Low Dose Streptokinase in the Treatment of Arterial Occlusions

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Twelve patients with arterial occlusions demonstrated by angiography were treated using intraarterial "low dose" streptokinase delivered to the site of occlusion via a 5 French catheter. The catheter was embedded at the site of arterial occlusion if possible, but if not, was placed immediately proximal to the occlusion. Streptokinase was infused at 5,000 U/hr in a volume of about 50 ml using an arterial infusion pump. The technique was applied to vessels of the upper and lower extremities as well as the renal arteries. Of 12 patients infused, 11 had successful thrombolysis. No hemorrhagic complications were encountered. This technique is extremely promising as a method of treatment of thromboses of recent origin, especially in the poor operative candidate, and for angioplasty-related thromboses.

Arterial occlusion, produced by thrombosis or embolus, is a common problem confronted by both clinician and angiographer. These lesions may arise de novo or as a complication of arterial surgery, arteriography, or transluminal angioplasty. Conventional therapy has included surgery and systemic anticoagulation, as well as transcatheter embolectomy [1, 2] and transluminal angioplasty [3, 4]. Thrombolytic agents have also been used, primarily by systemic infusion, but with a considerable complication rate [5, 6]. In 1972, Dotter et al. [7] described low dose, local infusion of streptokinase for the treatment of arterial occlusive disorders. Due to the smaller total dose of streptokinase and local application, complications were fewer than with systemic therapy. Thrombotic complications of diagnostic and therapeutic angiography are especially suited to local thrombolysis, as the best response is obtained in the treatment of acute lesions [5]. We present 12 patients with arterial occlusions of diverse etiology treated with locally delivered, low dose streptokinase.

Materials and Methods

Twelve patients with angiographically demonstrated arterial occlusions were treated by low dose streptokinase after diagnostic angiography. The catheter tip was embedded in the thrombus or was placed as close as possible to the site of occlusion. Streptokinase was infused at 5,000 U/hr, an arbitrarily determined dose 1/20th of the systemic dosage (100,000 U/hr).

The duration of infusion varied from 5 to 16 hr. Infusion was not terminated until follow-up arteriography was completed. Therefore, the precise duration of infusion before clot lysis was not always known.

All patients were monitored in an intensive care unit during therapy. Success of therapy was documented clinically by physical examination and repeat arteriography before removal of the catheter. Preliminary clotting status evaluation included measurement of thrombin time, prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products. Patients were typed and screened for two units of packed cells for possible transfusion. Strict orders were given to avoid intraarterial or intramuscular injections and to place intravenous punctures peripherally where they would be easily compressible.

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TABLE 1: **Patients Undergoing Low Dose Fibrinolytic Therapy**

Case No.	Nature of Occlusion	Location	Length of Infusion (hr)	Remarks
1	Chronic arteriosclerosis, ?acute exacerbation	Right common iliac	8	Subsequent angioplasty; asymptomatic at 4.5 yr follow-up.
2	Postangioplasty thrombosis	Right external iliac	6	Cold leg after angioplasty; asymptomatic 1 yr after angioplasty/streptokinase.
3	Chronic arteriosclerosis, subacute history	Right external iliac	5	Reocclusion, probably secondary to poor distal runoff.
4	Arteriosclerosis, 1 mo	Right axillary	7	Clinical improvement and rise in Doppler pressure.
5	Arteriosclerosis, 3 wk	Left common iliac	8	Axillary approach; asymptomatic at 1 yr follow-up.
6*	Embolism secondary to mitral valve disease	Left distal brachial	7	...
7	Chronic arteriosclerosis, 1 mo	Right common iliac	5	Pulse returned at 5 hr; patency demonstrated at 15 hr; subsequent angioplasty successful.
8	Embolus	Left popliteal	6	Diabetic, arteriosclerosis, atrial fibrillation.
9†	Unknown; chronic	Distal superficial femoral	16	Subsequent angioplasty.
10*	Thrombosis, 4 wk	Right iliac	16	Underlying stenosis; subsequent angioplasty
11	Unknown, 1 wk	Right renal	10	Subsequent angioplasty.
12	Thrombus, 7 dy	Dialysis graft	12	Underlying stenosis.

Note.—Data on four women and eight men aged 38–90 years. Each patient infused at 5,000 U/hr.
* Two patients had complications: mild temperature elevation (case 6) and minimal distal embolus (case 10).
† Only case in which fibrinolytic therapy did not restore patency.

