27 versus 24; *P* > .05). General anesthesia was used in 6 patients treated with the EkoSonic Endovascular System; conscious sedation was administered in 8 patients.

Time of onset to treatment (IV thrombolysis, endovascular treatment) commencement, length of the endovascular procedure, and recanalization at the end of the endovascular intervention are presented in Table 3. The mean time of onset to endovascular treatment start was 187.1 ± 80.6 minutes, and the mean length of the procedure was 62.5 ± 28.0 minutes. Complete recanalization of the MCA and BA after endovascular treatment (combined with percutaneous transluminal angioplasty with stent placement when indicated) was achieved in 4 (57.1%; 95% confidence interval [CI], 18.4%–90.1%) and 6 (85.7%; 95% CI, 42.1%–99.6%) patients, respectively. Furthermore, partial recanalization was achieved in 2 (28.6%; 95% CI, 3.7%–71.0%) patients with MCA occlusion and in 1 (14.3%; 95% CI, 0.4%–57.9%) patient with BA occlusion.

The NIHSS scores at day 7 and 90-day mRS scores were significantly better in patients with acute ischemic stroke after endovascular sonolysis (cPTAS when indicated) than in controls (Table 4). Early neurologic improvement and favorable clinical outcome at day 90 were achieved in 7 (100%; 95% CI, 65.2%–100%) and 5 (71.4%; 95% CI, 29.0%–96.3%) patients with MCA occlusion treated by using the EkoSonic Endovascular System compared with 2 (4.5%; 95% CI, 0.6%–15.5%) and 6 (13.6%; 95% CI, 5.2%–27.4%) patients in the control group (*P* = .0001 and *P* = .003). Symptomatic intracerebral hemorrhage did not occur in any patient treated by using the EkoSonic Endovascular System compared with 3.6% of patients in the control group (Table 4). No periprocedural complication occurred in patients who underwent endovascular treatment.

Seven-day and 3-month mortality were significantly lower in patients with BA occlusion treated by using endovascular sonolysis than in the control group (*P* < .05) (Table 4). No significant

**Table 4: Clinical results in the particular subgroups**

|                                          | EKOS<br>MCA | Control<br>MCA | P     | EKOS<br>BA   | Control<br>BA | P    |
|------------------------------------------|-------------|----------------|-------|--------------|---------------|------|
| Baseline NIHSS (median) (IQR)            | 15 (10–18)  | 15.5 (12–20)   | <.05  | 27 (14.5–33) | 24 (12–32)    | <.05 |
| NIHSS 24 hr (median) (IQR)               | 4 (2–6)     | 16 (12–20)     | .0001 | 10 (7–25)    | 24 (14–28)    | <.05 |
| NIHSS day 7 (median) (IQR)               | 2 (1.5–4)   | 15.5 (7–20)    | .0001 | 6 (4.5–19)   | 33 (8–33)     | .049 |
| Presence of ENI after 24 hours (No.) (%) | 7 (100%)    | 2 (4.6%)       | .0001 | 4 (57.1%)    | 2 (16.7%)     | <.05 |
| 90-day mRS (median) (IQR)                | 1 (1–3.5)   | 5 (3–5)        | .037  | 3 (2–4.5)    | 6 (4.5–6)     | .034 |
| mRS 0–3 at day 90 (No.) (%)              | 5 (71.4%)   | 8 (18.2%)      | .008  | 4 (57.1%)    | 2 (16.7%)     | <.05 |
| mRS 0–2 at day 90 (No.) (%)              | 5 (71.4%)   | 6 (13.6%)      | .003  | 2 (28.6%)    | 2 (16.7%)     | <.05 |
| SICH (No.) (%)                           | 0 (0%)      | 1 (2.3%)       | <.05  | 0 (0%)       | 1 (8.3%)      | <.05 |
| Malignant infarction (No.) (%)           | 0 (0%)      | 3 (6.8%)       | <.05  | 0 (0%)       | 0 (0%)        | <.05 |
| 7-day mortality (No.) (%)                | 0 (%)       | 3 (6.8%)       | <.05  | 0 (%)        | 6 (50.0%)     | .044 |
| 3-month mortality (No.) (%)              | 2 (28.6%)   | 10 (22.7%)     | <.05  | 0 (0%)       | 8 (66.7%)     | .013 |

**Note:**—ENI indicates early neurologic improvement; EKOS, EkoSonic Endovascular System; SICH, symptomatic intracerebral hemorrhage; IQR, interquartile range.

difference in mortality rates was detected in patients with MCA occlusion.

