Comparison of the effects of streptokinase and heparin on the early rate of resolution of major pulmonary embolism

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Summary: The extent of early resolution of major pulmonary embolism observed in 10 patients after 24 hours of treatment with heparin was compared with that seen in 17 patients after 24 hours of treatment with streptokinase. The patients in the streptokinase group also received a loading dose of heparin and were treated with heparin by continuous infusion when their thrombin time returned to normal levels. All had pulmonary hypertension. Pulmonary embolism was classified as acute in the 10 patients in the heparin group. Seven of these patients showed no angiographic change, two showed slight improvement and one showed angiographic deterioration. There was a moderate and statistically insignificant fall in mean pulmonary arterial pressure and total pulmonary resistance. Fourteen of the 17 patients who were studied before and after streptokinase were classified as acute and three as subacute progressive major pulmonary embolism. Eight showed marked angiographic improvement, four moderate and two slight angiographic improvement. There was a moderate and statistically significant fall in the mean pulmonary arterial pressure and pulmonary vascular resistance. In addition, all seven patients in whom no angiographic improvement occurred during heparin therapy showed moderate or marked angiographic improvement after a further 24 hours of treatment with streptokinase. The results strongly suggest that streptokinase therapy accelerates thrombolysis in patients with acute major pulmonary embolism.

There has been considerable recent interest in the use of fibrinolytic agents in the treatment of thromboembolic disease.[1, 2] Although early resolution of major pulmonary embolism has been demonstrated to follow the administration of the plasminogen activators, streptokinase and urokinase,[3-9] it remains uncertain whether resolution occurs more rapidly with fibrinolytic therapy than with the conventional heparin therapy. We have compared the degree of early resolution of major pulmonary embolism after heparin therapy with that occurring after streptokinase therapy. The initial aim of the study was to investigate the feasibility of using streptokinase in patients with acute major pulmonary embolism.[7] For this reason the earlier investigations were performed only before and after streptokinase, and it was only in the latter part of the study that observations on the effect of heparin treatment were also made.[10] This study is therefore limited by the fact that the patients were not allotted to the heparin or streptokinase groups in a random manner. Nevertheless, the decision to use one or other of these agents was not determined by clinical factors and the two groups were found to be well matched.

Patients and methods

Patients

Investigations were performed on 28 patients with severe pulmonary embolism. All had pulmonary hypertension and the pulmonary angiogram showed filling defects in the proximal pulmonary arteries with severe obstruction to both sides. The hemodynamic and angiographic changes were assessed in 10 patients before and after 24 hours of heparin treatment (Group A) and in 17 other patients before and after 24 hours of treatment with streptokinase (Group B). All 10 of the patients in the heparin group had had a recent episode of major pulmonary embolism within 48 hours of commencing

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therapy and were classified as acute. Fourteen of the 17 patients in the streptokinase group were classified as acute, and three patients who had had progressive symptoms of pulmonary vascular obstruction for at least three weeks before commencing treatment were classified as having subacute progressive pulmonary embolism. In addition seven of the 10 patients investigated after 24 hours of heparin treatment were studied again after 24 hours of treatment with streptokinase. The results in this group were analyzed separately and also in combination with those in the 14 patients with acute pulmonary embolism who were investigated only before and after 24 hours of streptokinase therapy. This combined streptokinase group of 21 patients was called Group C. One other patient with major pulmonary embolism treated with streptokinase could not be included in the analysis because she was investigated only before receiving streptokinase. This patient developed a cardiac arrest three hours after streptokinase was commenced and underwent successful pulmonary embolectomy.[7]

The patients in the heparin and streptokinase groups were compared with respect to age and sex, time lapse between the last embolic episode and the commencement of treatment, presence or absence of previous embolic episodes, presence of underlying cardiac or pulmonary disease, and severity of pulmonary vascular obstruction (Table I). The two groups were comparable in all respects except that the mean time lapse between onset of symptoms and treatment was less in the heparin group than in the streptokinase group (although the range was the same), and the sex distribution was different in the two groups.

