Ischemic Strokes After Cardiac Catheterization

Opportune Thrombolysis Candidates?

Pooja Khatri, MD; Scott E. Kasner, MD

Stroke is an important complication after cardiac catheterization procedures, resulting in death and disability for thousands of patients each year. Common risk factors include advanced age, vascular comorbidities, and more complicated and invasive procedures. Several lines of evidence suggest that these strokes are embolic, from either dislodgement of a clot or atheromatous debris off the aortic arch or from thrombus formation on the tip of a guide catheter. These strokes are likely amenable to thrombolysis, although the current literature regarding the use of thrombolysis in this setting is limited to case reports and series. Whether thrombolysis is safe and efficacious remains to be determined, but the existing evidence seems favorable for individual circumstances.

Since the 1940s, when cardiac catheterization became established for investigating basic cardiovascular pathophysiologic abnormalities, we have witnessed its significant clinical development. Today, more than 2 million cardiac catheterization procedures are performed annually in the United States.1 Rates of serious complications, including stroke, myocardial infarction, and death, are less than 1% for most catheterization procedures. However, because high volumes are performed, thousands of patients experience strokes after cardiac catheterization (SCCs) each year. As the population ages and more invasive percutaneous cardiac procedures dominate the clinical arena, these complications may become even more common. We review the limited literature regarding the clinical features, risk factors, outcome, and possible origins of SCCs and discuss the treatment options for this unique situation.

**CLINICAL FEATURES**

**Incidence**

Reported rates of SCCs, including both ischemic and hemorrhagic types, typically within 36 hours of the procedure, range widely from 0.07% to 7.0%.2-15 The most commonly quoted reports of stroke incidence are based on contemporary, large registries of diagnostic and invasive coronary procedures, reporting rates from 0.07% to 0.38%.12,13 However, stroke incidence rates appear higher with other invasive cardiac catheterization procedures, although only smaller studies have been published. Prospective cohort registries of valvuloplasties10,11 suggest a stroke risk of 1.2% to 2.0%. Electrophysiologic ablation cohorts, including heterogeneous indications and evolving procedure techniques, report risks of 0% to 7%.7,16-20 In contrast, SCCs after patent foramen ovale closure may be relatively rare.4,21

**Clinical Presentation**

Most existing registries have not discriminated between hemorrhagic and ischemic strokes, but up to 50% of SCCs are hemorrhagic when reported in retrospective studies.14,15 A disproportionate amount (50%-60%) of the ischemic strokes localize to the posterior circulation (compared with approximately 20% of strokes in general). Most procedure-related strokes occur during or immediately after the procedure.22,23

Author Affiliations: Department of Neurology, University of Cincinnati, Cincinnati, Ohio (Dr Khatri); and Department of Neurology, University of Pennsylvania, Philadelphia (Dr Kasner).
RISK FACTORS

Retrospective studies of coronary angiography and coronary angioplasty procedures suggest that older patients (specifically those older than 80 years compared with those younger than 50 years), those with more severe cardiovascular disease, and those with more vascular risk factors are particularly prone to SCCs of both hemorrhagic and ischemic types.13-15,22-24 Of note, the increased SCC risk with age is not statistically different from the 30-day stroke rates seen after conservative medical management in patients with acute coronary syndromes.25

Procedural considerations are also important because risk seems greater with emergent catheterizations, longer fluoroscopy times, and more contrast use.13-15,22-24,26 Solid cerebral microemboli are approximately twice as common with the transradial approach compared with the transfemoral approach.7 Furthermore, retrograde catheterization of the left ventricle in patients with aortic stenosis has been well described as a risk factor based on a prospective randomized trial.28 Retrograde catheterization (n=101) was associated with a 22% rate of focal diffusion imaging abnormalities and a 3% rate of clinically apparent strokes compared with no magnetic resonance imaging (MRI) or clinically evident strokes in those without retrograde passage (n=51) or in controls without aortic stenosis undergoing coronary angiography and left-sided heart catheterization (n=32).

Periprocedural use of the glycoprotein IIb/IIIa inhibitor abciximab, in addition to reteplase, was not shown to increase the risk of ischemic or hemorrhagic stroke in a meta-analysis of 4 large trials.15,22,29,30 However, the risk of hemorrhage was greater when abciximab was given along with standard-dose rather than low-dose heparin (0.27% vs 0.04%; P=.06).31,32

Studies regarding risk factors among catheterization procedures other than coronary interventions are profoundly limited. A single study7 identified age older than 60 years as a risk factor for stroke after pulmonary vein ablation for atrial fibrillation (3% vs 0%; P<.05).