Results (table 1)

Of 12 patients who underwent low dose infusion of streptokinase for occlusions of diverse etiology, effective clot lysis was accomplished in 11 (92%). In the single failure (case 9), infusion of a 4.5 cm superficial femoral artery occlusion was attempted before angioplasty in the hope of uncovering a stenosis as a cause of thrombosis and simplifying the angioplasty. Lysis did not occur, and recanalization and dilatation proceeded uneventfully. In three of 12 thromboses, clot lysis revealed underlying stenoses which were subsequently treated by transluminal angioplasty.

The clotting parameters and fibrinogen levels remained within normal limits in all patients. However, the fibrin split products were elevated in all patients. No evidence of fibrinogen depletion occurred in any patient including those in whom infusions extended up to 24 hr.

One patient developed a low grade fever up to 37.5°C, which returned to normal on cessation of therapy. Attempts to heparinize patients during low dose infusion in cases 4 and 5 resulted in puncture site bleeding, necessitating two units of packed cells in each case; it was controlled by cessation of heparin therapy and local compression. Streptokinase infusions were continued without difficulty. In one patient, after 24 hr of infusion, arteriography demonstrated small amounts of clot attached to the tip of the catheter despite successful fibrinolysis distally; no complications resulted. In patients with proximal lesions, no significant evidence of distal embolization occurred, although in two patients, brief parasthesias in the toes were noted during the course of the infusion suggesting distal propagation of thrombus fragments during lysis.

Representative Case Reports

Case 1

A 56-year-old man had a 3 month history of increasing pain in the right hip on walking and 1–2 weeks of sexual impotence. Aortography demonstrated a short, complete occlusion of the right common iliac artery (figs. 1A and 1B) which filled distally by poorly developed ileolumbar collateral vessels. Although chronic ischemia was present by history, a superimposed subacute iliac occlusion was suspected, and thrombolysis was attempted via a left common femoral catheterization. The catheter tip was embedded in the occluding thrombus; after 8 hr of streptokinase therapy (5,000 U/hr, a common femoral arterial pulse was palpated and the patient noted warmth in the right groin and testicular region. Repeat arteriography demonstrated patency of the right common iliac artery (fig. 1C) with an underlying short high grade stenosis which was successfully treated by transluminal angioplasty (fig. 1D). The patient was asymptomatic 5 years after angioplasty.

Case 2

A 50-year-old woman had increasing claudication in the right hip and both calves. Aortography demonstrated a long, high grade stenosis of the right external iliac artery (fig. 2A), and several high grade stenoses of both superficial and femoral arteries. She underwent successful transluminal angioplasty of both superficial femoral arteries, but after transluminal angioplasty of the right external iliac artery, a large intimal irregularity was demonstrated (fig. 2B). The right common femoral arterial pulse disappeared 15 min after the procedure and the patient's leg became ischemic. Immediate arteriography via a femoral approach demonstrated complete occlusion of the right external iliac artery at its origin (fig. 2C). A catheter was then placed at the site of the occlusion, and an infusion of streptokinase was initiated (5,000 U/hr). After about 6 hr of streptokinase

