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Peripheral Arterial Occlusive Disease – PAOD

Early Diagnosis and Intervention of Acute Renal Infarction with Catheter-Directed Thrombolytic Therapy

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Background: Acute renal infarction is a rare and under-diagnosed disease for which the optimal treatment is unknown.

Objectives: This study aimed to determine the utility of catheter-directed thrombolysis (CDT) to treat acute renal infarction.

Methods: From November 2010 to September 2017, 13 patients with acute renal infarction were treated with CDT. The diagnosis was confirmed by contrast-enhanced computed tomography and renal angiography.

Results: The most common symptoms and signs were flank pain (53.8%) and abdominal pain (30.8%). More than two-thirds of the patients (69.2%) had atrial fibrillation. In successful reperfusion cases, the median time from symptom onset to diagnosis was 6 hours, and the average time from diagnosis to treatment was 3.5 hours. Complete resolution of thrombi in the renal artery was achieved in 10 of the 13 patients (76.9%) and partial resolution in two patients (15.4%). Only one patient (7.7%) failed to respond to treatment. Compared with admission, renal function was significantly improved at 6 months. No major complications occurred during the course of CDT therapy.

Conclusions: CDT offers an alternative to surgical intervention and can achieve good angiographic results with an early diagnosis and intervention. It is relatively safe and can restore at least partial renal function.

Key Words: Acute renal infarction • Catheter-directed thrombolysis

INTRODUCTION

Acute renal infarction (ARI) is believed to be a rare and under-diagnosed disease. Domanovits et al. reported that the incidence of ARI was only 0.007% (17/248, 842).[1] Depending on the severity, renal infarction can lead to renovascular hypertension, chronic kidney disease, and most seriously, end-stage renal disease, requiring a rapid diagnosis and therapy to preserve renal function. However, the clinical manifestations of renal infarction are usually non-specific and easily confused with other diseases. Because of these characteristics, the diagnosis is usually not established before irreversible renal parenchymal damage has occurred. In addition, due to the paucity of literature, there is no consensus on the optimal treatment for ARI.

The three traditional treatment methods include anticoagulation, percutaneous endovascular treatment, and open surgery. Because surgery is invasive and requires a longer recovery time than other methods, it is not an ideal treatment. In 1973, Moyer et al. compared the outcomes of conservative and surgical management for unilateral renal artery thrombosis, and concluded that conservative therapy was favored.[2] Anticoagulation

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therapy may risk major bleeding although it is easier to execute. In recent years, percutaneous endovascular treatments, such as catheter-directed thrombolysis (CDT), have been used to treat renal infarction.[3-5] CDT has several advantages. First, it is less invasive than traditional surgery. Second, it delivers a higher concentration of the fibrinolytic agent to the clot, theoretically reducing the systemic effects and the risk of complications. However, due to the lack of large clinical studies, the actual advantage of CDT is not clear. In this study. we report our experience with 13 cases of angiographically confirmed acute renal artery infarction treated primarily with CDT, including the short-term effect as assessed by angiography and the long-term prognosis of the patients.

METHODS

From November 2010 to September 2017, all patients with ARI diagnosed at the emergency department of one hospital and treated by CDT were retrospectively evaluated. All patients with ARI were diagnosed by contrast-enhanced computed tomography (CT). Typical CT scan features included single or multiple triangular defects in the renal parenchyma. Data collected included demographics, clinical characteristics, laboratory and imaging results, the time interval from presentation to diagnosis, the time interval from diagnosis to intervention, risk factors or suspected causes, and final outcomes. Patients with inadequate documentation of the clinical course were excluded from this study.

A renal angiogram was obtained every 24 hours after treatment to evaluate whether the thrombosis had dissolved. The three "response" categories were: Complete Resolution: all thrombi had dissolved on follow-up angiogram; Partial Resolution: reduction in thrombus burden on follow-up angiogram; and No Response: no change or an increase in thrombus burden. Follow-up studies included laboratory examinations with serum creatinine and estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease equation, and cases which occurred during hospitalization, at discharge, 1 month after discharge, and 6 months after discharge. This study was approved by the ethics committee of our institution (No. B10603002) and all patients provided written informed consent before undergoing CDT.