## DISCUSSION

The results of the present study indicated the safety of endovascular sonolysis by using the EkoSonic Endovascular System without symptomatic intracerebral hemorrhage or periprocedural complications. No occurrence of symptomatic intracerebral hemorrhage is even more remarkable when comparing it with the results of the Interventional Management of Stroke (IMS) II trial, in which symptomatic intracerebral hemorrhage occurred mainly (in all except 1) in patients with NIHSS scores of  $\geq 20$ , though in the present study, the number of patients with NIHSS scores of  $\geq 20$  was 6 (42.9%)<sup>23</sup> and all patients received heparin, 5 (35.7%) received IV thrombolysis, 13 (92.9%) received intra-arterial thrombolysis, and 8 (57.1%) patients were treated with dual antiplatelet therapy. This result may be biased by a small number of patients.

In the study, 3-month mortality was observed in 14.3% of patients. The efficacy of endovascular sonolysis (cPTAS when indicated) was suggested. Complete or partial MCA recanalization after endovascular treatment was achieved in 92.9% of patients.

In the past decade, the number of methods used for the acceleration of arterial recanalization has increased greatly. In addition to pharmacologic methods, especially IV thrombolysis and intra-arterial thrombolysis, mechanical neurointerventional methods (eg, Merci retriever [Concentric Medical, Mountain View, California]; Penumbra System [Penumbra, Alameda, California]; Solitaire stent [ev3, Irvine, California]; Trevo Pro [Concentric Medical]; Catch device [Balt, Montmorency, France]; Phenox clot retriever [phenox, Bochum, Germany]; BONnet Intracranial Flow Restoration Device [phenox]; or pREset Thrombectomy Retriever [phenox]; EkoSonic Endovascular System [EKOS, Bothell, Washington]; or, direct stent placement) have been introduced into clinical practice.<sup>10–19</sup> One of these, the EkoSonic Endovascular System, is the first tool system approved by the FDA that allows local endovascular application of high-frequency (2 MHz) and low-power (400 W/cm<sup>2</sup>) sonography in clinical practice with or without simultaneous catheter-directed thrombolysis by application of thrombolytic drugs.<sup>22–24</sup>

Several in vitro, in vivo, and clinical studies have shown the potential effect of sonography (sonolysis) to accelerate clot lysis. The first clinical studies with endovascular sonolysis were used for

the recanalization of coronary arteries. In the Analysis of Coronary Sonography Thrombolysis Endpoints in Acute Myocardial Infarction study, low-frequency (45 kHz) sonography was used with high intensity (18 W/cm<sup>2</sup>) in the treatment of acute occlusion of the coronary arteries.<sup>29</sup> Complete recanalization was achieved in 87% of patients. No side effects were observed during therapy, and 80% of patients showed clinical improvement. Other studies showed the effect of endovascular sonolysis by the EkoSonic Endovascular System in patients with deep venous thrombosis of the lower extremities and in patients with pulmonary embolism.<sup>30–35</sup> Complete recanalization was achieved in 85.2%–96.0% of patients with arterial thrombosis<sup>34,35</sup> and in 83.0% patients with venous thrombosis.<sup>31</sup>

Mahon et al<sup>22</sup> published the first experience with endovascular sonolysis by using the EkoSonic Endovascular System in patients with acute ischemic stroke. It was a combination of intra-arterial thrombolysis using rtPA with endovascular sonography in 10 patients with MCA occlusion and in 4 patients with BA occlusion. Partial or complete recanalization was detected in 57% of patients, and there were no adverse effects during therapy. Three patients died within the first 24 hours. The mean mRS score in survivors with MCA occlusion was 2, and in survivors with vertebrobasilar occlusion, it was 3.

The system was tested subsequently in the IMS II trial with promising results.<sup>23</sup> Complete recanalization was achieved within 60 minutes and 120 minutes in 12 (41%) and 20 (68.9%) patients, respectively. Symptomatic intracerebral hemorrhage occurred in 9.9% of subjects in IMS-II, including 3.8% of patients treated with intravenous rtPA alone. Direct perforation of vessels, primary subarachnoid hemorrhage, or intracranial dissection was not documented in the subjects treated. The results of the present study showed an even higher prevalence of recanalization without symptomatic intracerebral hemorrhage.