Laboratory techniques

Blood samples for fibrinolytic and coagulation assays were taken into disposable plastic syringes by clean venepuncture. High spun plasma was prepared by centrifugation at 4° C. and the coagulation assays and the fibrinolytic assays were monitored according to methods previously described,[3] using the following tests: thrombin clotting time, prothrombin time, activated partial thromboplastin time, euglobulin lysis time, fibrin plate assay, plasma fibrinogen assay, plasma plasminogen assay, and streptokinase resistance test. The methods for serial measurement of the brachial and pulmonary arterial pressures and of cardiac output by the indicator dilution technique have all been previously described.[7] Pulmonary angiography was performed using a rapid x-ray film changer. The degree of pulmonary vascular obstruction was assessed independently by three observers and the mean value recorded. Total pulmonary resistance, i.e.

$$\frac{\text{Mean pulmonary arterial pressure}}{\text{Cardiac output}}$$

was used as an index of pulmonary vascular resistance.

Treatment

The patients were initially assessed in conjunction with the cardiothoracic surgical team and after investigations had been performed were nursed in a coronary care unit with continuous electrocardiographic monitoring. Both the heparin and streptokinase were administered through the angiographic catheter which was left in the pulmonary artery for the period of the investigation. The rate of delivery of these drugs was carefully controlled by means of either a peristaltic pump or a graduated plastic burette.[11] The patients in the heparin group were initially given heparin in a dose of 10,000 units intravenously and this was followed by 30,000 units given over 24 hours by continuous intravenous infusion. The dose was adjusted to maintain the clotting time at 2½ to 3 times control levels or the activated partial thromboplastin time 1½ to 2½ times control value.[12]

The patients in the streptokinase group had blood taken for a streptokinase resistance test as soon as the clinical diagnosis of major pulmonary embolism had been made. Heparin in a dose of 10,000 units was then given intravenously to all of the patients and this was followed by 30,000 units administered over 24 hours by continuous intravenous infusion. When the diagnosis had been confirm-

TABLE I
Clinical, angiographic and hemodynamic details before treatment

Group	No.	Age (years)	Sex M.	Sex F.	Time since last embolic episode (hours)	Previous recent embolism	Cardiac or pulmonary disease Yes	Cardiac or pulmonary disease No	Degree of pulmonary vascular obstruction (%)	Cardiac output l./min.	pulmonary arterial pressure (mm.Hg)	Total pulmonary resistance (units)
A. *Heparin*												
Acute	10	53.2 (23-73)	6	4	18.6 (5-48)	5	2	8	49.5 (35-70)	4.7 (2.8-6.6)	27.7 (19-37)	6.6 (3.1-12.5)
Subacute progressive	0	—	—	—	—	—	—	—	—	—	—	—
B. *Streptokinase*												
Acute	15*	54.8 (32-74)	5	10	24.5 (4-48)	8	3	12	53 (40-75)	4.5 (2.4-8.7)	30.0 (24-40)	7.0 (2.9-13.0)
Subacute progressive	3	58.7 (54-62)	3	0	3 weeks	3	3	0	58.3 (55-60)	—	38.3 (28-44)	—

Normal values: Mean pulmonary arterial pressure 15 mm.Hg
Total pulmonary resistance 3 units

*One patient was not studied after streptokinase therapy because she developed a cardiac arrest and was treated by pulmonary embolectomy.

ed by pulmonary angiography, heparin treatment was stopped and streptokinase was administered using a loading dose of 250,000 units over 30 minutes followed by 100,000 units per hour.[13] If the resistance was greater than 250,000 units the additional dose necessary to neutralize the streptokinase antibodies was administered over 30 minutes and treatment was then continued in a dose of 100,000 units per hour. It was found in earlier studies that the incidence of bleeding increased when heparin treatment was continued during streptokinase infusion. For this reason heparin therapy was stopped in the streptokinase group from the time of giving the loading dose of streptokinase until the thrombin clotting time fell to below 15 seconds (control 9 to 12 seconds). At this time heparin was given as a prophylactic measure against rethrombosis in a loading dose of 2000 units intravenously followed by 15,000 to 20,000 units over 24 hours by continuous intravenous infusion. Hydrocortisone hemisuccinate (200 mg. intravenously) was given prophylactically with the loading dose of streptokinase in order to prevent fever.