Catheter-directed thrombolysis (CDT) protocol

All renal angiograms were performed via the femoral artery approach. A 6 French catheter (Judkins right 4, Cordis Corp., Miami Lakes, FL) was used for bilateral renal angiograms to confirm arterial thrombosis. All angiograms were done with iodixanol isotonic contrast (Visipaqe™, GE Healthcare, Inc., Chicago, IL). After the diagnosis was confirmed, if feasible, we used the catheter as an aspiration device. The catheter was advanced to the site proximal to the occlusion. Aspiration was performed with suction pressure generated by a 20 ml syringe attached to the proximal tip of the catheter. If residual thrombi or distal emboli in the distal small branches still existed after aspiration thrombectomy, intra-arterial (IA) thrombolytic therapy with a bolus injection of 250,000 IU urokinase into the affected renal artery was performed. If suboptimal results were still obtained, we kept a 5 French catheter (Rosch curve 1, Cook Group, Bloomington, IN) in the renal artery for continuous infusion of urokinase at a rate of 50,000 IU/hour for up to 72 hours. We monitored for any possible complications such as hematuria, intracranial hemorrhage, or puncture site bleeding, and checked fibrinogen and hemoglobin levels every day. If serious complications developed, urokinase was discontinued immediately. Follow-up renal angiograms were taken every 24 hours to evaluate whether the thrombi had dissolved. If not, continuous infusion of urokinase was maintained. If the thrombi had not completely dissolved after 72 hours, IA urokinase infusion was deemed "ineffective" and was discontinued. Patients were recorded as having a complete resolution, partial resolution, or no response after 72 hours.

Most patients were discharged on oral anticoagulation therapy with coumadin to keep the blood coagulation international normalized ratio within the therapeutic range. In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) have been available in our hospital. Some patients received NOACs as anticoagulation therapy rather than coumadin. A representative case of ARI treated with CDT is described below.

Representative case

A 72-year-old female presented to our emergency department with acute right flank pain. Contrast-enhanced CT disclosed right renal artery occlusion (Figure 1A). We performed a renal angiogram which confirmed

right renal artery thrombus occlusion (Figure 1B). CDT was performed as per the procedures described above. A second renal angiogram was performed after 24 hours, which showed complete resolution of the thrombosis (Figure 1C).

Statistical analyses

Statistical analyses were carried out using JMP 12. 1.0 (SAS Institute Inc., Cary. NC). All data was expressed in terms of mean and standard deviation for numerical variables, and as number (percent) for categorical variables. Comparisons of continuous variables between groups were performed using the chi-square test. Time-to-event analysis involves estimating the probability that an event will occur at different points in time. The follow-up endpoint in the patients with successful reperfusion after ARI was the time between these symptoms (or diagnosis) and the intervention. The most common time-to-event statistical method is the Kaplan-Meier survival curve method, which we used to estimate the probability of successful reperfusion. p values < 0.05 were taken to indicate statistical significance.

RESULTS

Baseline characteristics of the study population

The baseline patient characteristics, time intervals from symptoms to intervention, and treatment outcomes are shown in Table 1. The mean age was 62.8 ± 10.2 years and the proportion of males and females was similar. Most patients had atrial fibrillation (AF) (69.2%) and hypertension (76.9%). The most common presenting symptoms were flank pain (53.8%) and abdominal pain (30.8%), both of which are non-specific. The median time interval from symptom onset to diagnosis was 8 hours, and the average time interval from diagnosis to treatment was 5.4 ± 3.0 hours. All cases were diagnosed by contrast-enhanced abdominal CT because of the high rate of abdominal CT use in our emergency department. Complete resolution of thrombi in the renal artery was achieved in 10 of the 13 patients (76.9%) and partial resolution in 2 of the 13 patients (15.4%). Only one case (7.7%) failed to respond to treatment. All patients without a complete resolution (case 3, case 7, and case 11 in Table 1) had a delayed hospital admission or longer time