POSSIBLE ORIGINS

Strokes after cardiac catheterization are likely to be of embolic origin according to several lines of evidence. Multiple acute infarctions in multiple vascular distributions, including clinically silent infarctions, are often demonstrated when MRI is performed.22 Vascular risk factors predominate in patients with postprocedure strokes, possibly contributing to atherosclerosis of the great vessels, a potential source of embolism. Furthermore, transcranial Doppler studies23,34 have demonstrated high rates of microembolic signals. A recent prospective study37 found higher rates of solid microemboli in patients with acute strokes that were apparent on MRI. These solid emboli were detected most often during catheter advancement and were also seen during catheter flushing, contrast injection, and ventriculography, suggesting active embolization.

Embolic SCCs could have many potential origins. For example, catheter tips traversing the aortic arch could dislodge atheromatous plaque. Keeley and Grines35 observed plaque dislodgement off the aortic arch with catheter advancement in more than 50% of 1000 percutaneous revascularization procedures studied. Thrombus formation in situ on catheter tips is another possible source of embolism.36 In addition, SCCs have been associated with longer fluoroscopy duration,22,27 which may reflect more catheter manipulation, allowing for more plaque dislodgement or more time for catheter tip thrombus formation. Other rarer potential causes include air emboli,27,38 peri-procedural hypotension, arterial dissection related to guidewire manipulation, and metallic embolus from a fractured guidewire.39

Specific types of cardiac procedures may be associated with specific stroke causes. For example, higher rates of stroke after electrophysiologic ablation suggest unique factors at play in this setting. In patients with atrial arrhythmia, a small left atrial thrombus missed by a preprocedural echocardiogram may cause stroke after restoration of normal sinus rhythm. In addition, ablation may denude endothelium and release tissue factor and other thrombogenic substances.20,40 Furthermore, ablation procedures often require larger catheters, thereby creating more hemostasis and subsequent catheter tip thrombosis.

Phenomenologically, SCCs may be analogous to strokes after coronary artery bypass graft surgery or cerebral angiography, which suggest a similar embolic pathogenesis. Silent infarcts, strokes in multiple vascular territories, and higher levels of vascular comorbidities are seen in patients with strokes after these procedures as well.41,42

Autopsy studies of strokes after cardiac procedures, primarily after surgery, provide additional support for an embolic origin. Cholesterol crystal emboli with varying amounts of other clot types, including fibrin and lipid-laden macrophages, are often found lodged in the small leptomeningeal arteries.33,34 Larger emboli that cause territorial strokes tend to consist of clusters of cholesterol crystals aggregated with larger amounts of platelets and fibrin. Postmortem examination of the one clinically observed SCC with posterior cerebral artery distribution in the literature45 revealed multiple leptomeningeal arterial occlusions, suggesting fragmentation of an initial large artery embolism as the cause.

CLINICAL OUTCOME

Strokes after cardiac catheterization may substantially affect long-term outcome. Patients with SCCs stay in the hospital 4 days longer than patients without this complication.45 Moreover, they have a high in-hospital mortality rate of 25% to 44%.13-15,22 In a retrospective cohort, SCCs were independently associated with in-hospital death, acute renal failure, and new dialysis.15 Among octogenarians in a large prospective study,36 patients with ischemic SCCs had a 16.7% mortality rate, 3 times higher than those without stroke (P<.001).

TREATMENT OF ISCHEMIC SCCs

Potential Role for Thrombolysis

Currently, no standard treatment for ischemic SCCs exists. Thrombolysis has been established as an effective treatment for acute ischemic stroke,37 but the benefits and
Table. Outcomes After Thrombolysis for Strokes After Cardiac Catheterization