Results

The effects of 24 hours of treatment with either heparin or streptokinase on pulmonary vascular obstruction are summarized in Table II. Included in this table are the results from the 10 patients who were studied before and after heparin (Group A), the 17 patients who were studied before and after streptokinase (Group B), and the 21 patients with acute pulmonary embolism from both groups who were studied before and after streptokinase therapy (Group C). The mean pulmonary arterial pressure fell from 27.7 to 24.7 mm.Hg ($P>0.1$) in the heparin group (Group A), from 30.0 to 21.3 mm.Hg ($P<0.01$) in the patients with acute pulmonary embolism in the streptokinase group (Group B), and from 38.3 to 34.7 mm.Hg ($P>0.2$) in the patients with subacute progressive pulmonary embolism in the streptokinase group (Group B.) The total pulmonary resistance fell from 5.76 to 4.90 units in the heparin group ($P>0.2$) and from 6.64 to 4.52 units ($P<0.05$) in patients with acute pulmonary embolism treated with streptokinase (Group B); because of insufficient data, this calculation could not be made in the patients with subacute progressive pulmonary embolism who were treated with streptokinase. Seven of the 10 patients treated with heparin showed no angiographic change, two showed slight improvement and there was angiographic deterioration in one. In contrast, eight of the 14 patients with acute pulmonary embolism who were treated with streptokinase showed marked improvement, four showed moderate improvement and two showed slight improvement. None of the patients with subacute progressive pulmonary embolism who were treated with streptokinase showed angiographic improvement. The seven patients who showed no angiographic change after 24 hours of treatment with heparin had studies repeated after 24 hours of treatment with streptokinase. Four showed marked angiographic improvement and three showed moderate improvement.

The hemodynamic and angiographic findings from all patients treated with streptokinase (Group C), including the seven patients who were studied before and after heparin, are shown at the bottom of Table II. All 21 patients had acute major pulmonary embolism. There was a fall in mean pulmonary arterial pressure from 28.6 to 20.2 mm.Hg and a fall in total pulmonary resistance from 6.05 to 4.3 units ($P<0.02$). Of the 21 patients in whom the pulmonary angiogram was analyzed before and after streptokinase therapy, 12 showed marked improvement, seven moderate improvement and two slight improvement.

There were no deaths during the 24-hour period of treatment with heparin. One patient (not included in the analysis) had a cardiac arrest three hours after commencing streptokinase therapy and had a successful embolectomy. A second patient developed a recurrent pulmonary embolus 12 hours after stopping streptokinase and while being treated with heparin, and underwent successful pulmonary embolectomy. Two patients with acute pulmonary embolism who were treated with streptokinase died from causes unrelated

TABLE II
Comparison of effects of heparin with streptokinase

Group	No.	*Pulmonary arterial pressure (mm.Hg.)* Before	After	*Total pulmonary resistance (units)* Before	After	*Angiographic change* Improved: Marked	Moderate	Slight	None	Deteriorated
A. *Heparin*										
Acute	10	27.1 (N=10)	24.7 (P>0.1)	5.76 (N=5)	4.90 (P>0.2)	0	0	2	7	1
B. *Streptokinase*										
Acute	14	30.0 (N=13)	21.3 (P<0.01)	6.64 (N=5)	4.52 (P<0.05)	8	4	2	0	0
Subacute progressive	3	38.3 (N=3)	34.7 (P>0.2)	—	—	0	0	0	3	0
C. *Total streptokinase*										
Acute	21	28.6 (N=19)	20.2 (P<0.01)	6.05 (N=8)	4.3 (P<0.02)	12	7	2	0	0

to pulmonary embolism seven days and six months after starting streptokinase therapy. All three patients with subacute progressive pulmonary embolism died, one after 40 hours of treatment with streptokinase, another seven days after streptokinase therapy had been stopped, and a third two weeks after pulmonary embolectomy which was performed because the pulmonary angiogram showed no change after 24 hours of treatment with streptokinase. Bleeding occurred more frequently in the streptokinase group than in the heparin group. It occurred at sites of arterial puncture in three patients, into the buttock after an inadvertent intramuscular injection in one patient and from venepuncture sites in five patients. In addition there was an unexplained fall in hematocrit severe enough to require blood transfusion in three patients.