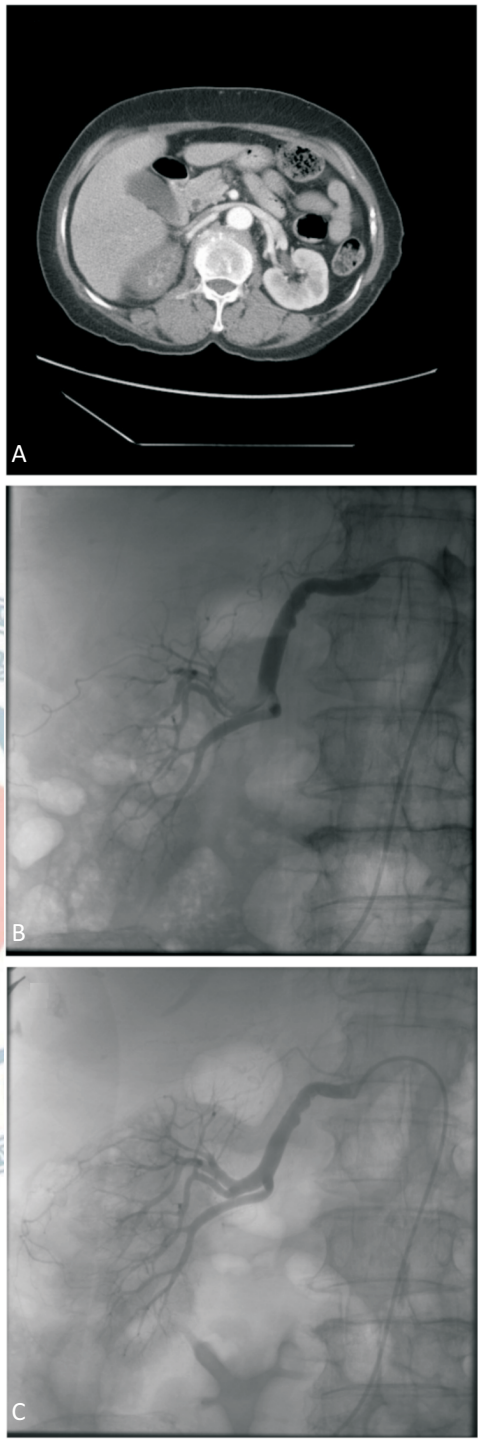


Figure 1. *Representative images of one patient. A 72-year-old female presented to our emergent department with acute right flank pain. (A) The contrast-enhanced computed tomography disclosed a small enhanced area of the right kidney compared to the normally perfused left kidney, suggesting right renal artery occlusion. (B) Selective right renal angiogram showed a filling defect at the distal right renal artery. (C) Renal angiogram, repeated after 24 hours of continuous local infusion of urokinase, showed complete resolution of thrombosis.*

Table 1. Demographic characteristics, clinical features, and final outcomes of 13 patients with acute renal infarction

Case No.	Sex	Age, years	Kidney involved	Presenting symptoms	Risk factors	Time interval of symptoms to diagnosis, hours	Time interval of diagnosis to intervention, hours	Outcome
1	M	71	R	Left flank pain	AF, CHF, HL, HTN, Smoking	6	3	CR
2	F	72	R	Right flank pain	AF, HTN	4	2	CR
3	M	53	R	Abdominal pain	HTN, Smoking	168	5	PR
4	F	63	R	Right flank pain	AF, CHF, HTN, Old CVA	6	3.5	CR
5	F	51	R	Right abdominal pain	HTN	4	3	CR
6	M	62	R	Right flank pain	AF, DM, HL, HTN, Old CVA	6	3	CR
7	F	53	L	Left flank pain	None	36	9	NR
8	M	71	L	Left flank pain	AF, HTN, Smoking	6	3	CR
9	F	57	R	Abdominal pain	AF	24	4	CR
10	M	55	L	Left flank pain	HTN, Smoking	15	7	CR
11	M	74	L	Left abdominal pain	AF, Smoking	32	12	PR
12	F	66	L	Left flank pain	AF, HTN	6	2	CR
13	F	86	R	Abdominal pain	AF, HTN	24	5	CR

AF, atrial fibrillation; CHF, congestive heart failure; CR, complete resolution; CVA, cerebrovascular accident (stroke); F, female; HL, hyperlipidemia; HTN, hypertension; L, left; M, male; NR, non-response; PR, partial resolution; R, right.

interval from symptom onset to diagnosis (168 hours in case 3, 32 hours in case 7, 32 hours in case 11). All patients completed CDT and no major complications occurred during the course of thrombolytic therapy.

