

Intracranial intraarterial thrombolysis facilitated by microcatheter navigation through an occluded cervical internal carotid artery

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✓ This report covers a series of four patients with acute cervical carotid occlusion and profound neurological deficits who were treated with intracranial intraarterial thrombolysis. All of the patients presented with arm plegia with variable leg involvement and two of them had global aphasia. Angiography identified occlusion of the proximal internal carotid artery (ICA) in each case and intracranial thromboembolus of the supraclinoid ICA and/or its branches.

Catheter navigation through the occluded ICA segment was straightforward in three patients and somewhat difficult in one patient with an 80% ICA stenosis. Intraarterial urokinase infusion along with mechanical clot disruption was performed at the clot site in the middle cerebral artery, supraclinoid ICA, and/or anterior cerebral artery. All patients had recanalization of the treated artery after urokinase infusion. Antegrade flow through the ICA was reestablished in two patients, and good collateral filling across the anterior communicating artery was established in the other two. All patients had major pretreatment deficits (mean National Institutes of Health (NIH) Stroke Score 24 ± 4) with significant improvement noted at 3 months posttreatment (NIH Stroke Score 7 ± 6 ; $p = 0.03$). Two patients made a dramatic early recovery. Postprocedure computerized tomography revealed no abnormality in one and asymptomatic basal ganglia high density from repeated local contrast injections in two patients.

On the basis of their findings in this small study group the authors suggest that catheter navigation through a presumably occluded carotid artery is feasible and possibly effective in thrombolytic therapy of intracranial thrombolysis. Further study with clinical trials is necessary to determine the safety and efficacy of this technique.

KEY WORDS • internal carotid artery • carotid artery occlusion • fibrinolysis • middle cerebral artery • thrombosis

THE natural history of patients with acute cervical internal carotid artery (ICA) occlusion and middle cerebral artery (MCA) occlusion with the associated neurological deficits is poor with a 40% to 69% outcome of significant disability and a 16% to 55% outcome of death.²⁰ Surgical options for patients with symptomatic carotid artery occlusion include thromboendarterectomy, embolectomy, and surgical bypass. However, profound neurological deficit is a strong exclusion criterion in most recent studies evaluating thromboendarterectomy. Intraarterial thrombolysis for the treatment of acute stroke has yielded promising early results.^{3,4,6,8,27,28,34,35} However, cervical ICA occlusion shown by angiography has been considered an obstacle to intracranial catheter navigation and thrombolytic therapy. We report four cases admitted with acute, profound stroke in whom catheter navigation through an occluded ICA facilitated intracranial arterial thrombolysis.

Clinical Material and Methods

Between March 1992 and April 1994, 23 consecutive patients presenting with acute ischemic stroke were treated with intraarterial infusion of urokinase and mechanical clot disruption. Of this group, four patients presented with acute stroke and profound neurological deficits and had angiographic evidence of proximal cervical carotid occlusion. All of these patients or their relatives gave written informed consent to participate with treatment being offered on a compassionate use basis. Our selection criteria have been previously published³ and included: 1) a significant neurological deficit suggestive of an MCA or combination MCA-anterior cerebral artery occlusion; 2) a computerized tomography (CT) scan that appears normal or shows very subtle sulcal effacement or thrombus in the MCA without evidence of hemorrhage; and 3) angiographic evidence of proximal ICA occlusion with no col-