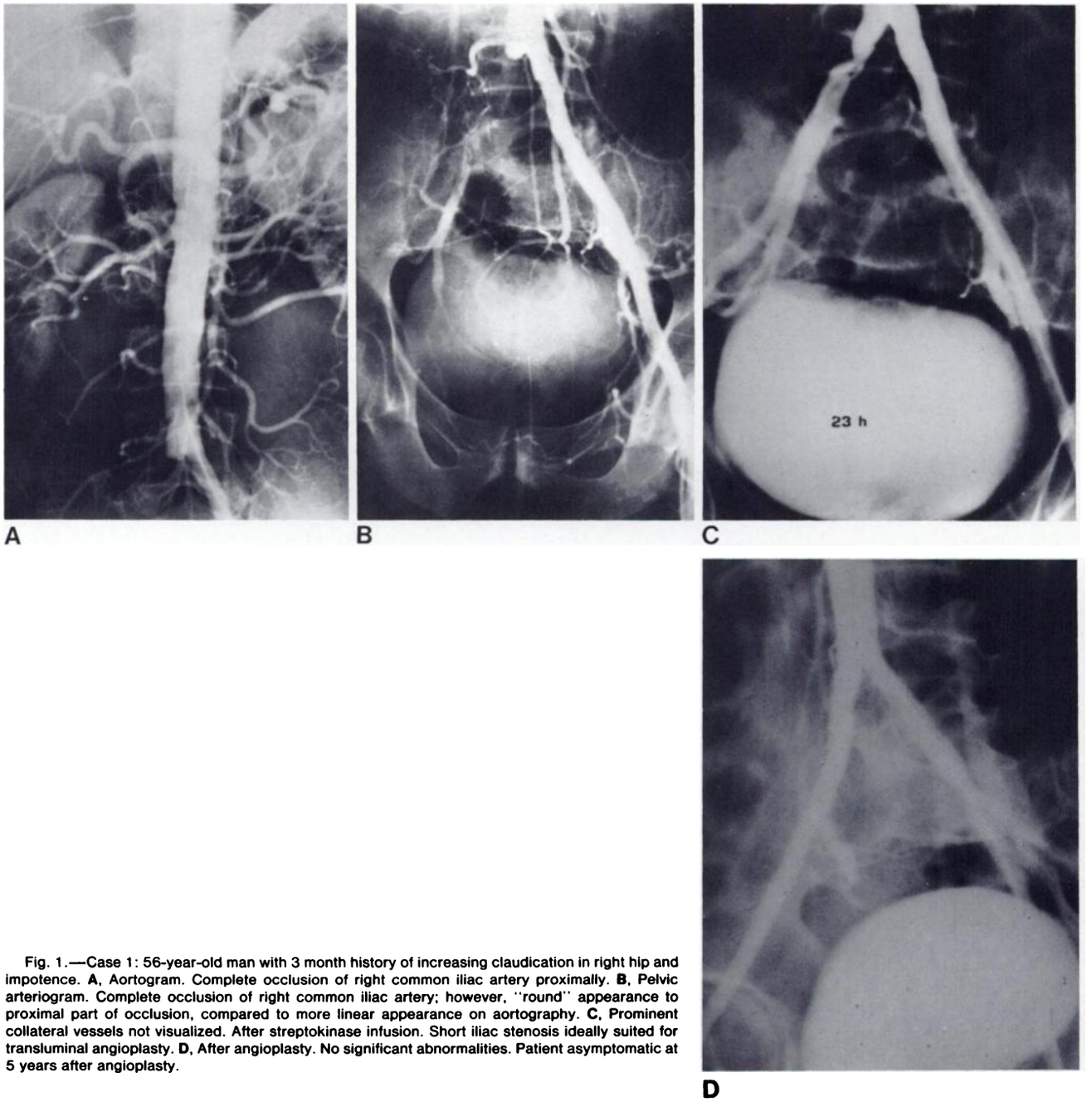


Fig. 1.—Case 1: 56-year-old man with 3 month history of increasing claudication in right hip and impotence. **A**, Aortogram. Complete occlusion of right common iliac artery proximally. **B**, Pelvic arteriogram. Complete occlusion of right common iliac artery; however, "round" appearance to proximal part of occlusion, compared to more linear appearance on aortography. **C**, Prominent collateral vessels not visualized. After streptokinase infusion. Short iliac stenosis ideally suited for transluminal angioplasty. **D**, After angioplasty. No significant abnormalities. Patient asymptomatic at 5 years after angioplasty.

therapy, the right common femoral arterial pulse was again palpable. The infusion was maintained for another 6 hr with decreasing concentrations of streptokinase. Repeat arteriography (fig. 2D) demonstrated reestablishment of the lumen, with persistance of a long intimal defect. The catheter was infused with normal saline to maintain the patency for an additional 24 hr and then removed. The patient had a normal femoral pulse 1 year after angioplasty.

Case 4

A 48-year-old woman with exogenous obesity was unable to use her right hand due to claudication. She had a history of vascular disease, having undergone transluminal angioplasty of the right superficial femoral artery and a bilateral aortofemoral bypass graft. The patient had coronary arteriography performed via the right brachial approach. She had had mild claudication in the right upper extremity for at least 18 months, but had the almost complete inability to use the right upper extremity for only 2 months. Preliminary examination revealed no palpable pulses in the right upper extremity.

