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Treatment of Acute Myocardial Infarction with Streptokinase Does Not Appear to Modulate Circulating Neutrophil Function

SUSAN A. ADAMS, M.B., CH.B., STEVEN P. FROESE, M.B., CH.B., BELINDA K.W. GREEN, F.C.P.(S.A.),*
PATRICK J. COMMERFORD, F.C.P.(S.A.), F.A.C.C.,* RALPH E. KIRSCH, F.C.P.(S.A.), PH.D., D.SC.(MED), ENID G. SHEPHARD, PH.D.,
SIMON C. ROBSON, F.C.P.(S.A.), PH.D.

MRC/UCT Liver Research Centre, Department of Medicine; *Cardiac Clinic and Department of Medicine, University of Cape Town and Groote Schuur Hospital, Capetown, South Africa

Summary: The administration of thrombolytic therapy is the most common method of achieving patency of the occluded coronary artery in patients with acute myocardial infarction (AMI). However, thrombolytic agents and the byproducts of fibrinolysis have the potential to affect neutrophil activation and thus function, thereby augmenting myocardial damage further. This study assessed the effect of streptokinase administration on the function of circulating neutrophils in patients with AMI. For this neutrophil adherence to human umbilical vein endothelial cells, homotypic neutrophil aggregation, and CD11b and L-selectin expression on the neutrophil membrane prior to and 1 h and 6 h after thrombolytic therapy was monitored. The study population included patients with AMI who received aspirin and streptokinase, and healthy laboratory workers who received aspirin only; all subjects acted as their own controls. Circulating fibrin degradation products and white cells were markedly raised following administration of streptokinase. No significant differences in neutrophil adherence to endothelium, homotypic neutrophil interactions, and CD11b or L-selectin expression were demonstrated between neutrophils, either pre- or post-thrombolytic therapy in the infarct group, or between neutrophils from the infarct group and from the control group. It was concluded that streptokinase produces an abrupt neutrophil leukocytosis together with a marked increase in circulating levels of fibrin degradation products. The assay systems used were unable to show significant sequential changes in circulating neutrophil adhesion

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Address for reprints:

Professor Ralph Kirsch
MRC/UCT Liver Research Centre
Department of Medicine
University of Cape Town
Observatory 7925
Capetown, South Africa

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and L-selectin or CD11b expression in patients with AMI following thrombolytic therapy or when these patients were compared with controls.

Key words: myocardial infarction, streptokinase, neutrophil adhesion, integrin, selectin

Introduction

Acute myocardial infarction (AMI) is the usual consequence of the sudden closure of a major epicardial coronary artery.[1] Timeous dissolution of the thrombus by thrombolytic agents facilitates reperfusion of an occluded vessel and reduces infarct size, preserves ventricular function, and decreases cardiac mortality.[2] The reperfusion process, however, is associated with the migration of neutrophils into the myocardium. In experimental infarction, neutrophils have been demonstrated to play a major role in reperfusion injury. Prevention of neutrophil adherence to endothelium and subsequent transmigration by blocking specific adhesion receptors (integrins, selectins, and the immunoglobulin superfamily) has been shown to limit or reduce infarct size in these models.[3,4] It is tenable, when the clinical situation is considered, that thrombolytic agents or the byproducts of induced fibrinolysis significantly influence leukocyte activity and thus indirectly neutrophil-mediated reperfusion injury in patients with AMI, as has been suggested by other studies.[5–7]

This study was designed to evaluate the status of circulating neutrophils from patients with AMI just prior to and after treatment with streptokinase with respect to adherence to human umbilical vein endothelial cells, expression of integrin and selectin adhesion receptors, and homotypic aggregation. Neutrophils from healthy laboratory workers were used as standards for comparison.

Patients and Methods

Materials

All chemicals and reagents were obtained from Sigma Chemical Company (St. Louis, Mo., USA) unless otherwise stated.

