Papers and Originals

FEASIBILITY OF ADEQUATE THROMBOLYTIC THERAPY WITH STREPTOKINASE IN PERIPHERAL ARTERIAL OCCLUSIONS

I. CLINICAL AND ARTERIOGRAPHIC RESULTS

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[WITH SPECIAL PLATE]

Convincing evidence of the efficacy of thrombolytic agents in man is scanty, although numerous studies related to this problem have been published during the last three years. Attracted by the fascinating work of Johnson on induced lysis of experimental thrombi in animals (Johnson and Tillett, 1952) and in man (Johnson and McCarty, 1959), we decided to embark on a controlled study of thrombolytic therapy in peripheral arteries occluded by spontaneous thrombi.

Materials and Methods

We have given thrombolytic agents to approximately 60 patients, of whom 18 have been treated with streptokinase because of a sudden arterial occlusion, a few having two arterial emboli. The assumption of an embolus was made in a patient with auricular fibrillation without previous history of intermittent claudication. It was accepted that a thrombosis was present only if the patient had previously complained of intermittent claudication and had normal sinus rhythm. If one or both criteria could not be applied, the occlusion was classified as of unknown nature.

In each of these 18 patients a series of arteriograms were taken immediately before therapy and if possible after the trial. An Ödman catheter was introduced percutaneously into an artery and the contrast medium injected with a Gitlund pump. Six exposures were made in each series with a time interval of at least 12 seconds between the first and last exposure. It is important to have a series of exposures in order to interpret the pictures with confidence and evaluate the collateral blood flow.

The tip of the catheter was inserted as close as possible to the occlusion. The thrombolytic therapy was initiated with a loading dose of streptokinase* calculated according to the result of *in vitro* streptokinase reactivity test (Amery, Maes, Vermyn, and Verstraete, 1963); this titrated priming dose was given in 5–10 minutes through the intra-arterial catheter and the perfusions were subsequently continued with series of standard doses of 250,000 units of streptokinase and 100 mg. of azapetine in 500 ml. of glucose supplemented or not with heparin (80 mg./500 ml.), each bottle being administered over an eight-hour period (52 units streptokinase/min.). The rate of the infusion as well as the dosage of streptokinase given intermittently had

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to be changed according to the values of the various control tests obtained in each patient individually during the course of the thrombolytic trial.

Fourteen cases with 15 arterial occlusions are described. Their selection was based upon arteriographic evidence of the vascular occlusion before treatment. In a second paper technical details of the laboratory data are presented and the values of various control tests correlated with the clinical and arteriographic results of the thrombolytic trial (Amery, Vermyn, and Verstraete, 1963).

Case 1

A man aged 72, with a 10-year history of intermittent claudication, had a sudden onset of severe pain in the right leg, which was white and cold from the knee downwards. Arteriography revealed an occlusion of the right common iliac artery (Special Plate, Fig. 1A). Thirteen hours after the onset of the present illness continuous intra-arterial streptokinase infusion was begun, being maintained for 108 hours. The total amount of streptokinase given was 2,400,000 units. The pain disappeared and the colour and the temperature of the right leg became progressively normal. Approximately 100 hours after the start of the infusion the pulse of the right femoral and popliteal arteries became palpable again.

The second arteriogram (Special Plate, Fig. 1B) demonstrated the permeability of the right iliac artery. The maximum and minimum recorded plasma fibrinogen levels during therapy were 153 and 45 mg./100 ml. respectively and a fibrinogen level under 100 mg./100 ml. was maintained for a period of 50 hours.

Case 2

A woman aged 56 had had clinical signs of mitral stenosis and auricular fibrillation since 1940. She fell suddenly in the street and was admitted the following day in subcoma and with a right hemiplegia. Cerebral arteriography was performed, and the middle cerebral artery did not fill during two series of exposures. Streptokinase infusions were given intravenously: for each 250,000 units 100 mg. of hydrocortisone was added the first day and 12.5 mg. a day subsequently. The patient was given 6,800,000 units of streptokinase in continuous intravenous infusion over a period of 108 hours. Allergic side-reactions such as fever, chills, or fall in blood-pressure were not observed. There was no sustained clinical improvement. Heparin was not associated with the lytic treatment, and the lowest fibrinogen value obtained during the course of treatment was 150 mg./100 ml.

Control arteriography 14 days later did not show any improvement in the cerebral circulation.