Discussion

The majority of patients who die from major pulmonary embolism do so within a few hours of the embolic episode, before they can be adequately investigated by pulmonary angiography.[14, 15] Therefore studies such as the present one must of necessity be performed on a selected group of patients who have a relatively favourable prognosis. Similarly, any information that is obtained on the rate of early resolution can only be indirectly applied to the more important question of mortality. A direct answer to the question of mortality requires a rigidly controlled trial, and one that either includes a very large number of patients or commences treatment within a very short time of the embolic episode.

Although the patients were not randomly allocated to heparin and streptokinase groups, they were nevertheless well matched. The average time lapse between the last episode of major embolism and commencement of treatment was slightly longer in the streptokinase group than in the heparin group, but since the severity of pulmonary vascular obstruction was similar in the two groups, it is unlikely that this could account for the marked difference in the angiographic change. The results therefore strongly suggest that streptokinase did accelerate lysis of the pulmonary emboli. The hemodynamic changes after streptokinase therapy were less impressive than the angiographic changes but still greater than those which occurred during treatment with heparin. The apparent discrepancy between the hemodynamic and angiographic findings seen after 24 hours of treatment with streptokinase could be due to embolic obstruction in small pulmonary vessels which are not visible in the pulmonary angiogram,[16] to persistent pulmonary arteriolar constriction[17] or to a combination of these factors.

Despite the lack of resolution seen in the pulmonary angiograms, none of the patients in the heparin group died during the 24-hour period of observation. This confirms other evidence that most patients with major pulmonary embolism who survive long enough to be investigated by pulmonary angiography make a clinical recovery provided that recurrent episodes of pulmonary embolism can be prevented.[18, 19]

Rapid removal of obstructing embolic material by pulmonary embolectomy under cardiopulmonary by-pass has proved to be life-saving in selected patients critically ill with major pulmonary embolism,[20] but the mortality of the operation in this group of patients is high.[21] Thrombolytic therapy may bridge an important gap between pulmonary embolectomy and conventional anticoagulant therapy and so reduce mortality in the following groups of patients: (1) those who are critically ill with severe mechanical obstruction if treatment is commenced within a short time of the embolic episode; (2) the small group who survive for 24 to 48 hours after the embolic episode but who die from the consequences of persistent embolic obstruction; (3) those with underlying cardiac or respiratory disease who have a reduced reserve capacity and in whom spontaneous resolution is often delayed.[22] In the latter group rapid resolution has been demonstrated following streptokinase therapy.[7] Resolution in this group not only may improve immediate mortality from the recent episode of pulmonary embolism but may decrease morbidity from the consequences of persistent embolic obstruction.

In order to place thrombolytic therapy in its correct perspective, it should be emphasized that major pulmonary embolism is likely to remain a common cause of death in hospital patients until more attention is directed to prophylaxis in high-risk patients and to early and adequate heparin treatment of patients with venous thrombosis and minor pulmonary embolism. However, until adequate prophylaxis is more widely practised, thrombolytic therapy may reduce morbidity and mortality in a proportion of patients with major pulmonary embolism.

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(Résumé on page 516)

portion of the face (through the vomer) to maintain reduction. This could be expected to hold well even with the loose medial fragment. The K-wire holds the zygomatic bone and the middle portion of the face and also forms a sling inside the maxillary antrum to prevent the orbital floor from collapsing. Before the operation the patient had complete paralysis of his eye musculature, and this situation has not altered to date. This can be due to neural compression in the superior fissure, muscular entrapment or periorbital hematoma.

DR. BELMAN: Was the optic artery damaged?

DR. LABELLE: The optic artery was not visualized. It would certainly be susceptible to injury as it lies in the superior orbital fissure.

DR. HRENO: Is his vision affected?

DR. LABELLE: As far as I can tell, he has no vision in his left eye and cannot see light. With his right eye he says he can detect light but that is all.

DR. HRENO: The right one is then a blind, paralyzed eye.

DR. LABELLE: This may be due to the so-called sympathetic ophthalmia which occurs when the other eye is damaged or blinded. This happens in a very small percentage of cases; the figure of 0.4% is given. Nevertheless it is a point to be considered, and possibly the Ophthalmology Service might advise removal of the left eye and its replacement with a prosthesis.