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients (Treatment)</th>
<th>Route</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaidat et al, 2005^51</td>
<td>21 (9 rt-PA and 12 UK)</td>
<td>IA</td>
<td>10 With independent function, 3 (14%) sICH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(unrelated to intraprocedure anticoagulation),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 deaths (1 ICH, 1 large stroke, 2 CAD)</td>
</tr>
<tr>
<td>Al-Mubarak et al, 2002^52</td>
<td>8 (3 UK, 2 rt-PA, 1 abciximab, 2 UK with abciximab, all with mechanical fragmentation)</td>
<td>IA</td>
<td>4 Full recovery, 2 “nondisabling minimal” deficit, 1 with no recovery, 1 death (sICH)</td>
</tr>
<tr>
<td>Segal et al, 2001^53</td>
<td>2 (Urokinase and balloon angioplasty)</td>
<td>IA</td>
<td>1 With full neurological recovery, 1 with no outcome reported</td>
</tr>
<tr>
<td>Battikh et al, 2001^54</td>
<td>1 (Urokinase)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Sandoval and Laufer, 1998^54</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Kumar et al, 1999^55</td>
<td>1 (Urokinase)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Ozbek et al, 1991^56</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Battikh et al, 2001^57</td>
<td>1 (abciximab)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Sandoval and Laufer, 1998^54</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Kumar et al, 1999^55</td>
<td>1 (Urokinase)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Ozbek et al, 1991^56</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Battikh et al, 2001^57</td>
<td>1 (abciximab)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Sandoval and Laufer, 1998^54</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Kumar et al, 1999^55</td>
<td>1 (Urokinase)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Ozbek et al, 1991^56</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Battikh et al, 2001^57</td>
<td>1 (abciximab)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Sandoval and Laufer, 1998^54</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Partial recovery</td>
</tr>
<tr>
<td>Kumar et al, 1999^55</td>
<td>1 (Urokinase)</td>
<td>IA</td>
<td>Full recovery</td>
</tr>
<tr>
<td>Ozbek et al, 1991^56</td>
<td>1 (rt-PA)</td>
<td>IV and IA</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; IA, intra-arterial; ICH, intracerebral hemorrhage; IV, intravenous; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracerebral hemorrhage; UK, urokinase.

The literature regarding the use of thrombolysis in this setting is limited to case reports and series (Table). Of the 35 patients described in the published literature as of June 2005, all were treated via the intra-arterial approach, although 2 patients received intravenous recombinant tissue plasminogen activator (rt-PA) as well. Independent function or full recovery was achieved in 20 (57%) with thrombolysis. These outcomes must be interpreted with great caution because these sporadic cases may be subject to publication bias, and poor outcomes are much less likely to be reported. No study has yet attempted to systematically collect data on all SCCs and their treatment in either a single- or multiple-center cohort.

Safety of Thrombolysis

The safety of thrombolysis for SCCs by either intravenous or intra-arterial routes has not been systematically studied. In the only case series of consecutive intra-arterial rt-PA SCC cases, 3 (14%) of 21 patients experienced a symptomatic intracerebral hemorrhage, similar to the rate of 10% seen in the only randomized trial of intra-arterial thrombolysis, Recombinant Prourokinase in Acute Cerebral Thromboembolism II (PROACT-II).^57^  

Furthermore, the risks of thrombolysis in this patient population may be unique. As with efficacy, the safety of thrombolytics may relate to the underlying cause of SCCs. In particular, if calcified emboli are lysed, distal embolization of that clot or recurrent embolization from a more proximal source may be a risk. Case reports of visualized calcific emboli treated with rt-PA have shown mixed results regarding clinical outcome. If a calcified clot is visualized, the optimal management must be based on individual considerations.

Recent local vascular intervention such as femoral artery access, albeit at a compressible site, introduces the risk of significant blood loss with retroperitoneal extension. However, substantial experience with intra-arterial thrombolysis of stroke suggests that this risk is low. For example, in the Interventional Management of Stroke phase 1 study of combined intravenous and intra-arterial rt-PA, among the subset of 62 patients receiving both intravenous and intra-arterial rt-PA, 3 patients (3.2%) experienced serious bleeding related to the groin site.

Recent myocardial infarction, as well as recent coronary artery manipulation, may increase the risk of hemopericardium. Heparin is often administered during cardiac catheterization procedures and, if associated with a prolonged partial thromboplastin time, is an absolute contraindication for intravenous rt-PA in the standard protocol. Intra-arterial rt-PA remains a consideration in this situation, depending on the dose and timing of heparin received. The PROACT-I trial showed significantly higher rates of hemorrhagic transformation in intra-arterial thrombolytic-treated patients given high-dose heparin.