Arch aortography demonstrated a 4.5 cm occlusion of the right axillary artery, distal to the lateral thoracic artery (fig. 3A). The axillary artery was reconstituted by collaterals through the circumflex humeral artery. The more distal vessels in the right upper

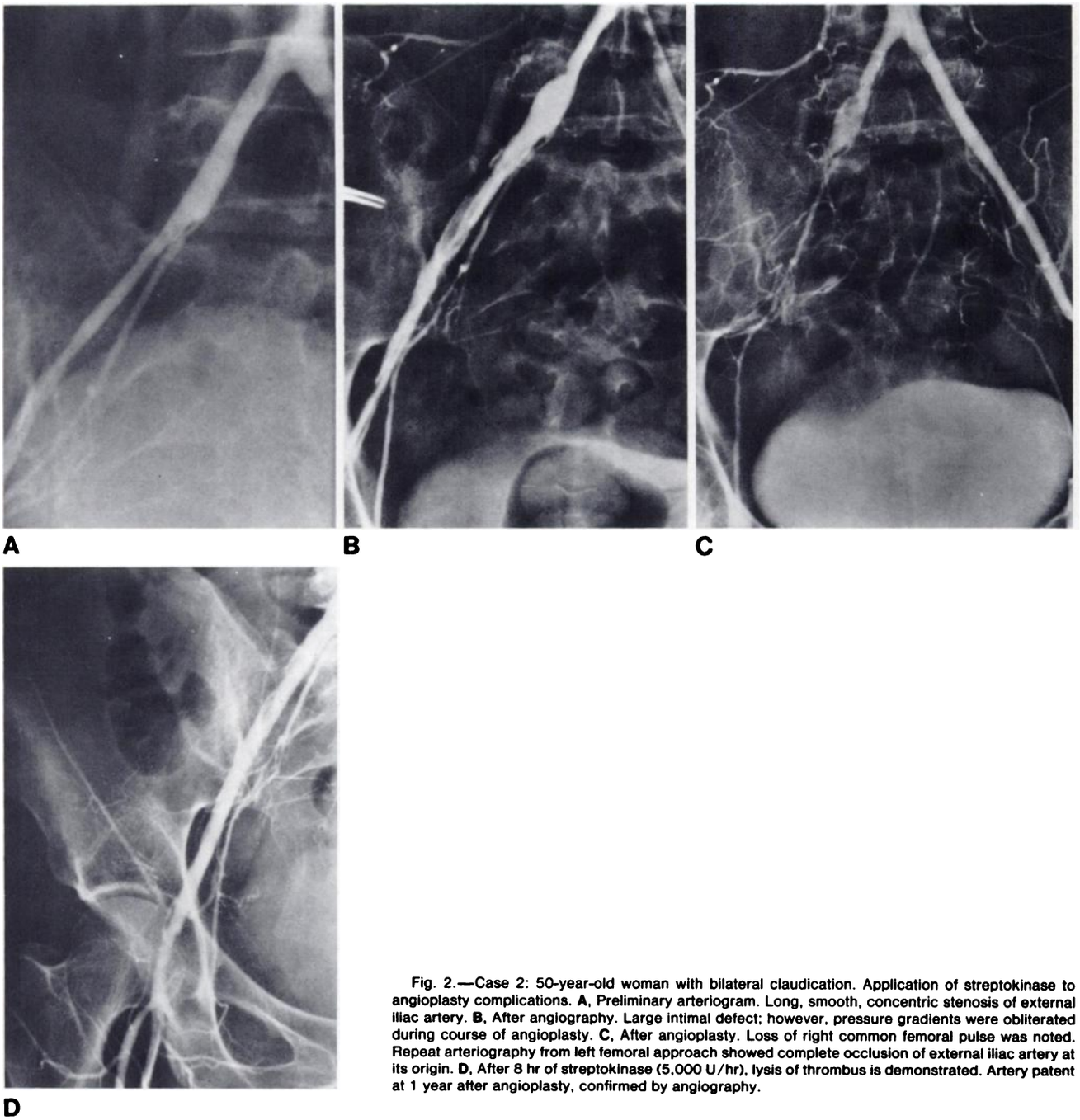


Fig. 2.—Case 2: 50-year-old woman with bilateral claudication. Application of streptokinase to angioplasty complications. **A**, Preliminary arteriogram. Long, smooth, concentric stenosis of external iliac artery. **B**, After angiography. Large intimal defect; however, pressure gradients were obliterated during course of angioplasty. **C**, After angioplasty. Loss of right common femoral pulse was noted. Repeat arteriography from left femoral approach showed complete occlusion of external iliac artery at its origin. **D**, After 8 hr of streptokinase (5,000 U/hr), lysis of thrombus is demonstrated. Artery patent at 1 year after angioplasty, confirmed by angiography.