Treatment and outcomes

The eGFR values of all patients at the time of admission, discharge, 1 month after discharge and 6 months after discharge are demonstrated in Table 2. Figure 2 demonstrates the changes in renal function (eGFR) over time, from admission, to discharge and over the follow-up period. Renal function improved gradually after CDT, although there was no significant difference between admission and discharge. Compared with the renal function at the time of admission, renal function at 6 months showed a significant improvement ($p = 0.034$).

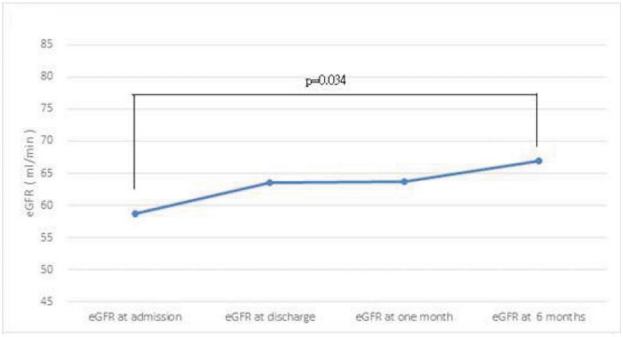
Table 2. The eGFR (mL/min/1.73 m^2) values of all patients from admission to six months after discharge

Case No.	Admission	Discharge	One month after discharge	Six months after discharge	Angiographic outcome
1	117.93	91.52	99.57	111.15	CR
2	64.58	71.4	64.38	64.28	CR
3	58.78	48.56	54.36	45.7	PR
4	53.53	79.28	56.68	57.87	CR
5	33.68	39.29	42.67	40.29	CR
6	47.63	47.99	53.57	53.57	CR
7	78.83	91.03	89.55	100.61	NR
8	77.03	100.35	71.72	82.43	CR
9	44.23	54.81	51.85	48.12	CR
10	60.48	66.9	81.29	73.08	CR
11	53.84	64.59	60.81	63.79	PR
12	28.76	35.49	49.47	53.29	CR
13	43.97	34.6	53.15	76.75	CR

CR, complete resolution; eGFR, estimated glomerular filtration rate; NR, non-response; PR, partial resolution.

Relationship between the time to CDT and successful reperfusion rate

Figure 3 demonstrates the successful reperfusion rate according to the time from diagnosis to CDT and the time from symptom onset to CDT as determined by Kaplan-Meier survival curve analysis. When we performed CDT within 3.5 hours of diagnosis, there was a 50% probability of successful reperfusion. Furthermore, when we performed CDT within 3 hours of diagnosis, the probability of successful reperfusion reached 80%. Considering the time from symptom onset to CDT (i.e., total ischemic time) needed to achieve 50% and 80% successful reperfusion rates, CDT should be performed within 12 hours and 10 hours, respectively. The shorter the time from symptom onset to intervention, the greater the rate of successful reperfusion.



eGFR, mean (SD), ml/min	58.71 (23.11)	63.52 (22.31)	63.78 (17.01)	66.99 (21.23)*

Figure 2. *Changes in eGFR during follow-up. At 6 months, the eGFR significantly improved compared to that at admission. eGFR, estimated glomerular filtration rate. * Statistically significant compared to admission.*