Case 5

A man aged 62 had had chronic bronchitis for 10 years, dyspnoea on exertion for six years, and ankle oedema for five months. One night he was awakened by a sharp pain in the left leg; the pain receded on administration of vasodilating drugs, and normal pulsations were observed in the femoral artery, but there was no pulsation in the popliteal artery or peripheral arteries.

A series of arteriographic films showed an irregular opacification of the left superficial femoral artery from Hunter's canal downward. Large portions did not show opacity, suggesting long parietal clots. The popliteal artery and more peripheral blood vessels were not opaque even in the latest exposure (Special Plate, Fig. 2A). The diagnosis of partial occlusion of the distal portion of the left femoral artery and total occlusion of the popliteal artery was made. The first symptoms appeared about 50 hours before the start of lytic therapy.

The patient was treated during 100 hours with a total amount of 5,000,000 units of streptokinase given in continuous intra-arterial infusion; heparin and vasodilating drugs were also added to the different bottles. Digitalization was maintained. The pain diminished rapidly, temperature and sensibility of the right thigh became normal, and the popliteal artery could be felt 71 hours after the start of lytic therapy. The left foot remained insensitive and gangrene of the toes set in. Arteriography still showed a strong but slightly irregular opacity of the femoral and popliteal arteries. The most distant ramifications were not visible (Special Plate, Fig. 2B). The patient later died from heart failure. The lowest fibrinogen level had been 37 mg./100 ml. and a fibrinogen value under 100 mg./100 ml. had been maintained for 30 hours.

Case 7

A woman aged 64 had tuberculosis of the apex of the right lung. Ten years previously temporary paralysis of the facial nerve occurred. For more than three months auricular fibrillation had been present. There was no history of cold feet or of intermittent claudication. Severe pain in the left leg below the knee occurred suddenly. Arterial pulsation was normal in the right leg, but on the left a pulse was felt only in the femoral artery to the proximity of Hunter's canal. An intravenous infusion of vasodilating drugs was given immediately.

An arteriogram showed a sharply outlined "stop" in the form of an arch half-way in Hunter's canal. The left popliteal artery was filled by small collateral arteries (Special Plate, Fig. 3A).

Treatment was started five hours after the embolus occurred and continued 73 hours, 1,850,000 units of streptokinase being administered continuously through a catheter in the femoral artery. Heparin was added, but no steroids. A sustained decrease of the pretreatment fibrinogen level (606 mg./100 ml.) was noted: during 72 hours this level was maintained under 150 mg./100 ml. (lowest value 90 mg.). On her discharge the ischaemic pains had disappeared completely. The power of the leg and sensation were normal, as well as the arterial pulsation in both legs. Arteriography at this time showed normal opacity of the femoral and popliteal arteries (Special Plate, Fig. 3B).

Case 8

A man aged 66 had had angina pectoris and intermittent claudication for more than seven years. The day before admission his lower limbs suddenly became cold and painful. No pulsation could be felt in the femoral or peripheral arteries, the distal part of both legs was pale and cold, and the feet appeared cadaveric. Translumbar aortography showed an occluded abdominal aorta with some collateral circulation filling the femoral arteries. Because of the very poor general condition, diffuse atheromatosis with calcified plaques, and the presence of some collateral circulation

surgical treatment was not attempted. Thrombolytic therapy with streptokinase supplemented with heparin and azapetine was started 30 hours after the occlusion of the aorta.

During 75 hours' continuous intravenous infusion, 3,200,000 units of streptokinase were given. The fibrinogen concentration dropped from an initial 504 to 105 mg./100 ml., the minimum value determined; during 19 hours the fibrinogen level was lower than 150 mg./100 ml. Arterial pulsation was felt and vascular sounds could be heard over both femoral arteries 65 hours after the start of treatment. A progressive fall in blood-pressure and haematocrit values was noted but no important ecchymoses besides those at puncture places were observed. Within a few hours the situation was deteriorating and the patient died in irreversible shock 120 hours after the start of streptokinase administration.

At necropsy a very large retroperitoneal haematoma was found (estimated amount 3 litres) with approximately 1 litre of haemorrhagic fluid in both pleural cavities. There was a hole at the puncture site of the abdominal aorta. Aortography performed at necropsy showed an almost complete occlusion of the aorta at the same place as in the first aortograph. It is possible this was a re-formed clot, because at one time a definite clinical improvement in both legs was noted and vascular sounds reappeared. The streptokinase and heparin administration had to be interrupted 24 hours before death.

This patient was the only one in this series subjected to translumbar aortography before thrombolytic therapy.