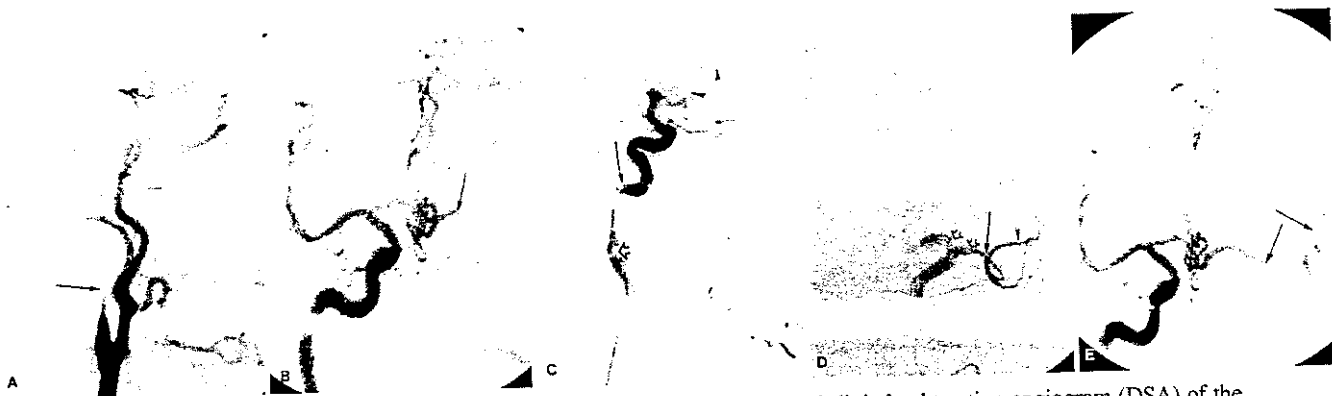


FIG. 1. Case 3. Left internal carotid artery (ICA) occlusion. A: Lateral digital subtraction angiogram (DSA) of the left common carotid artery revealing tapered occlusion (arrow) of the left ICA, suggestive of an arterial dissection. B: Anteroposterior DSA of the right ICA showing the A₁ segment of the left anterior cerebral artery (ACA) as it fills across the anterior communicating artery and abruptly stops (arrow). C: Lateral DSA of the left ICA showing the tip of the guiding catheter (arrow) in the lateral petrous segment across a high-grade stenosis. The ACA (arrowheads) fills but no middle cerebral artery (MCA) is seen. The proximal ICA contains nonocclusive thrombus (open arrow) but is otherwise patent. D: Anteroposterior DSA of the left MCA displaying the microcatheter tip (arrow) in the M₁ segment. A few anterior division branches (arrowhead) fill and thrombus (open arrows) is seen in the proximal ACA and MCA, which is occlusive in the distal M₁ segment. E: Anteroposterior DSA of the right ICA after thrombolysis revealing the left MCA (arrows) now filling with no residual thrombus. Given this excellent collateral filling, the high-grade stenosis in the ICA, seen in Fig. 1B, was not treated.

lateral flow into the ipsilateral MCA consistent with the patient's symptoms. All patients were excluded from a recombinant prourokinase study because of the proximal ICA occlusion.

All four patients had a complete neurological examination, routine laboratory tests, and a CT scan of the head prior to obtaining the angiogram. The patients' initial neurological examination and posttreatment examinations were rated using the 42-point National Institutes of Health (NIH) Stroke Scale with a four-point decrease on this scale defined as a major neurological improvement.⁵ All patients were initially treated with hypervolemic therapy and administration of heparin (500 ml colloid solution, 5000 U heparin bolus, and then 1000 U/hour).

Angiography of the ipsilateral and contralateral common carotid arteries and a vertebral artery (Fig. 1A and B) was performed to document the occlusion and collateral flow. On the side of the occlusion (Fig. 1C), the catheter was advanced into the proximal ICA to help localize the site of occlusion. Through this catheter, a Tracker 18 catheter was navigated over a 0.014-in. taper guidewire. In two patients a multiple side-hole catheter with 3-cm infusion length was used, and in two patients a single end-hole catheter was used. This microcatheter was navigated through the occluded segment up to the petrous ICA where a second test injection was performed and then up into the supraclinoid ICA or MCA (Fig. 1D) where thrombolytic therapy was performed. Urokinase was infused using a gentle pulse spray of 0.10 ml every 1 to 2 minutes, delivering 1 ml (50,000 U/ml) over 5 to 10 minutes. Mechanical disruption was performed using the catheter and guidewire, which were passed through the thrombus, and the thrombus was infused with urokinase. The effects of thrombolysis were evaluated using small injections of contrast material through the Tracker catheter; when antegrade flow through the occluded segment was clearly

established or the thrombolytic therapy was stopped, follow-up angiography (Fig. 1E) was performed using the guiding catheter. A CT scan was obtained immediately after the thrombolytic therapy. Hypervolemic therapy was continued and intravenous heparin infusion also continued to maintain a partial thromboplastin time of 45 to 65 seconds. Hemostasis at the femoral artery puncture site was obtained within 15 to 30 minutes. All patients were monitored in the neurological intensive care unit for at least 24 hours. Follow-up NIH Stroke Scale assessments were performed at 48 hours and again at 3 months.