The complex effect of sonography on the acceleration of thrombus lysis is incompletely understood, but it is assumed that the sonographic waves accelerate enzymatic fibrinolysis primarily by nonthermal mechanisms. Mechanisms that have been postulated include the following: increasing the transport of fibrinolytic agents into the thrombus by mechanical disruption of its structure<sup>36</sup>; direct activation of fibrinolytic enzymes (either mechanical dissociation of the complex molecules, in which fibrinolytic enzymes are inactivated by binding to their inhibitors, or irrita-



tion of the endothelium with increased production of fibrinolytic enzymes<sup>37,38</sup>); and transient peripheral (capillary) vasodilation caused probably by increased production of nitric oxide in the endothelium.<sup>39,40</sup> Radiation force and acoustic cavitation are mechanical effects of sonography that have also been postulated to be a potential mechanism.<sup>41</sup>

Several clinical studies have tested the feasibility and safety of other mechanical devices, especially of the Merci Retrieval System, Penumbra System, Solitaire stents, and direct placement of stents. The reported prevalence of recanalization in those studies ranged from 46% for the Merci retriever system,<sup>10</sup> 84% for the Penumbra system,<sup>11,12</sup> 90% for the Solitaire stent,<sup>13</sup> and up to 100% for direct stent placement.<sup>18,19</sup> Periprocedural complications varied between 3.4% and 9.0%. Symptomatic intracerebral hemorrhage occurred in 10%–11%, and the mortality rate was 32.8%–35.0%. Favorable clinical outcome (defined as mRS, 0–2) ranged from 36% up to 74%.<sup>10–19</sup> The present study showed that the prevalence of recanalization and favorable outcome in patients treated by endovascular sonolysis in combination with local or systemic thrombolysis (and cPTAS if indicated) was comparable with (or even superior to) other endovascular methods, especially in patients with MCA occlusion. Moreover, it seemed to be safer.

Previous studies primarily involved patients with occlusion in the anterior circulation. Nevertheless, the likelihood of achieving a favorable outcome in patients with a BA occlusion is worse than in those with an MCA occlusion. More than 90% of patients with a BA occlusion and any type of treatment die or have a permanent disability.<sup>42,43</sup> Studies have shown that patients treated by anti-thrombotic drugs have a chance of favorable outcome of 7%, but patients treated by IV thrombolysis (or by a combination of IV thrombolysis with intra-arterial treatment) have a chance of favorable outcome of 41%. In patients treated intra-arterially, partial or complete recanalization (defined as a Thrombolysis in Myocardial Infarction score of 2–3) of the BA at the end of an intra-arterial procedure was found in 72% of patients and symptomatic intracerebral hemorrhage was reported in 14% of patients.<sup>44</sup> Jung et al<sup>45</sup> reported similar results in patients with BA occlusion treated by intra-arterial thrombolysis (prothrombinase) and/or mechanical interventions. Complete or partial recanalization was achieved in 69.8% of patients, with favorable 3-month clinical outcome (defined as an mRS score of 0–3) achieved in 44% patients and an occurrence of symptomatic intracerebral hemorrhage of 0.9%. Those results are in agreement with those of the present study, in which recanalization was achieved in 100% of patients, with a favorable 3-month clinical outcome (defined as an mRS score of 0–3, especially for the BA group) achieved in 57.1% of patients and an occurrence of symptomatic intracerebral hemorrhage of 0%.

Several limitations of the present study should be mentioned. It was a case control study in which the main goal was to assess the safety and prevalence of recanalization with endovascular sonolysis by using the EkoSonic Endovascular System. Although the criteria for symptomatic intracerebral hemorrhage evaluation are well-defined, the evaluation of the recanalization of brain arteries remains subjective (even though in the present study, a radiologist blinded to the study protocol evaluated vascular status). Finally,

the open-label design of the present study with only blinded evaluation of recanalization in the TICI scale cannot prevent bias in the clinical evaluation of dependency (mRS) after 3 months. Furthermore, a low reliability of the TICI scale for stroke trials should be also taken into account,<sup>46,47</sup> and even though it was independently reviewed, the interobserver correlation of the TICI scale was not evaluated in the present study due to a small number of patients.

## CONCLUSIONS

Endovascular treatment by using the EkoSonic Endovascular System in combination with thrombolysis and cerebral percutaneous transluminal angioplasty and stent placement seems to be a potentially effective therapeutic method for patients with acute ischemic stroke with MCA or BA occlusion after IV thrombolysis failure or with a contraindication to IV thrombolysis. Nevertheless, the efficacy of this endovascular treatment must be confirmed by large prospective randomized trials.

Disclosures: David Školoudík—RELATED: Grant: IGA MH CR NT/11386-5/2010, grant of Moravian-Silesian Region.\* \*Money paid to the institution.