Case 9

A man aged 68 had had auricular fibrillation since 1943. He had had two cerebrovascular accidents, in 1943 and 1957 respectively, and bilateral intermittent claudication for 20 years. At one time he felt sudden pain in his left leg, and 24 hours after treatment with heparin he was admitted to hospital. Arteriography showed a very irregular delineation of both superficial femoral arteries and of the right popliteal artery. At the left side a partial stenosis of the superficial femoral artery was present half-way to Hunter's canal; some contrast medium was present beyond this point but did not reach the popliteal artery even in the last exposures, and very few collaterals were visualized. Half an hour after arteriography was completed the patient had a chill which decreased after administration of antihistaminics. It was nevertheless decided to treat him with proteolytic agents, and an intra-arterial continuous perfusion of streptokinase, heparin, and azapetine was started 26 hours after the first symptoms of the occlusion.

Because of high temperature (40° C.) antibiotics as well as antipyretics were added; cardiac glucosides were given a few hours later. The streptokinase infusion was stopped for 75 minutes because of bleeding at the puncture sites. The fibrinogen level had dropped in the meantime from 390 to 144 mg./100 ml. Some improvement of the clinical signs was noted and the streptokinase infusion was resumed 75 minutes later for a further three hours. At that time the general condition was worsening and the temperature rose to 39.5–40° C. Respiration was rapid (56/min.); the blood-pressure dropped progressively and the patient died after a few hours in irreversible shock (12 hours after the initiation of therapy). Necropsy was not performed. The total amount of streptokinase administered was 1,900,000 units. The lowest fibrinogen level noted at one time was 144 mg./100 ml.

Case 10

A girl aged 11 had suffered for weeks from repeated bouts of angina with high temperature, and awoke one morning with speech difficulties, left hemiplegia, and pain in the right arm and hand. A paralysed facial nerve on the left side and a complete paralysis of the left arm and partial paralysis and strongly positive Babinski sign of the left leg were found upon admission. The right hand and wrist were cold

and no pulsations of the radial or ulnar arteries were felt, although the right brachial artery was pulsating normally. A large constant splitting of the second heart sound was related to a complete right bundle-branch block. The anti-streptolysin titre was 1/1,000, and after two days the blood-culture became positive (Gram-negative bacteria); *Streptococcus viridans*, staphylococci, and pseudodiphtheria bacilli were grown from a throat swab. Cerebral arteriography showed an occlusion of the right middle cerebral artery. Arteriography of the brachial artery revealed an occlusion proximal to the bifurcation. The origin of the emboli still remained undiagnosed eight months later, as normal oxygen saturation and pressure values were found at all levels during a right heart catheterization. The patient was treated with kanamycin and sulphonamides according to the results of *in-vitro* sensitivity tests.

A continuous perfusion of streptokinase was started approximately 48 hours after the onset of the clinical symptoms and five hours after admission; 2.5 mg. of heparin and 100 mg. of azapetine were added to each bottle of 250,000 units streptokinase. Ten hours after the start of therapy normal strength and motion of the left leg appeared, but only small movements of the left arm were possible. The right arm became progressively less cold, and 34 hours after the start of the lytic therapy weak pulsations in the right radial artery were felt. At that time the paralysis of the left leg had regressed completely and the left arm could be lifted up to the face. The facial-nerve paralysis remained unchanged; five hours later both radial and ulnar arteries pulsated with equal strength. Control arteriography of the right arm, performed later, showed that the brachial artery was patent; a second cerebral angiograph was not performed.

A total amount of 3,750,000 units of streptokinase was administered in continuous arterial perfusion during 49 hours. After two "shot" doses of streptokinase (500,000 and 250,000 units) a rapid pulse rate of 108/min. was observed and at one time some somnolence was noted. The initial fibrinogen level of 318 mg./100 ml. never dropped under 140 mg./100 ml. although large amounts of streptokinase were given to this girl of 35 kg. weight. This resistance is probably related to the high initial antistreptolysin titre (1/1,000) and high titrated initial dose. At one time the available plasminogen was exhausted and Cohn's fraction I, prepared from 1.5 litres of plasma, was given twice in order to replete the plasminogen deficit. The clots formed in the patient's plasma during plasminogen exhaustion could not be lysed *in vitro* with streptokinase or urokinase. The fibrinolytic activity of these blood samples on standard fibrin film was very high, and either low or no activity was noted on heated film. This would suggest a very low direct fibrinolytic activity and a high activator activity in the circulating blood.