DR. STRATFORD: This point was raised last year with another patient who had a very similar type of injury. Ophthalmology kept her under close observation and she had no use in her eye at all. The question arose whether this eye should be removed. They were less worried about sympathetic ophthalmia and decided not to operate.

DR. WOOLHOUSE: Apparently, there has been progressively less concern about this problem amongst ophthalmologists lately.

DR. WILLIAMS: Was he able to see out of that eye following the accident or has this been a progressive disability?

DR. BOUCHARD: We do not have a clear record of what occurred at the other hospital, and on admission here the patient was so confused that one couldn't tell whether he could see or not, although the ophthalmology resident who saw him said that he was conscious enough that he could verify that the patient could not see.

DR. WILLIAMS: With the lateral displacement of the brain, the third and fourth nerves certainly could be compressed, causing ophthalmoplegia. Do you think this was the reason the eye was paralyzed?

DR. STRATFORD: No, I think this was more due to orbital injury.

DR. WILLIAMS: But does he have any fracture through the superior fissure?

DR. LABELLE: The fragments which Dr. Stratford described were probably those which form the lateral portion of the orbit. At the time of operation I thought that probably this was what had collapsed, including the superior fissure. You could see narrowing of the optic artery on the angiograms.

DR. WOOLHOUSE: Do you normally see the optic artery in the angiogram?

DR. LABELLE: Yes, you do. There is a constriction at the fissure area in this particular case.

DR. BOUCHARD: I have no doubt that at the moment he was admitted to this hospital he was completely ophthalmoplegic.

DR. WOOLHOUSE: I think Dr. Stratford's description of the operation is very interesting. This is the new intracranial approach to reduction of a fracture of the zygoma.

DR. BELMAN: What about the pelvic fracture?

DR. GREENWOOD: It is the result of a direct contusion. It would not present any problem unless there were continuing hemorrhage. The skin might break down over the contused area. There is no special treatment for the fracture itself.

DR. STRATFORD: What was the opinion about his chest? There was some mention of a lung contusion and this was one reason for delaying a general anesthetic.

DR. BOUCHARD: Apparently six months before the accident he saw a physician in another area who told him he should be seen by a specialist about his chest. We reviewed the chest x-ray while he was in the intensive care unit and there was evidence of some edema. We attributed these findings to his chronic bronchitis, and it was known that he was a heavy smoker. He has had no chest complications postoperatively.

(Continued from page 491)

Résumé

Comparaison entre les effets de la streptokinase et de l'héparine sur la première phase de la résolution de l'embolie pulmonaire majeure

Sur 27 malades souffrant d'embolie pulmonaire majeure, 10 ont été examinés après 24 heures de traitement héparinique et 17 après 24 heures de traitement à la streptokinase. On a alors comparé l'ampleur de la première phase de la résolution dans les deux groupes. Il faut remarquer que les malades du groupe traité à la streptokinase avaient reçu également une dose d'attaque d'héparine dès que le diagnostic clinique fut posé et avaient reçu subséquemment de l'héparine en perfusion continue dès que le temps de thrombine fut revenu à la normale. Chez les 10 malades du groupe de l'héparine, l'embolie pulmonaire a été considérée comme étant de forme aiguë. Sept de ces malades ne présentaient aucun changement angiographique, deux étaient légèrement améliorés et chez le dernier, il y avait aggravation angiographique. Des 17 malades 14 observés avant et après streptokinase ont été classés comme des cas aigus et trois comme des cas subaigus d'embolie pulmonaire majeure évolutive. Huit présentaient une amélioration angiographique majeure, quatre une amélioration modérée et deux une amélioration légère. On notait une baisse modérée et significative de la pression de l'artère pulmonaire et de la résistance des vaisseaux pulmonaires. En outre, la totalité des sept malades chez lesquels ne s'était manifestée aucune amélioration angiographiques au cours du traitement héparinique ont eu une amélioration angiographique modérée ou prononcée, après un traitement supplémentaire de 24 heures à la streptokinase. Les résultats de cette étude comparée permettent de croire que le traitement à la streptokinase a nettement accéléré la thrombolyse chez les malades souffrant d'embolie pulmonaire majeure de forme aiguë.