extremity were normal. A 6 French catheter was passed into the distal subclavian artery and an infusion of streptokinase was initiated (5,000 U/hr). Attempts to place the catheter directly against the occlusion site were unsuccessful. After about 7 hr of infusion, a Doppler radial pulse was obtained and a palpable pulse was intermittently present at both the radial and brachial levels. Considerable clinical improvement was noted. Repeat angiography before attempted angioplasty (fig. 3B) confirmed reestablishment of the lumen although a high grade stenosis persisted. Attempts to traverse the diseased segment with a catheter were unsuccessful due to tortuosity of the arch and the distance from the femoral puncture site. Prestreptokinase radial Doppler pressures were 50 mm Hg rising to 92–100 mm Hg after infusion. The patient has been followed for 8 months without clinical evidence of progression of disease.

Case 5

A 48-year-old man had bilateral hip claudication. A pelvic arteriogram demonstrated bilateral iliac stenoses, slightly greater on the

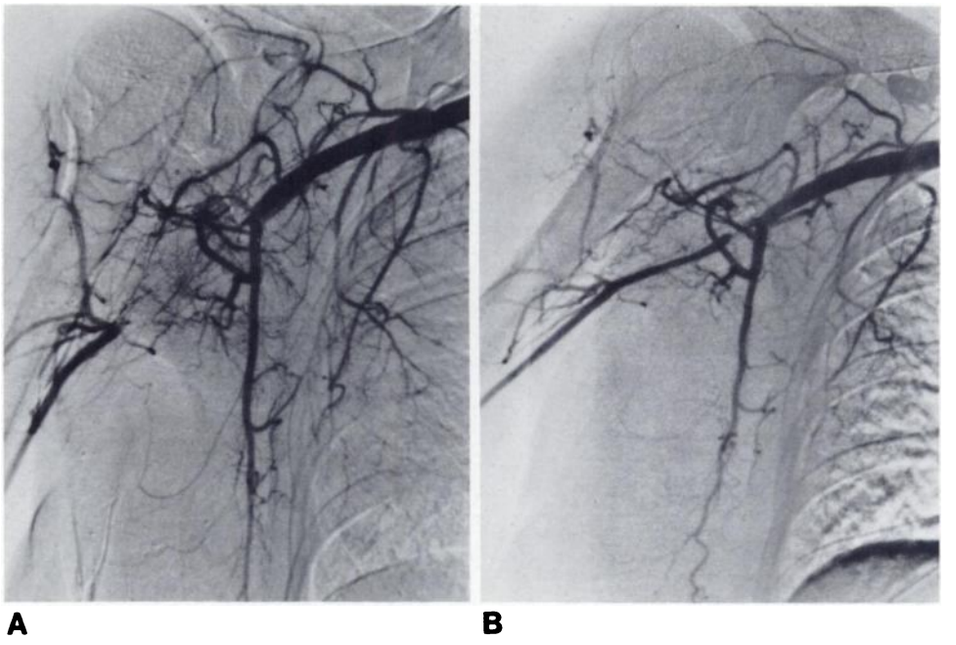


Fig. 3.—Case 4: 48-year-old woman with increasing claudication in right upper extremity over 12 months, with 2 month history of disability restricting ability to type and to prepare food. **A**, Selective subclavian arteriogram. Complete occlusion of axillary artery at level of long thoracic artery. **B**, After 12 hr of streptokinase infusion (5,000 U/hr), occlusion was lysed revealing underlying axillary artery stenosis. Radial pressure rose from 30 mm Hg (Doppler) to 92–100 mm Hg (Doppler).