Case 11

This patient, a man aged 73 without history of intermittent claudication, had a sudden occlusion of the left common femoral artery, and the left leg had to be amputated in another institution. Three weeks later he awoke at night because his right foot was very cold and was becoming increasingly painful.

Upon admission no pulsation in the popliteal artery could be felt, and arteriography showed an occlusion of the superficial femoral artery at the distant end of Hunter's canal, with poor development of collateral circulation.

Streptokinase therapy was started approximately 20 hours after the arterial occlusion, the nature of which remained unknown. A total amount of 3,950,000 units of streptokinase, with heparin and azapetine, was administered in continuous intra-arterial perfusion during 86 hours. The fibrinogen level decreased from 660 mg./100 ml. to a minimum value of 136 mg./100 ml. A control arteriography was performed; arterial filling seemed to have regressed 16 cm. compared with the pretreatment picture. Notwith-

standing intensive streptokinase therapy the leg eventually had to be amputated.

Case 12

A woman aged 53, with a tight mitral stenosis, had a regular heart rhythm and peripheral arteries pulsating normally before operation. Valvotomy was performed and no thrombi were found in the left atrium. On the second post-operative day a rise in temperature (39° C.) and atrial fibrillation were noted for the first time. On the sixth post-operative day the patient suddenly complained of an acute pain in the right leg and of a tingling sensation in the left hand. The right foot was cold and no pulsation was felt in the right femoral artery or in the brachial artery and its more distant branches. Aortography showed a normal aortic bifurcation but a sharp stop in the right common iliac artery, about 1.5 cm. distant from its origin (Special Plate, Fig. 4A). Arteriography of the left axillary artery was not attempted, but the clinical diagnosis of acute embolism in the left brachial artery was regarded as evident by all observers.

The patient was treated with streptokinase nine hours after the first complaints of the two (septic ?) emboli. A total amount of 2,750,000 units of streptokinase was administered over 66 hours' continuous intra-arterial infusion; azapetine and heparin were associated with the proteolytic agent. Arterial pulsation was felt at the elbow and the blood-pressure was identical at both sides, respectively 27 and 36 hours after the start of the infusion. Pulsation in the right common femoral artery reappeared 60 hours after the beginning of therapy. Control arteriography of the abdominal aorta and right common iliac artery showed patency of the previously occluded vessel and all distant branches (Special Plate, 4B).

A fibrinogen level lower than 100 mg./100 ml. was maintained during 10 hours and was under 150 mg./100 ml. during 26 hours; the initial level was 525 mg./100 ml. When taking the first aortograph a part of the contrast material was injected into the renal arteries; this led to a transitory anuria. Tests performed four months later showed no impairment of renal function.

Case 13*

A man aged 66 who had never complained of intermittent claudication suddenly felt a sharp pain in the left leg while waiting in an inland revenue office. He was treated with anticoagulants and vasodilators before being admitted to hospital 24 hours later.

On examination the heart rhythm was regular. An occlusion of the left common femoral artery with good filling of the deep iliac artery could be seen in the arteriogram. Streptokinase was administered 38 hours after the acute thrombosis. A total amount of 1,600,000 units streptokinase was given over 52 hours in a continuous intra-arterial infusion, associated with heparin and azapetine in the usual doses. A large haematoma in the left inguinal area increased in size the following day, necessitating a transfusion of 800 ml. of whole blood. At one time definite mental agitation was noted; because of a subsequent drop in blood-pressure phenylephrine was administered. As no clinical improvement was obtained in the ischaemic leg the streptokinase infusion was stopped after 52 hours of intensive proteolysis. A control arteriograph still showed a completely blocked artery. Although the position of the patient and the radiographic intensity were not identical in both series, the possibility of some extension of the thrombus could not be excluded. Eventually the leg had to be amputated.

Case 14

A man aged 61 had had intermittent claudication for several years. Because of increasing symptoms due to an occluded left superficial femoral artery a dacron by-pass was

*We are indebted to Professor Morelle and Dr. C. Challant for having referred this patient.

placed between the left common femoral and popliteal arteries. This proved successful.