risks of this therapy for ischemic SCCs are unclear. These strokes typically occur in hospitalized patients under close observation, and therefore they may be ideal candidates for rapid neurologic evaluation and early thrombolysis. For example, during the last 3 years, approximately 25% of patients with strokes after catheterization at the Hospital of the University of Pennsylvania have been treated with thrombolysis (P.K., unpublished data, 2005) compared with 1% to 4% of the general population receiving thrombolysis. However, bleeding risks may be increased in this setting. Moreover, it may be argued that SCCs are less likely to respond to thrombolysis than other strokes because the composition of the embolus is not amenable to this treatment. For example, if dislodged aortic arch plaque is the predominant origin, this calcified, fibrin-dense clot may not be amenable to lysis. On the other hand, a fresh thrombus on the tip of a guidewire may be easier to destabilize. The current stroke literature suggests that ischemic stroke subtype may ultimately be irrelevant. Thrombolysis was shown to be equally effective across the major stroke subtypes (small vessel, large vessel, and cardioembolic). Limited evidence suggests that diagnostically confirmed cardioembolic origins may be particularly amenable to thrombolysis. Regardless of origin, superimposed fresh fibrin deposition on atheroma or other components may make these emboli at least partially responsive to thrombolysis. Autopsy studies of patients who have undergone coronary artery bypass graft surgery suggest that larger clots that cause territorial infarcts tend to be particularly rich in platelets and fibrin.

The literature regarding the use of thrombolysis in this setting is limited to case reports and series (Table). Of the 35 patients described in the published literature as of June 2005, all were treated via the intra-arterial approach, although 2 patients received intravenous recombinant tissue plasminogen activator (rt-PA) as well. Independent function or full recovery was achieved in 20 (57%) with thrombolysis. These outcomes must be interpreted with great caution because these sporadic cases may be subject to publication bias, and poor outcomes are much less likely to be reported. No study has yet attempted to systematically collect data on all SCCs and their treatment in either a single- or multiple-center cohort.
Thrombolysis.52-56 However, because SCCs can be hemorrhagic in up to 50% of cases,14 head CT before thrombolysis administration remains mandatory. If the catheter used for the cardiac procedure has not been removed, it can remain in place during CT and then subsequently be accessed for intra-arterial lysis. In addition, leaving in a femoral or brachial artery catheter is not an obstacle to intravenous rt-PA. In either case, the catheter and sheath may be left in place for several hours after thrombolysis to minimize bleeding at the puncture site and the need for excessive vascular compression after their removal.

Recent myocardial infarction, a relative contraindication, needs to be considered on an individual basis, possibly based on evidence of pericarditis. If heparin has been used, urgent coagulation studies should be performed before thrombolytic administration and intra-arterial rt-PA may be considered. In addition, if glycoprotein IIb/IIIa inhibitors were used, the risk of rt-PA therapy is unknown. When antithrombotic therapy excludes thrombolysis owing to a superimposed fibrin clot, introduce other treatment possibilities as well. If intravascular hypodensity suggestive of an air embolus is seen on CT or suspected because of the introduction of air during the procedure, hyperbaric oxygenation may be a consideration.37,38 If a metallic tip were observed to fragment during the procedure or were identified on CT, it could potentially be removed endovascularly with a snare device.

Other Treatment Considerations

The less common proposed causes of SCCs, although potentially amenable to thrombolysis owing to a superimposed fibrin clot, introduce other treatment possibilities as well. If intravascular hypodensity suggestive of an air embolus is seen on CT or suspected because of the introduction of air during the procedure, hyperbaric oxygenation may be a consideration.37,38 If a metallic tip were observed to fragment during the procedure or were identified on CT, it could potentially be removed endovascularly with a snare device.

FUTURE DIRECTIONS

Whether thrombolysis is safe and efficacious for SCCs remains to be determined, but the clinical setting seems amenable and the existing evidence seems favorable. We have designed a multicenter retrospective cohort study to investigate all SCCs and compare patients treated with thrombolysis with those without treatment to begin to address practice patterns and determine the efficacy and safety of thrombolysis for SCCs. Data regarding thrombolysis for this opportune patient population are forthcoming.

Accepted for Publication: September 9, 2005.
Correspondence: Scott E. Kasner, MD, Comprehensive Stroke Center, Department of Neurology, University of Pennsylvania Medical Center, 3400 Spruce St, Philadelphia, PA 19104 (kasner@mail.med.upenn.edu).

Author Contributions: Study concept and design: Khatri and Kasner. Acquisition of data: Khatri. Analysis and interpretation of data: Khatri. Drafting of the manuscript: Khatri. Critical revision of the manuscript for important intellectual content: Khatri and Kasner. Obtained funding: Khatri and Kasner. Administrative, technical, and material support: Kasner and Kasner. Study supervision: Kasner.

Funding/Support: This work was supported by a University of Pennsylvania Research Foundation grant. Dr Kasner was also supported by grant K23 NS02147 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Role of the Sponsor: The funding sources had no role in the development of this manuscript.

REFERENCES