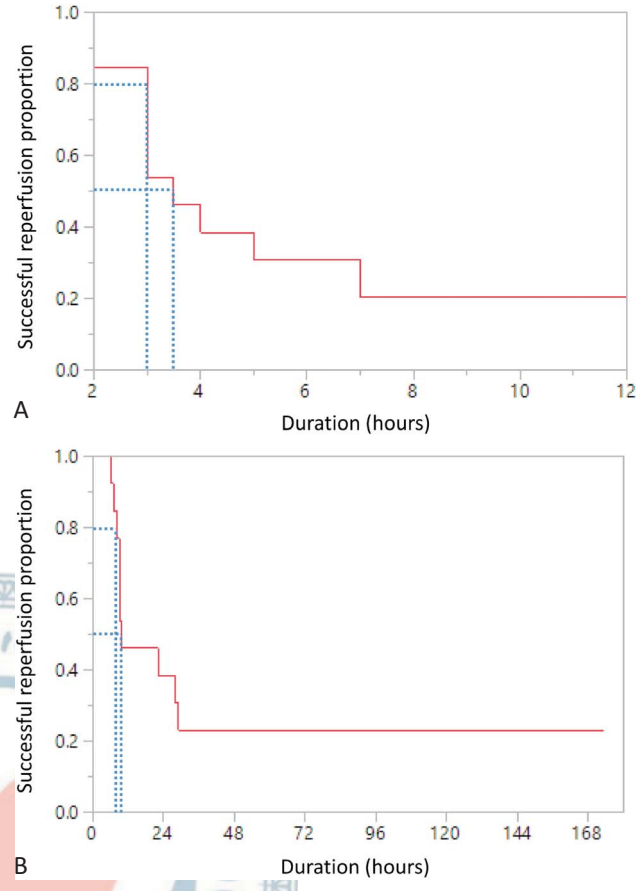


Figure 3. *Kaplan-Meier survival curve analysis of reperfusion rates of the study population. (A) The relationship of successful reperfusion after acute renal infarction with the time interval from diagnosis to intervention. (B) A successful reperfusion rate in those with acute renal infarction was associated with a shorter time interval between symptom onset and intervention.*

DISCUSSION

ARI is a rare condition with an incidence of 1.4% determined post-mortem and 0.007% in hospitalized patients.[6] ARI is difficult to diagnose because the symptoms are non-specific. Many other disorders also show similar symptoms, including renal calculi, intestinal diseases, spinal diseases, genital diseases, muscle inflammation, myocardial infarction, or ischemia. ARI, therefore, is often misdiagnosed or the diagnosis is delayed.[7-9] In our patients, the median time interval from symptom onset to diagnosis was only 8 hours (average 26.1 hours, although one patient had a prolonged time interval of 168 hours), a relatively short time compared with those reported in previous studies.[10] The reason for this rapid diagnosis is because contrast-enhanced CT is often the initial tool used at our emergency department to investigate patients with flank/abdominal pain in whom the initial diagnosis remains unclear after basic examination. The classic finding is of a wedge-shaped zone of peripheral diminished density without enhancement.[11] All of our patients could therefore be diagnosed promptly by contrast-enhanced CT before undergoing CDT.

Many etiologies are known to be related to renal infarction, but AF is currently considered to be the most important risk factor. Other risk factors for renal infarction include valvular or ischemic heart disease, hypercoagulation disorders, and spontaneous renal artery dissection, reflecting the multiplicity of underlying causal mechanisms.[12] However, despite extensive investigations, the cause of renal infarction often remains undetermined. Bolderman et al. studied 27 patients with renal infarction diagnosed by CT, and found that 16 of these patients (59%) were idiopathic.[13] In our patients, the two most common risk factors were hypertension (76.9%, 10 of 13) and AF (69.2%, 9 of 13).

Regarding prognosis, a retrospective study of 67 patients with renal infarction reported that 41% of the patients suffered from acute kidney injury, 11% developed new-onset renal insufficiency, and 2.1% progressed to end-stage renal disease.[14] Therefore, early diagnosis and timely treatment of renal infarction are pivotal for maintaining renal function and improving the prognosis of patients. However, controversy exists about the utility of treatment. Therapeutic options include conservative management with anticoagulation, surgical interven-

tion, systemic thrombolysis, and CDT.[15,16] Surgical intervention is rarely undertaken due to its invasiveness, high complication rate, and poor tolerance by some patients. Systemic thrombolysis is seldom used due to concerns about the complication of severe bleeding. In theory, CDT has the advantages of being less invasive and of having a lower rate of complications than other treatment modalities. Therefore, local thrombolytic therapy seems to be a promising treatment.

A study by Sanfelippo and Goldin demonstrated that infusion of streptokinase directly into the canine renal artery within 1 hour of embolization resulted in immediate dissolution of the thrombus and restoration of normal renal function.[17] This study was followed by several case reports describing the use of streptokinase in acute renal artery occlusion with successful restoration of arterial flow.[5,18,19] Although the results of the treatment were acceptable in most case reports, due to the few number of cases and limited treatment experience, this treatment has not been used widely. To our knowledge, our study has the largest number of cases in the literature, and may provide some evidence of the value of using CDT for ARI.