Four months later he awoke at night with severe pain in the left leg, which was cold and pale to the knee. A sharp occlusion of the by-pass was seen 1 cm. from its origin at the common femoral artery. Branches of the deep femoral artery could be seen but not the superficial femoral artery. The symptoms of the occlusion were present for about 12 hours before streptokinase therapy was started. A total amount of 5,175,000 units was given over a period of 70 hours, intra-arterially only during the first 28 hours ("kinalysin"). The catheter was inadvertently pulled out and the streptokinase was subsequently given intravenously for the remaining 42 hours ("streptase" *). The patient bled very heavily at the arterial puncture site after the catheter had been pulled out and a large haematoma appeared in the right groin. He developed a progressive renal insufficiency with complete anuria for two days. As renal function was resumed after 48 hours he was not dialysed. A tentative vessel repair was subsequently tried: the clots of the completely thrombosed by-pass were removed, giving a limited blood flow for a short time. Pulsation of the popliteal artery, however, was not felt at the end of the operation, and after a few weeks the left leg had to be amputated.

This patient had been treated unsuccessfully during 70 hours, receiving a total amount of 5,175,000 units of streptokinase associated with heparin. A fibrinogen level under 150 mg./100 ml. was maintained during 26 hours, and an intensive proteolytic activity was found in the peripheral blood. The question can be raised to what extent the artificial nature of the vessel is related to this failure.

Case 15

A man aged 61, without previous complaints of intermittent claudication, was admitted to hospital with hypertension (diastolic value 100–120 mm. Hg) and several signs of heart failure of unknown origin; the heart rhythm was regular. On treatment with digitoxin and several diuretics his weight fell from 81 to 68 kg. in seven days. One day he complained of increasing pain in both legs. The left leg was cold and somewhat cyanotic from the knee downwards: arterial pulsations were normal in the inguinal area but absent in the more distant arteries. The right leg was cold and slightly cyanotic below the thigh; only femoral pulsation was palpable. The arteriography revealed a normal right iliac artery; the right superficial femoral artery was filled to 16 cm. above the knee, a thrombus or embolus being at that level (Special Plate, Fig. 5A). A second stop could be presumed in the right deep femoral artery.

The occlusion(s) had lasted about 50 hours when thrombolytic therapy was initiated and 1,600,000 units of streptokinase were injected through the intra-arterial catheter. Half an hour later the 12-hour administration of a bottle containing 1,600,000 units of streptokinase was begun. The next morning the patient was unconscious, the blood-pressure was 180/90 mm. Hg, and the right facial nerve, right arm, and right leg were paralysed. There was no change in arterial pulsation. The treatment was interrupted, 3,000,000 units of streptokinase having been given in 14 hours. The fibrinogen level initially was 520 mg./100 ml., and at one moment fell below 25 mg.

The patient died the next day. The necropsy findings were as follows. The left femoral artery was open, a lesion of the intima could be seen in Hunter's canal (Special Plate, Fig. 5B). No important thrombus was found between the inguinal and popliteal areas. The right femoral artery was open; the origin of the popliteal artery was occluded by a partially organized thrombus about 8 cm. long. Diffuse but not massive haemorrhage of the subdural and submeningeal areas covering both occipital poles of the

hemispheres and to some extent the cerebellum was noted. A more diffuse extravasation was observed at the base of the left temporal zone. All vessels had extensive plaques of atheromatosis with some calcification.

Case 16

A man aged 73 with a history of recent myocardial infarction was operated on because of a prostatic adenoma. The pulse rate was 64 and blood-pressure 138/70 mm. Hg. The radial and femoral arteries on both sides pulsated normally. At 3 a.m. on the eighth post-operative day the patient complained of pain in the right leg. At this moment the E.C.G. showed sinus rhythm. At 4 p.m. arteriography showed a complete occlusion of the right common iliac artery (Special Plate, Fig. 6A).

The catheter was left to permit local administration of streptokinase. At 7.45 p.m. 300,000 units were administered intra-arterially. At 8 p.m. an intravenous drip was started, and 300,000 units of streptokinase and 100 mg. of azapetine was given over 12 hours; at 9.30 p.m. a new intra-arterial shot of 200,000 units of streptokinase was given. Some bleeding occurred at the site of the cystostomy, but it ceased rapidly. The initial fibrinogen level of 270 mg./100 ml. had fallen to 54 mg. Physical examination the following morning showed a warmer right foot, diminished pain, but no pulsation in the right femoral artery. Two bottles containing 200,000 units of streptokinase and 100 mg. of azapetine were administered over the following 24 hours. The next morning pulsation in the right femoral artery was as strong as in the left femoral artery. The right leg below the knee and the right foot were still cold. At 10 a.m. his temperature, which had been normal for the last four days, suddenly rose to 39.6° C. At midday treatment with streptokinase was stopped: a total dose of 1,040,000 units having been given in 41 hours. A control arteriograph showed patency of the previously occluded vessel (Fig. 6B). The patient's general condition worsened, and four days later he died of progressive and irreversible heart failure and shock without evidence of blood loss.