## REFERENCES

1. Bar M, Školoudík D, Roubec M, et al. **Transcranial duplex sonography and CT angiography in acute stroke patients.** *J Neuroimaging* 2010;20:240–45
2. Fieschi C, Argentino C, Lenzi GL, et al. **Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours.** *J Neurol Sci* 1989;91:311–21
3. Furlan A, Higashida R, Wechsler L, et al. **Intra-arterial prothrombinase for acute ischemic stroke: the PROACT II study—a randomized controlled trial Prolyse in Acute Cerebral Thromboembolism.** *JAMA* 1999;282:2003–11
4. Wunderlich MT, Goertler M, Postert T, et al. **Recanalization after thrombolysis—does a recanalization time window exist?** *Neurology* 2007;68:1364–68
5. Rha JH, Saver JL. **The impact of recanalization on ischemic stroke outcome: a meta-analysis.** *Stroke* 2007;38:967–73
6. van der Worp HB, van Gijn J. **Clinical practice: acute ischemic stroke.** *N Engl J Med* 2007;357:572–79
7. **Tissue plasminogen activator for acute ischemic stroke: National Institute of Neurological Disorders and Stroke rt-PA Study Group.** *N Engl J Med* 1995;333:1581–87
8. Smith WS, Sung G, Starkman S, et al. **Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial.** *Stroke* 2005;36:1432–38
9. Kerber CW, Barr JD, Berger RM, et al. **Snare retrieval of intracranial thrombus in patients with acute stroke.** *J Vasc Interv Radiol* 2002;13:1269–74
10. Smith WS, Sung G, Saver J, et al. **Mechanical Thrombectomy for Acute Ischemic Stroke: final results of the Multi MERCI trial.** *Stroke* 2008;39:1205–12
11. Penumbra Pivotal Stroke Trial Investigators. **The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease.** *Stroke* 2009;40:2761–68
12. Grunwald IQ, Wakhloo AK, Walter S, et al. **Endovascular stroke treatment today.** *AJNR Am J Neuroradiol* 2011;32:238–43
13. Machi P, Costalat V, Lobotesis K, et al. **Solitaire FR thrombectomy system: immediate results in 56 consecutive acute ischemic stroke patients.** *J Neurointerv Surg* 2012;4:62–66
14. Costalat V, Machi P, Lobotesis K, et al. **Rescue, combined, and stand-alone thrombectomy in the management of large vessel occlusion**