Many factors may play a role in the restoration of renal function after successful revascularization, including the time delay between the onset of symptoms and treatment, the presence of collateral circulation, and the etiology of ARI. Quriel et al. reported that restoration of renal function after successful revascularization depends on the etiology.[20] They reviewed 35 patients with ARI and found that revascularization of embolic arterial occlusion was successful in the relief of hypertension but was ineffective in the restoration of renal function. In contrast, they found that revascularization in cases of thrombotic occlusion frequently resulted in return of renal function, and that traumatic renal occlusion did not benefit from revascularization despite early intervention.[20]

Acute thrombi, a major cause of ARI, are formed initially with a dense fibrin mesh and cell layers.[21,22] The fibrin component is continuously being remodeled, undergoing both polymerization and degradation. This process makes acute thrombi highly sensitive to thrombolytic therapies.[23] However, the activation of leukocytes and other inflammatory mediators results in the thrombus becoming increasingly resistant to thrombolytic therapies.[24] Taken together, it can be inferred that the earlier ARI is treated by CDT, the higher the probability of successful reperfusion. Our study also showed that, to achieve an 80% successful reperfusion rate, CDT must be performed within 3 hours of diagnosis. Considering the time from symptom onset to CDT (i.e., the total ischemic time), to achieve an 80% successful reperfusion rate, CDT should be performed within 10 hours of the onset of symptoms. The shorter the time from symptom onset to intervention, the greater the successful reperfusion rate.

The success rate in this study was 76.9% (10 of 13 patients) with completely restored renal artery perfusion, and 15.4% (2 of 13 patients) with partially resolved thrombi proven angiographically. The only case that failed had a prolonged time interval from symptom onset to diagnosis at the emergency department. Reperfusion therapy is only useful when the ischemic renal tissue is still viable, which is within 12 hours of the onset of renal ischemia. In humans, the kidney tolerates complete ischemia for about 60-90 minutes at normothermia. Ischemia for 4 hours has been shown to cause irreversible renal damage in dogs.[15] The “golden time” to ensure good treatment results is unknown, however early diagnosis of ARI ensures earlier and therefore more effective therapeutic intervention. In our series, the median time from symptom onset to diagnosis at department admission was 6 hours (average time interval: 25.9 hours, with a prolonged time interval in one patient of 168 hours). In the successful reperfusion cases, the average time from diagnosis to treatment was only 3.5 hours, a relatively short interval. This expedited care may explain why we had a high rate of successful reperfusion. It is worth noting that there were no complications such as major bleeding or anaphylaxis. This may be attributed to the local infusion of thrombolytic agents, avoiding systemic side effects.

Successful revascularization of the renal artery does not guarantee the recovery of renal function. Salam et al. reported restoration of renal function after successful revascularization in only 3 of 7 patients.[19] In our cases, there was no significant improvement in renal function at the time of discharge. However, during the follow-up period, the average eGFR increased gradually, so that at 6 months after discharge it was significantly improved over that at admission. The reason why the renal function did not improve significantly until 6 months after discharge may be because successful revascularization salvaged viable ischemic kidney that did not undergo complete infarction during the initial insult. Such “hiber-

nating" tissue might benefit from early revascularization in situations such as ischemic brain tissue during acute stroke and myocardial tissue during acute myocardial infarction. The concept is similar to "stunned myocardium". When the ischemia is relieved by reperfusion, the tissue is viable but stunned, exhibiting post-ischemic dysfunction. Recovery of the stunned tissue eventually occurs but may take days to weeks.

Our study had several limitations. Due to the low incidence of disease, our case number is small. In addition, the lack of a control group made it impossible to define the advantages of this treatment. Finally, using eGFR as the primary follow-up tool for ARI may be inappropriate, because the eGFR level may be normalized by hyperfiltration of the unaffected kidney. We believe that functional studies, e.g., those measuring effective renal plasma flow, should be incorporated into future studies of the renal outcomes of different treatment modalities for ARI.

CONCLUSIONS

In conclusion, ARI is a rare disease requiring a rapid diagnosis and treatment to prevent kidney loss. CDT offers an alternative to surgical intervention, and it can achieve good angiographic and clinic results if it is performed within 10 hours of symptom onset. It is relatively safe and can restore at least partial renal function.

DECLARATION OF CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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