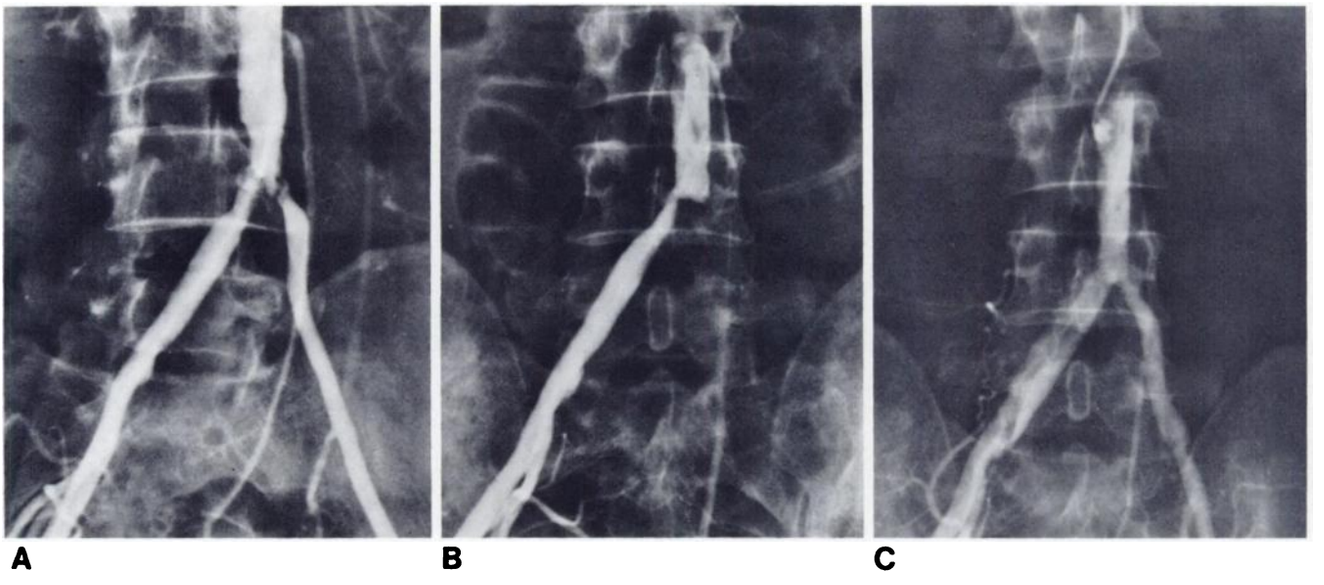
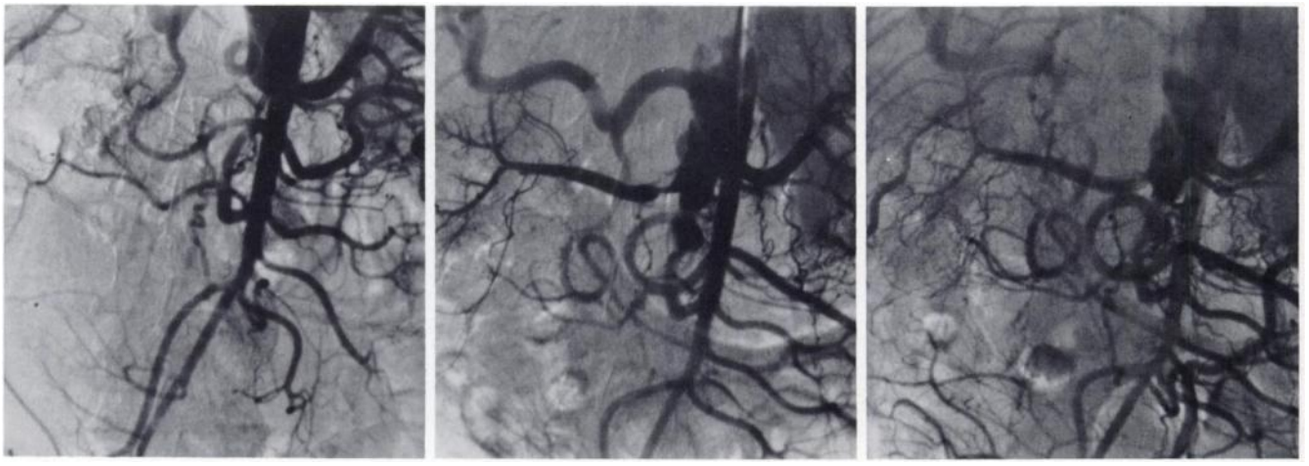


Fig. 4.—Case 5: 48-year-old man with bilateral iliac claudication. **A**, Pelvic arteriogram. Bilateral iliac stenosis. **B**, On admission for transluminal angioplasty 1½ months later. Repeat angiogram. High grade stenosis of right common iliac artery with complete occlusion of left common iliac artery. **C**, After placement of catheter from left axillary approach into left iliac occlusion, streptokinase was infused (5,000 U/hr). After infusion, recanalization of left common iliac artery. Transluminal angioplasty not performed, since no pressure gradient was demonstrated.

left than the right (fig. 4A). Repeat arteriography 6 weeks later because of worsening claudication and impotency demonstrated occlusion of the left common iliac artery with persistent stenosis of the right common iliac origin (fig 4B). Transluminal angioplasty successfully obliterated the pressure gradient at the right common iliac stenosis, although an intimal flap was present at the angioplasty site. Via the left axillary approach, a catheter was placed at the left common iliac occlusion site, and streptokinase was infused (5,000 U/hr). After 8 hr of infusion at this dosage, the left common femoral pulse was palpable. Repeat arteriography demonstrated lysis of the left iliac occlusion (fig. 4C). The patient has been followed for 1 year requiring no further therapy.