Case 17

A 62-year-old woman with mitral stenosis and auricular fibrillation was admitted to the department of surgery for pain in the right leg and foot. She had never complained of intermittent claudication. The pain had begun suddenly two days earlier and the right leg became cold and white. The pulse was absent above the right knee, although pulsation was felt in the common femoral artery. The diagnosis of embolus in the right superficial femoral artery was made and it was decided to perform an embolectomy.

The patient was operated on 56 hours after the onset of symptoms. A large embolus extending to the deep femoral artery, causing occlusion, was removed. After the operation pulsation was felt in the fossa poplitea, but the distal part of the leg remained cold. Arteriography performed 12 hours after embolectomy (Special Plate, Fig. 7A) revealed a sharp occlusion of the distal part of the popliteal artery. This was interpreted as an embolic fragment disseminated during operation. It was decided, notwithstanding the recent operation, to treat this patient with lytic agents.

Streptokinase and azapetine treatment was instituted 80 hours after the beginning of the first symptoms, and 2,650,000 units were given over 66 hours. Forty-eight hours after the beginning of streptokinase treatment some bleeding was noted in the operation areas. At that time the fibrinogen level had decreased from 404 to 172 mg./100 ml. Because she bled more profusely the next day, streptokinase administration was interrupted. The subjective improvement was confirmed by an increase in temperature of the distant part of the right leg. A control arteriography was carried out, and good visualization of the popliteal artery and its bifurcation into arteria tibialis anterior and arteria fibularis was obtained without filling of the arteria tibialis

*We are indebted to Behring Werke (Marburg), who supplied the additional streptokinase ("streptase") for the treatment of this patient.

M. VERSTRAETE *ET AL.*: THROMBOLYTIC THERAPY WITH STREPTOKINASE

FIG. 1.—A Before. B After.

FIG. 2.—A Before. B After.

FIG. 3.—A Before. B After.

FIG. 4.—A Before. B After.

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FIG. 5.—A Before. B After.

FIG. 7.—A Before. B After.

FIG. 6.—A Before. B After.

J. BOUTON *ET AL.*: B.C.G. DISSEMINATION IN
CONGENITAL HYPOGAMMAGLOBULINAEMIA

FIG. 1. — Section of lung showing alveoli filled by "honeycomb" exudate. (H. and E. $\times 52$.)

FIG. 2. — Section of lung showing *Pneumocystis carinii* organisms, which appear as black dots surrounded by a pale envelope. (P.A.S. $\times 520$.)

posterior (Special Plate, Fig. 7B). Although the main obstructing embolus could be lysed in the popliteal artery no complete clearing of more distant arteries could be obtained. Because the distant parts of the right foot remained very painful and almost in a pregangrenic state it was decided, 16 days after the acute onset of the first symptoms, to amputate the distal part of the right leg.

Results

A therapeutic course with streptokinase was given to 14 patients (15 arterial occlusions) with an average age of 57 years (Table I). Three thromboses and five emboli were diagnosed; the nature of six additional arterial occlusions remaining undefined. The time-interval between the first symptom and the beginning of treatment was 0–23 hours in 8, 24–47 hours in 4, 48–71 hours in 1, and 72–80 hours in 1. In all patients arteriography was performed before treatment and in nine also after thrombolytic therapy. Of 18 patients with clinical symptoms diagnostic for acute arterial occlusion, selection was based upon the certain arteriographic evidence of the occlusion before treatment.

TABLE I.—*Diagnostic Details*

Case No.	Auricular Fibrillation on Admission	Other Possible Cause of Embolism	History of Claudication before Acute Occlusion	Diagnosis	Time-interval between First Symptom and Start of Therapy
1	—	—	+	Thrombosis	13
2	+	—	—	Embolism	29
5	—	—	—	Uncertain	58
7	+	—	—	Embolism	5
8	—	—	+	Thrombosis	30
9	+	—	+	Uncertain	26
10	—	+	—	Embolism	20
		(septicaemia)			
11	—	—	—	Uncertain	20
12	+	—	—	Embolism	9
13	—	—	—	Uncertain	38
14	—	—	+	Thrombosis	12
15	—	—	—	Uncertain	14
16	—	—	—	Uncertain	17
17	+	—	—	Embolism	80

All patients have been treated with continuous, usually intra-arterial, perfusions during an average of 65 hours, and an average of 3,216,000 units of streptokinase were given (Table II). In eight patients (Cases 5, 7, 8, 10, 11, 12, 13, and 14) heparin was added to the bottles containing the streptokinase; two patients (Cases 2 and 10) were given steroids.