Results

The overall results, clinical, CT, and angiographic features are summarized in Table 1. The mean age of the patients in this small study group was 46 years (range 31–60 years). All four patients presented with arm plegia, along with complete leg involvement in two patients, mild-to-moderate leg involvement in one, and minimal leg involvement in one patient. The patient in Case 1 presented with headache, lethargy, disorientation, and neglect. The patient in Case 2 presented with a left homonymous hemianopsia and neglect. The patients in Cases 3 and 4, who had left carotid occlusion, presented with associated dense aphasia.

On the initial angiographic studies, all four patients demonstrated an angiographic occlusion to the antegrade flow of contrast material in the proximal cervical ICA. The patients in Cases 1 and 4 had occlusions in the proximal ICA similar to that seen in Fig. 1A. However, those in Cases 2 and 3 had occlusions in the distal petrous ICA (Fig. 1C). The "pseudoproximal" occlusion of these latter two patients had an angiographic appearance very similar to a carotid dissection caused by posterior layering of the contrast material, giving a tapered appearance to the ICA.

TABLE 1
 Characteristics of four patients with acute cervical carotid occlusion and neurological deficits treated with intracranial intraarterial thrombolysis*

| Case No. | Age (yrs), Sex | Cause of Occlusion | Site of Occlusion | Ictus to Treatment Time (hrs) | Urokinase Dose (IU) | Complication | Findings on CT | | | Recanalization Grade & Vessel† | ICA Status | NIHSS Score | | |
|----------|----------------|------------------------------|------------------------------|-------------------------------|---------------------|------------------------|----------------|---------------|---------------------------------|--------------------------------|---------------------------------------|-------------|--------------|----|
| | | | | | | | Initial | Within 6 Hrs | Follow Up (3-6 mos) | | | Initial | 48 Hrs 3 Mos | |
| 1 | 31, F | carotid dissection | rt ICA-proximal MCA, ACA | 6.5 | 250,000 | hemorrhagic conversion | — | BG hemorrhage | small BG & parietal infarct | 2 MCA, ACA 0 ICA | occluded coil embolized | 22 | 10 | 4 |
| 2 | 46, M | embolus | rt ICA-petrous MCA | 6.0 | 800,000 | none | — | BG density | NA | 1 MCA 2 ICA | patent mild stenosis | 18 | 18 | 13 |
| 3 | 60, M | carotid stenosis embolus | lt ICA-supracarotid MCA, ACA | 4.5 | 750,000 | none | — | — | small frontal & putamen infarct | 2 MCA/ACA 1 ICA | high-grade stenosis at C ₁ | 27 | 3 | 0 |
| 4 | 45, M | carotid atheroma, thrombosis | lt ICA-proximal MCA | 3.3 | 750,000 | none | — | BG density | medium anterior MCA infarct | 2 MCA 0 ICA | occluded | 27 | 25 | 11 |

* Abbreviations: ACA = anterior cerebral artery; BG = basal ganglia; CT = computerized tomography; ICA = internal carotid artery; MCA = middle cerebral artery; NA = not available; NIHSS = National Institutes of Health Stroke Scale; — = no hemorrhage, sulcal effacement, or low density as sign of acute stroke.
 † Recanalization: 0 = none; 1 = partial with distal embolus; 2 = complete.

contrast column (Fig. 1A). The contralateral carotid and vertebrobasilar angiograms performed prior to thrombolysis demonstrated patent collateral segments of the circle of Willis with no filling of the symptomatic distal ICA and MCA (Fig. 1B). The combination of collateral evaluation and site of occlusion allowed for intraarterial urokinase thrombolysis of the appropriate vascular segments to maximize antegrade flow while minimizing the amount of thrombus to be dissolved. The interval from the onset of symptoms to initiation of intraarterial urokinase therapy was 5.1 ± 1.5 hours (mean \pm standard deviation (SD); range 3.3–6.5 hours). The total urokinase used was $637,000 \pm 211,000$ IU (mean \pm SD; range 250,000–800,000), which was infused in 82 ± 17 minutes (range 60–100 minutes).