Case 11

A 50-year-old man, a bilateral amputee with known complete occlusion of the aorta below the level of the renal arteries, had



A B C

Fig. 5.—Case 11: 50-year-old man, bilateral amputee with known occlusion of aorta, with pain in right flank and hematuria. **A**, Aortogram by axillary approach. Right renal artery occlusion and aortic occlusion. **B**, After 12 hr of low dose fibrinolysis, reperfusion of renal artery is achieved revealing renal artery stenosis. **C**, After angioplasty. Good physiologic and morphologic results were achieved. Delay in diagnosis and initiation of therapy contributed to eventual reduction in renal function.

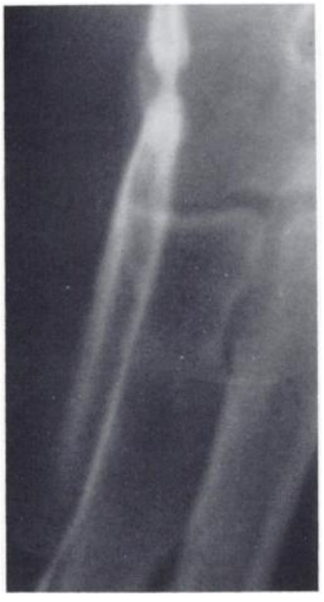


Fig. 6.—Case 12: 60-year-old woman with increased venous pressure noted during dialysis through a synthetic graft. Contrast injection through 19 gauge Butterfly needle. Intraluminal clot, effectively lysed with 10 hr of low dose fibrinolytic therapy.

acute abdominal pain and ileus. After 2 days of hospitalization, pain localized to the right flank and hematuria developed. A radionuclide flow study showed extremely diminished flow to the right kidney. Aortography (fig. 5) performed by left axillary approach revealed complete occlusion of the abdominal aorta as well as the right renal artery. A 5 French catheter was then embedded in the thrombus in renal artery orifice, and repeat arteriography demonstrated renewed patency of the main renal artery but with underlying renal artery stenosis. Transluminal angioplasty was performed to allow resumption of normal flow; however, function in the right kidney was still considerably diminished 2 months later and irreversible parenchymal damage probably occurred during the ischemic period.

Case 12

A 60-year-old woman with chronic renal failure on hemodialysis was noted to have elevated pressures in an arteriovenous shunt graft. Injection of contrast material in the graft demonstrated intraluminal thrombus (fig. 6) which was restricting flow at the venous anastomosis and an anastomotic stenosis. Streptokinase was infused (5,000 U/hr) through a 19 gauge Butterfly needle resulting in complete lysis of the clot in 12 hr.

Discussion

The most extensively studied thrombolytic agents, streptokinase and urokinase, activate conversion of plasminogen to the proteolytic enzyme plasmin [8, 9]. Plasmin is the primary endogenous homeostatic fibrinolysin. Anticoagulants such as heparin do have lytic properties.

Commercially available urokinase (Abbokinase, Abbott Labs.) is an enzymatic protein that is prepared from human renal cell tissue cultures. It is nonantigenic, but is expensive, averaging $3,000.00 for 12 hr of standard systemic use at the recommended dose of 4,400 IU/kg/hr [10].

Streptokinase (Streptase, Hoechst-Roussel), a nonenzymatic protein, is derived from beta hemolytic streptococci and is inherently antigenic. This property accounts for a higher incidence of mild side effects, primarily febrile reactions, occurring in systemic use. It also leads to some inactivation of streptokinase by circulating antibodies. The systemic loading dose of streptokinase is 250,000 U over 36 min, followed by 100,000 U/hr. A daily systemic dose of streptokinase costs about $200.00 [10].

Most clinical studies of these agents have been in the treatment of pulmonary embolism, comparing heparin therapy with systemic fibrinolysis [5, 6] and in the treatment of acute and chronic arterial occlusive disorders [11–13], where success rates of up to 77% were achieved if infusion

was started within 12 hr of onset of thrombosis. However, hemorrhagic complications occurred in up to 45% of patients treated for arterial occlusions, and are more difficult to reverse. No single laboratory test reflects the degree of thrombolytic therapy or the propensity to hemorrhage [13], and the dosage is arbitrarily standardized [14].