For clinical evaluation the following symbols were used: (+) if definite arterial pulsation was felt distally to the occluded artery by all observers, provided that no pulsation was present before thrombolytic treatment;

(?) means that the return of arterial pulsation could not be obtained because of the topography of the artery—for example, cerebral artery—or the death of the patient before adequate treatment could be hoped for. The arteriograms are: (+) when there is disappearance of the arterial occlusion and filling of the artery or its branches, (—) when persistent presence of the arterial occlusion is visualized in the control arteriography; (?) means that no control arteriography could be made for various reasons, one being the death of the patient. The clinical findings and arteriographic evidence are presented in Table II.

When only one clinical criterion is taken into consideration, the return of arterial pulsation, 8 of the 15 occlusions with thrombo-emboli were lysed after an average of 60 hours' intensive treatment; in four cases this criterion could not be applied because of the topography of the occluded vessel (two cases) or the death of the patient (two cases). The arteriographic criterion corresponds well with the previous evaluation: 7 of the 15 clots were proved to have disappeared, two occlusions were still present, and six occlusions could not be controlled by arteriographic means after thrombolytic trial.

The correlation between the nature of the occlusion and the success or failure of the streptokinase therapy is summarized in Table III. With the clinical criteria the treatment was as effective in the group with thrombosis as in the group with embolism. With the arteriographic criteria the thrombolytic treatment seems to be more effective in the group with embolism, but these differences are not significant.

TABLE III.—*Correlation Between Nature of Occlusion and Success of Streptokinase Treatment*

	Clinical Criteria				Arteriographic Criteria			
	+	—	?	Total	+	—	?	Total
Thrombosis ..	2	1	0	3	1	0	2	3
Emboli ..	4	0	2	6	4	0	2	6
Uncertain ..	2	2	2	6	2	2	2	6
Total ..	8	3	4	15	7	2	6	15

On the basis of these figures it is impossible to confirm the statement that thrombolytic therapy is more effective in patients with arterial thrombosis than in those with arterial embolism.

It is important to correlate the duration of the arterial occlusion and the efficacy of streptokinase therapy (Table IV).

TABLE II.—*Therapeutic Details and Efficiency of the Thrombolytic Experiment*

Case No.	Time-interval (Hours) between Start and End of S.K. Treatment	Total Amount of S.K. Administered (× 1,000 Units)	Heparin added During S.K. Treatment	Steroids Added During S.K. Treatment	Clinical Criteria*	Arteriographic Criteria
1	108	2,400	—	—	+ after 108 hours	+
2	108	6,800	—	+	? topography	? No control arteriography
3	100	5,000	+	—	+ " 71 "	+
7	73	1,850	+	—	+ " 46 "	+
8	75	3,200	+	—	+ " 65 "	? No control arteriography
9	12	1,900	—	—	? death	? Death
10a	49	3,750	+	+	+ after 34 hours	+
10b			—	—	? topography	? No control arteriography
11	86	3,950	+	—	—	—
12	66	2,750	+	—	+ after 54 hours	+
13	52	1,600	+	—	—	—
14	70	5,175	+	—	—	? No control arteriography
15	14	3,000	—	—	? death	? Death
16	41	1,040	—	—	+ after 37 hours	+
17	66	2,650	—	—	+ " 66 "	+
	Mean = 65	Mean = 3,216	+ = 8 — = 6	+ = 2 — = 12	+ = 8/15 (53%) after 60 hours — = 3/15 (20%) ? = 4/15 (25%)	+ = 7/15 (45%) — = 2/15 (15%) ? = 6/15 (40%)

S.K. = Streptokinase. * If +, the time-interval in hours between start of therapy and reappearing of pulsations is recorded.

The majority of the arterial occlusions have been subjected to streptokinase therapy within 24 hours of the start of the clinical symptoms (8/15). In five of these thrombolysis was proved by arteriography. It is interesting to note that two vascular occlusions of 48 to 80 hours' duration were also successfully treated; the disappearance of the occlusion has in both instances been proved by arteriography.