Following the urokinase infusion, good antegrade flow was demonstrated in the proximal MCA in all four patients with no branch occlusions identified in three. In Case 2, a few MCA branch occlusions were noted immediately after infusion of urokinase but were too distal to treat with local fibrinolytic therapy. In Cases 1 and 3, the proximal ipsilateral anterior cerebral artery was also occluded and intraarterial urokinase infusion in the ICA resulted in a recanalization allowing collateral filling across the anterior communicating artery (ACoA) (Fig. 1E).

The CT scan obtained within 6 hours after the procedure was normal in Case 3, and showed markedly dense regions in the ipsilateral basal ganglia in three other cases. The patients in those 3 cases had no neurological deterioration. The patient in Case 1 developed hemorrhagic infarction without hematoma involving the right caudate nucleus; the patient in Case 4 obtained rapid resolution of the density, but developed an anterior left MCA infarction, and the patient in Case 2 had no follow-up imaging studies.

The status of the ICA after therapy depended on the underlying cause of the initial occlusion. The patient in Case 1, who underwent a carotid dissection, had permanent coil occlusion of her ICA to minimize the risk of recanalization and possible future embolic events. In the two patients with pseudoproximal occlusions, the ICA remained patent with residual mild irregularity in one patient and a residual high-grade stenosis in the other. In the latter patient, Case 3, this stenosis (Fig. 1C) was not treated because of the excellent collateral flow from the contralateral carotid artery and vertebrobasilar system and his rapid neurological recovery. The ICA in the patient with atheromatous and thrombotic occlusion of the ICA remained occluded and was not treated.

The neurological recovery of our patients after thrombolytic therapy is summarized by the NIH Stroke Scale values shown in Table 1. The average pretreatment score was 24 ± 4 (mean \pm SD) with a neurological improvement at 48 hours of 12 ± 5 and at 3 months of 7 ± 6 . This improvement was statistically significant with a probability value of 0.03. The patients in Cases 1 and 3 made dramatic early neurological recoveries within 12 to 24 hours and showed continued progressive recoveries at 3 months. The patients in Cases 2 and 4 had minimal neurological recovery at 48 hours and a more modest long-term recovery. The time to treatment did not correlate with recanalization or neurological recovery.

Discussion

Natural History and Surgical Therapy

The natural history of patients with profound neurological deficits and acute carotid occlusion is dismal. A review of the literature by Meyer, *et al.*,²⁰ revealed that 16% to 55% of these patients will die from infarction, 40% to 69% will have severe neurological disability, and only 2% to 12% will make a good recovery. A review of the surgical literature^{20,30} concerning emergency thromboendarterectomy yields variable results and controversial opinions on the benefits of surgery in patients with profound neurological deficits. However, expert opinion^{19,32} considers ICA occlusion with severe acute neurological deficit a contraindication to surgery unless it occurs in a hospital where reestablishment of flow can be achieved in less than 1 to 2 hours. In the most optimistic study of carotid endarterectomy in patients with profound neurological deficits, Meyer, *et al.*,²⁰ reported good outcome in 38.3%, fair outcome in 29.4%, poor outcome in 11.8%, and surgical mortality in 20.6% of cases. The clinical outcome in the patients who survived endarterectomy in that study group is a significant improvement over what occurs in the natural history of the disease and the surgical mortality is similar to that found in the natural history; however, these results are far from ideal. That study also found two important prognostic factors, the presence of an associated MCA embolus and lack of collateral flow, both of which correlated with poor clinical outcome. In the study, seven of the 11 patients who did poorly or died of infarction had an associated MCA embolus and nine of those 11 had poor collateral flow.

Although our study group contains only four patients in this preliminary Phase I trial, initial results are very encouraging compared to previously available therapies. All of our patients would be considered poor candidates for thromboendarterectomy given their profound neurological deficits, evidence of MCA embolus, and lack of collateral circulation. Despite their poor candidacy, moderate-to-marked improvement in clinical outcome and no morbidity or mortality were seen.