Localized, low dose fibrinolysis avoids the potential for systemic hemorrhage complications by acting selectively at the site of the thrombosis. The dose required for local infusion is lower than the usual systemic dose: 5,000 U/hr vs. 100,00 U/hr. Although the results are preliminary, the incidence as well as severity of complications seems to be lower.

Dotter et al. [7] reported 17 patients treated with similar technique for thromboembolism. They demonstrated at least partial lysis in two-thirds of patients, with better results in occlusions of more recent duration. Systemic thrombolytic side effects were noted in three of 17 patients, requiring termination of treatment. In addition, two other patients had downstream bleeding in the perfused extremity requiring the termination of treatment.

We believe that localized streptokinase infusion bears further scrutiny in light of the current surge of interest in balloon angioplasty. Dissolution of a thrombus may be therapeutic itself, or allow application of angioplasty techniques to underlying stenoses. Recent occlusions, especially those complicating angiography or attempted transluminal angioplasty, are ideally suited because the age of the thrombus is precisely known. Because of the risk of embolization related to angioplasty may be increased in treatment of occlusions, a trial of low dose fibrinolysis may be warranted before angiography even when the thrombus is not known to be acute; this is investigated [16].

The technique may have application in treatment of visceral or renal artery occlusion as well as systemic and portal venous thrombosis. Localized streptokinase has been of value in lysis of thrombosed arteriovenous dialysis shunts [15] and may reveal underlying graft stenosis as the etiology for thrombosis.

A suitable catheter should be selected and its tip positioned as closely as possible or lodged within the site of the thrombus. Infusion of 5,000 U/hr of streptokinase is administered with an infusion pump, adjusting volume according to clinical fluid balance.

Recently, intracoronary infusion of streptokinase has been described resulting in significant clot lysis in acute myocardial infarction [17]. Although perfusion was localized, dosage was systemic at 1,000–2,000 U/min, carried out for 15–95 min. Perhaps this approach might be used in the peripheral circulation as well, although there is considerable difference in the quantity of thrombus that may form in the left anterior descending coronary artery compared to, for example, a common iliac artery.

From our initial experience, infusion for 12–18 hr or less should be sufficient for lysis of most acute clots, but if progress is being made as documented by angiography or if thrombosis of a total extremity is present, continued infusion may be warranted.

The decision to treat a patient with low dose fibrinolysis should be made jointly by the clinician and the interventional radiologist. If severe pain or extremity anesthesia is noted, there may not be time to attempt thrombolytic therapy, and surgical intervention may be necessary. The limiting question should be: "How well is the patient tolerating the ischemia?" Therapy should be halted immediately if there is evidence of distal bleeding, and the infusion should be slowed or stopped if there is evidence of systemic streptokinase effect with significant fall in fibrinogen. A closely monitored setting such as an intensive care unit allows for care of the catheter, close monitoring of distal pulses and pressures, and immediate evaluation of any clinical deterioration. With evidence of successful thrombolysis, the catheter may be kept open with saline infusion and the pulses monitored for an additional 4–6 hr, or it may be removed immediately depending on clinical factors. Transluminal angioplasty was carried out immediately in patients with underlying stenosis. Surgical colleagues should be consulted at the onset of therapy to avoid delays if surgical intervention is deemed necessary.

Contraindications to localized fibrinolysis should not be as extensive as those described with systemic therapy; however, they remain to be better defined. It should be avoided in patients with known severe hemostatic disorders. In patients with an existing bleeding site or recent surgery, extreme caution is warranted; however, the low dose technique has been used in patients with recent uncomplicated arterial punctures and arterial lines in place.

In conclusion, selective infusion of low dose streptokinase is a promising therapeutic alternative to surgical thrombectomy or in some cases bypass surgery, with less morbidity than systemic fibrinolysis. Relatively little experience with low dose streptokinase has been reported to date. This will doubtless change as streptokinase is now available as an adjunct to current interventional angiographic techniques.

Many questions remain to be answered: Should dosage be increased if no result is achieved initially? Should streptokinase be tapered rather than discontinued? Streptokinase vs. urokinase? Can localized perfusion of streptokinase be presumed to have a purely localized effect? and Could it be used in an acute operative field? Unfortunately, we do not have the answer to these questions, but this exciting method should be investigated further to better delineate its application.

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