TABLE IV.—Correlation Between Duration of Occlusion Before Treatment and Success of Treatment

Hours	Clinical Criteria				Arteriographic Criteria			
	+	—	?	Total	+	—	?	Total
0-23	5	2	1	8	5	1	2	8
24-47	1	1	3	5	0	1	4	5
48-71	1	0	0	1	1	0	0	1
72-80	1	0	0	1	1	0	0	1
Total	8	3	4	15	7	2	6	15

Steroids were associated with streptokinase treatment in only two patients having three recent arterial occlusions (Table V). This series, however, is too small to draw any conclusion.

TABLE V.—Correlation Between Use of Steroids and Success of Treatment

	Clinical Criteria				Arteriographic Criteria			
	+	—	?	Total	+	—	?	Total
Steroids	1	0	2	3	1	0	2	3
No steroids	7	3	2	12	6	2	4	12
Total	8	3	4	15	7	2	6	15

Discussion

The streptokinase used (kinalysin) was surprisingly well tolerated even if large priming doses such as 1,400,000 units (Case 9) were given intra-arterially within five minutes. Also, the prolonged administration (Cases 1, 2, and 5: 100-108 hours) caused few untoward reactions. Mental disorientation and excitability or the reverse were manifest in two patients (Cases 7 and 13) and to a minor degree in three others (Cases 8, 10, and 11). These case histories, including the visualization with two series of arteriograms, indicate the possibility of obtaining satisfactory thrombolysis with proper administration of streptokinase.

In the cases where patency of the artery was visualized by control arteriography no re-formation of the clot was noted in the subsequent days or weeks after therapy. It has been shown that re-obstruction of blood-vessels occurs in almost all animals where A.C.T.H. is associated with the streptokinase trial (Johnson and Tillett, 1952). No conclusion can be drawn from our limited experience in this regard.

Most patients had ecchymoses at the puncture sites (frequent venous-blood sampling) and five experienced serious bleeding (massive haematoma spontaneously in Case 13 and after inadvertently pulling out the intra-arterial catheter in Case 14, important loss of blood at the operation site 12 hours after surgery in Case 17, retroperitoneal haematoma at the puncture site for translumbar aortography in Case 8, and cerebral bleeding in hypertensive Case 15; the last two patients died because of the haemorrhagic manifestation). This tendency to bleed is partly related to the associated heparin treatment (240 mg./24 hours in continuous

infusion). The hazard of sustained anticoagulation is not to be underrated during a streptokinase administration with decreased levels of various clotting factors (fibrinogen, factors V and VIII). It was therefore decided, upon completion of this study, to add anticoagulants only at the end of the treatment course with streptokinase. However, there seems to be a slightly higher incidence of proved thrombolysis in patients with the combined treatment (Moser and Hajjar, 1960); this series is, however, too small for valid conclusions to be drawn.

At present it is not possible to define the indications for thrombolytic therapy in arterial occlusion. Well-controlled large-scale experiments are urgently needed to discover the possibilities and limitations of these powerful enzymes used as thrombolytic agents.

The tests to be recommended for guidance of the dosage are another major unsettled problem (fibrinogen level, antithrombin VI assay, thrombin time, plasminogen level).

Still more questions than answers emerge from this trial:—Must thrombolytic agents be administered locally in order to obtain the highest possible concentration on the clot's surface? Must a continuous infusion be given or will intermittent administration suffice, or is a combination of both to be recommended? Should heparin, steroids, vasodilators be given concurrently with thrombolytic agents? It is hoped that these problems, which cannot be answered adequately at present, will be solved before these drugs are released for more liberal use.

Conclusion and Summary

Thrombolytic treatment was initiated in 14 patients having 15 recent arterial occlusions (three thromboses, six emboli, six of unknown nature). The arterial occlusion was visualized in all patients with arteriography, and in nine patients a control arteriography was obtained.

On the basis of arteriographic criteria 7 of the 15 clots were lysed, and in eight instances a definite return of arterial pulsation was noted after an average of 60 hours of intensive streptokinase treatment.

The majority of the patients were treated within 24 hours of the onset of the arterial occlusion, and an average of 3,216,000 units of streptokinase were administered in continuous infusion over 65 hours (mean value). According to these limited but well-controlled experiments emboli can be lysed as well as thrombi, and the addition of heparin or steroids during the streptokinase treatment does not seem to interfere with the possible adequacy of the treatment.

This clinical trial and the laboratory investigations were made possible because of the ever-willing help of all members of the laboratory of coagulation and proteolysis, more particularly D.Sc. R. A. De Vreker, Drs. C. Vermynen and H. Maes, and Miss A. Van Hoonacker. We are indebted to the assistants of the department of medicine, cardiology, and surgery for their clinical interest.

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