Thrombolytic Therapy for Stroke

Existing studies of thrombolysis for acute stroke consist of numerous case reports and small open trials with only seven randomized controlled trials, two of which were conducted prior to CT.^{31,33} Intravenous thrombolytic therapy for ischemic stroke has resulted in an increase in neurological improvement of 14% to 38% above the control population in the seven controlled trials of intravenous thrombolysis.^{1,2,16,21,22,24,25,33} The lack of large randomized, controlled trials of thrombolysis in stroke currently leaves the question "Does it work?" unanswered.³¹

To increase delivery of the thrombolytic agent to the thrombus and decrease the effects of systemic thrombolysis, the intraarterial route has been favored by many authors and is currently being studied in randomized trials. Case reports and small open studies of intraarterial thrombolysis appear to have a higher rate of recanalization (58%–100%) and clinical improvement (53%–94%) than intravenous treatment (36%–89% and 26%–85%, respectively).^{3,4,6,8,27,28,31,34,35} without a significant increase in

hemorrhagic transformation. However, the data supporting intraarterial thrombolysis have even less statistical power than those from intravenous studies.^{8,11} Intraarterial thrombolysis has been performed via proximal ICA infusions (intracarotid) and direct local thrombolysis (local) into the thrombus, and techniques and amounts of thrombolytic agent administered have varied widely among the studies. In a recent study comparing these techniques with intravenous thrombolysis, Sasaki and colleagues²⁶ found that intracarotid infusion resulted in partial recanalization in only 11% of patients with the remainder angiographically unchanged and that local thrombolysis resulted in complete recanalization in 52% and partial recanalization in 32% of patients. The clinical outcome based on the Glasgow Outcome Scale at discharge in this study was good recovery in 18% of patients for intravenous, 17% for intracarotid, and 36% for local thrombolysis with a mortality of 30%, 18%, and 5% of patients, respectively. A recent report of 32 patients with distal ICA occlusions treated with intracarotid or intravenous thrombolysis by Hacke, *et al.*,¹² demonstrated only a 12.5% recanalization rate for either intracarotid or intravenous therapy and an overall 53% mortality rate.

The poor outcome of less direct thrombolysis in ICA occlusions also involving the MCA is probably due to poor drug delivery to the thrombus and the lack of collateral flow from lenticulostriate arteries. Given the stasis in the ICA proximal to the occlusion, intravenous and intracarotid infusion delivers little thrombolytic agent to the thrombus, which can be inferred in our two cases of pseudoproximal occlusions. Therefore if recanalization is the goal, direct delivery is the only effective means. The lack of collateral flow from the lenticulostriate branches of the M₁ and A₁ segments results in minimal, if any, cerebral blood flow to the deep nuclei and probably accounts for the high incidence of hemorrhagic transformation in these patients. A correlation between cerebral blood flow and the risk of hemorrhagic transformation in local thrombolysis has been found to support this theory.²⁹

Navigation Through an Occluded Carotid Artery

Traversing an occluded proximal ICA has not been routinely attempted because of concerns about: dislodging more thrombus and creating more embolus; "blind" wire and catheter manipulation with the risk of perforation; encountering a carotid dissection; and the overall amount of thrombolysis anticipated to be treated. Traversing an occluded vascular segment has been performed with success in the extremities, in coronary arteries, and in peripheral and coronary bypass grafts with very low risks of perforation and distal emboli.^{18,23} In our study, catheter navigation through the occluded segment was performed with ease in three of our four patients and with only slight difficulty in one. These procedures resulted in no deterioration of neurological status. Although thrombus dislodgment and an embolization may be clinically occult in these patients, the amount of thrombus in the MCA and distal ICA was small and was consistent with the patients' initial clinical symptoms. Thrombus dislodgment may become a significant concern if the proximal ICA regains flow, as the dislodged thrombus may reocclude the MCA after a successful thrombolysis. Crossing an atheromatous

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stenosis also has the potential of creating atheroemboli, which would significantly limit the efficacy of thrombolysis.

The risk of perforation in a normal cervical or petrous carotid artery is quite low. In reports of complications of cerebral angiography, direct perforation is not separately listed and thus the exact incidence is not known.^{9,10,14,17} The patient group we evaluated may have underlying carotid dissection or significant carotid atherosclerotic disease, which is not usually catheterized. The risk of perforation in these patients is almost certainly higher but the degree of risk is not known. Although in our one patient with carotid dissection catheter navigation was straightforward, if the wire and catheter had instead entered the subintimal false lumen, difficulty may have been encountered, significantly raising the risk of perforation. One approach to avoid the embolic and cervical carotid perforation risk would be to cross the ACoA from the contralateral ICA to perform the thrombolysis. In our opinion, the risk of intracranial vascular perforation is much higher with this approach.