- stroke using the Solitaire device: a prospective 50-patient single-center study—timing, safety, and efficacy. *Stroke* 2011;42:1929–35
15. Nogueira RG, Levy EI, Gounis M, et al. **The Trevo device: preclinical data of a novel stroke thrombectomy device in two different animal models of arterial thrombo-occlusive disease.** *J Neurointerv Surg* 2011;4:295–300
16. Mendonça N, Flores A, Pagola J, et al. **Trevo system: single-center experience with a novel mechanical thrombectomy device.** *J Neuroimaging* 2011 Dec 30. [Epub ahead of print]
17. Mourand I, Brunel H, Costalat V, et al. **Mechanical thrombectomy in acute ischemic stroke: catch device.** *AJNR Am J Neuroradiol* 2011;32:1381–85
18. Levy EI, Siddiqui AH, Crumlish A, et al. **First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke: SARIS (Stent-Assisted Recanalization In Acute Ischemic Stroke).** *Stroke* 2009;40:3552–56
19. Linfante I, Samaniego EA, Geisbüsch P, et al. **Self-expandable stents in the treatment of acute ischemic stroke refractory to current thrombectomy devices.** *Stroke* 2011;42:2636–68
20. Skoloudik D, Bar M, Skoda O, et al. **Safety and efficacy of the sonographic acceleration of the middle cerebral artery recanalization: results of the pilot thrombotripsy study.** *Ultrasound Med Biol* 2008;34:1775–82
21. Alexandrov AV, Molina CA, Grotta JC, et al. **Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke.** *N Engl J Med* 2004;351:2170–78
22. Mahon BR, Nesbit GM, Barnwell SL, et al. **North American clinical experience with the EKOS MicroLysUS infusion catheter for the treatment of embolic stroke.** *AJNR Am J Neuroradiol* 2003;24:534–38
23. IMS II Trial Investigators. **The Interventional Management of Stroke (IMS) II Study.** *Stroke* 2007;38:2127–35
24. Jonszta T, Czerný D, Skoloudik D, et al. **EkoSonicSV endovascular system for recanalization of the basilar artery occlusion.** *Vasa* 2011;40:408–13
25. Hacke W, Kaste M, Bluhmki E, et al. **Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.** *N Engl J Med* 2008;359:1317–29
26. European Stroke Organisation [ESO] Executive Committee and the ESO Writing Committee 2008. Update Guidelines January 2009 New Elements. [http://www.eso-stroke.org/pdf/ESO\\_Guideline\\_Update\\_Jan\\_2009.pdf](http://www.eso-stroke.org/pdf/ESO_Guideline_Update_Jan_2009.pdf). Accessed September 15, 2012
27. Toni D, Lorenzano S, Puca E, et al. **The SITS-MOST registry.** *Neurol Sci* 2006;27(suppl 3):260–62
28. Noser EA, Shaltoni HM, Hall CE, et al. **Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke?** *Stroke* 2005;36:292–96
29. Rosenschein U, Roth A, Rassin T, et al. **Analysis of coronary ultrasound thrombolysis endpoints in acute myocardial infarction (ACUTE trial): results of the feasibility phase.** *Circulation* 1997;95:1411–16
30. Ganguli S, Kalva S, Oklu R, et al. **Efficacy of lower-extremity venous thrombolysis in the setting of congenital absence or atresia of the inferior vena cava.** *Cardiovasc Intervent Radiol* 2011; 35:1053–58
31. Grommes J, Strijkers R, Greiner A, et al. **Safety and feasibility of ultrasound-accelerated catheter-directed thrombolysis in deep vein thrombosis.** *Eur J Vasc Endovasc Surg* 2011;41:526–32
32. Shah KJ, Scileppi RM, Franz RW. **Treatment of pulmonary embolism using ultrasound-accelerated thrombolysis directly into pulmonary arteries.** *Vasc Endovascular Surg* 2011;45:541–48
33. Lin PH, Annambhotla S, Bechara CF, et al. **Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism.** *Vascular* 2009;17(suppl 3):S137–47
34. Motarjeme A. **Ultrasound-enhanced thrombolysis.** *J Endovasc Ther* 2007;14:251–56
35. Ouriel K, Veith FJ, Sasahara AA. **A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs: Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators.** *N Engl J Med* 1998;338:1105–11
36. Francis CW, Blinc A, Lee S, et al. **Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots.** *Ultrasound Med Biol* 1995;21:419–24
37. Skoloudik D, Fadrna T, Roubec M, et al. **Changes in hemocoagulation in acute stroke patients after one-hour sono-thrombolysis using a diagnostic probe.** *Ultrasound Med Biol* 2010;36:1052–59
38. Skoloudik D, Fadrná T, Bar M, et al. **Changes in haemocoagulation in healthy volunteers after a 1-hour thrombotripsy using a diagnostic 2–4 MHz transcranial probe.** *J Thromb Thrombolysis* 2008;26:119–24
39. Suchkova VN, Baggs RB, Francis CW. **Effect of 40-kHz ultrasound on acute thrombotic ischemia in a rabbit femoral artery thrombosis model: enhancement of thrombolysis and improvement in capillary muscle perfusion.** *Circulation* 2000;101:2296–301
40. Bardoň P, Skoloudik D, Langova K, et al. **Changes in blood flow velocity in the radial artery during 1-hour ultrasound monitoring with a 2-MHz transcranial probe: a pilot study.** *J Clin Ultrasound* 2010;38:493–96
41. Harvey EN. **Biological aspects of ultrasonic waves, a general survey.** *Biol Bull* 1930;59:306–25
42. Schonewille WJ, Algra A, Serena J, et al. **Outcome in patients with basilar artery occlusion treated conventionally.** *J Neurol Neurosurg Psychiatry* 2005;76:1238–41
43. Baird TA, Muir KW, Bone I. **Basilar artery occlusion.** *Neurocrit Care* 2004;1:319–29
44. Schonewille WJ, Wijman CA, Michel P, et al. **Treatment and outcomes of acute basilar artery occlusion in the Basilar Artery International Cooperation Study (BASICS): a prospective registry study.** *Lancet Neurol* 2009;8:724–30
45. Jung S, Mono ML, Fischer U, et al. **Three-month and long-term outcomes and their predictors in acute basilar artery occlusion treated with intra-arterial thrombolysis.** *Stroke* 2011;42:1946–51
46. Tomsick T. **TIMI, TIBI, TICI: I came, I saw, I got confused.** *AJNR Am J Neuroradiol* 2007;28:382–84
47. Kallmes DF. **If you are not confused, then you are not paying attention.** *AJNR Am J Neuroradiol* 2012;33:975–76