Perforation of intracranial vessels is an important consideration in local thrombolysis as it requires navigation into the supraclinoid ICA, MCA, basilar artery, and posterior cerebral artery. A risk of 1.25% was found by Halbach, *et al.*,¹³ in a review of their neurointerventional procedures. In neurointerventionalists' hands the incidence of intracranial perforation in stroke therapy would probably be much less because the catheter is normally placed in larger, more proximal vessels than those seen in their study. Intracranial atheromatous stenosis infrequently may be encountered in patients with acute occlusion, which may increase the risk of perforation; however, intracranial vascular perforation has not been described as a complication in the anecdotal reports of local thrombolysis.^{3,4,6,8,15,27-29,34,35}

Treatment of the Proximal ICA

Initial assessment of the collateral flow from the contralateral carotid artery and vertebrobasilar system (Fig. 1B) is essential in determining the amount of thrombus that requires treatment and the appropriate treatment of the ICA to maintain adequate flow. If an adequate A₁-ACoA or posterior communicating artery is present, then treatment of the MCA, the distal ICA, and, possibly, the A₁ segment may be all that is necessary. If these are not adequate, thrombolysis and angioplasty of the proximal ICA or emergency endarterectomy or bypass may be performed. All four of our patients had excellent collateral flow after intracranial thrombolysis and no direct recanalization of the proximal ICA was performed. Two previous case reports describe thrombolysis of an occluded ICA and MCA, both of which underwent cervical ICA angioplasty after thrombolysis. One of these patients returned to baseline neurological status and the other continued to have moderate neurological disability.^{15,28}

The two patients with pseudoproximal occlusions presented some interesting points. First, the angiographic appearance of a tapered occlusion (Fig. 1A) is characteristic for dissection and was seen in both of these patients. This appearance is due to slow "reflux" of contrast material into the nonthrombosed segment which results in depen-

dent layering of high-density contrast material and the tapered appearance. Further investigation with slow catheter advancement and repeat contrast injections delineate the true location and nature of the occlusion (Fig. 1C). Although prolonged injections with delayed filming, first described by Countee and Vijayanathan,⁷ can differentiate high-grade stenosis from occlusion, they would not delineate the location of occlusion because there is very little mixing in a static occluded vessel. Therefore, in patients with proximal occlusions, especially with tapered narrowing on angiography, gentle catheter navigation into, and evaluation of, the ICA is required if intraarterial treatment is attempted.

The second point concerns the pathophysiological mechanisms of distal thromboemboli associated with proximal occlusion. It is generally accepted that proximal ICA occlusions result in distal thrombosis of the ICA to the next major branch, usually the ophthalmic artery, and that the supraclinoid or MCA embolus is a "distal stump embolus" that forms in the petrous or cavernous ICA and breaks off to embolize distally. Our cases support an alternative mechanism: that initially a nonocclusive embolus forms proximally and embolizes distally. This significantly decreased flow from the MCA or distal ICA occlusion results in proximal ICA rethrombosis which propagates to occlusion. This is supported by the fact that investigation of the proximal ICA in Case 3 revealed floating nonocclusive thrombus in the ICA proximal to the stenosis, with total occlusion in the supraclinoid ICA. In a short time, this patient would have almost certainly developed a proximal ICA occlusion. The incidence of formation of proximal ICA thrombus following MCA embolus is unknown and is probably variable depending upon the residual flow to the anterior cerebral artery, ophthalmic artery, posterior communicating artery, and anterior choroidal artery, and the thrombogenicity of the proximal ICA. Nonetheless, in a significant percentage of patients with proximal and distal occlusions, the proximal thrombus, although significant in volume, is relatively fresh because it may have formed after the onset of clinical symptoms and should easily dissolve if necessary.

Conclusions

The results in the four patients in this preliminary study indicate that distal ICA and MCA occlusion in patients with proximal occlusion of the ICA associated with severe neurological deficits may be treated with direct thrombolysis with a potential for significant neurological improvement. However, the risks of arterial perforation and distal embolization must be considered and further study is needed. Despite recent reports, proximal or distal ICA occlusions should not necessarily be an exclusion criterion for local thrombolysis, and these results of our patients and this technique should be considered in future local thrombolysis efficacy studies.

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