Study Population

Patients admitted to Coronary Care Unit with AMI on electrocardiographic (ECG) criteria and subsequently confirmed by elevated levels of serum creatine kinase were included in the study. Healthy laboratory workers on no medication were chosen as a standard (control) group for comparison. Consent was obtained from all participants, and the study was approved by the ethics committee of the University of Cape Town. In both groups, 150 mg of aspirin was given 1 h before the first blood samples were taken. Blood was taken from patients prior to administration of standard streptokinase therapy (1.5 million units infused over 1 h) and at 1 and 6 h after streptokinase administration. The control group had blood taken at matched time intervals.

The full blood count [performed using the Coulter S-Plus System (Raritan, N. J., USA)], concentration of plasma fibrin degradation products, neutrophil aggregation, neutrophil binding to endothelial cells, and neutrophil membrane expression of CD11b/CD18 integrin and L-selectin were determined at each time point.

Methods

Fibrin(ogen) degradation products: These products were measured by an enzyme-linked immunoassay developed in our laboratory.[8]

Isolation of neutrophils: Neutrophils were separated from heparinized venous blood by dextran sedimentation and Ficoll-Hypaque density centrifugation. This was followed by hypotonic erythrocyte lysis. Cell purity was always > 90% and viability > 98% (trypan blue exclusion).

Culture of endothelial cells: Umbilical cords were obtained from the Groote Schuur Hospital maternity unit in accordance with legislation and standard practice and with the approval of the hospital ethics committee. Confluent human umbilical vein endothelial cell (HUVEC) monolayers were obtained by collagenase treatment of vessels and cultured on gelatin-coated tissue culture dishes in minimal essential medium (MEM) supplemented with 20% fetal calf serum, as described.[9,10]

Adherence assay: ^{51}Cr-labelled neutrophils[10] (0.2×10^6/100 µl in HBSS and 0.5% BSA) were added to confluent HUVEC in microtiter wells that had or had not been treated with bovine thrombin (0.2 u/ml for 5 min at 37°C).[10,11] After a 30 min incubation (37°C), nonadherent cells were washed away with warm assay buffer, adherent cells lysed with 2% NP-40 (BDH, Poole) and radioactivity was quantified. Results were expressed as the mean percent of cells binding from triplicate wells.[10,12]

Neutrophil aggregation: Purified neutrophils were resuspended at 1×10^7 cells/ml in HBSS + 0.5% BSA and placed on ice until ready for use. Five hundred µl aliquots of this solution were used in the whole blood aggregometer (Chronolog Corporation, Havertown, Pa., USA) to measure neutrophil aggregation. This was performed at 37°C with constant stirring, phorbol myristate acetate (PMA) was added (10 ng), and light transmittance was then measured over a 20 min period.

Integrin/selectin expression: Integrin and selectin expression on both stimulated and unstimulated neutrophils was studied. Two IgG2b murine monoclonal antibodies were used: Leu-8(Becton Dickinson, San Jose, Calif., USA), directed against L-selectin on human neutrophils, and OKM1(Ortho-Diagnostic, Raritan, N. J., USA), directed against CD11b on human leukocytes. n-Formyl-methionyl-leucyl-phenylalanine (FMLP) (10^{-8}M) stimulated neutrophils were labelled with these antibodies as described[12] and binding of the antibodies to neutrophils was then investigated using fluorescence-activated cell sorting (FACS) analysis (EPICS-Profile II, Coulter Electronics Inc., Fla., USA).

Results

The study group consisted of 13 patients with AMI treated with streptokinase. The breakdown of age, gender, duration of chest pain, and site of infarction is shown in Table I. Ten healthy laboratory workers with no history of ischemic heart disease were used as controls. Because of technical difficulties, not all parameters were tested on every patient and standard.

The plasma concentrations of circulating fibrin degradation products in patients with AMI are shown in Table II. These values represent the median and range, with the normal range from 0–1.34 μg/ml. The values following administration of streptokinase were markedly raised.

Table IIIa reflects the percentage of nonstimulated and stimulated neutrophils binding the monoclonal antibodies Leu-8 and OKM1 in both an unstimulated state and with in vitro stimulation. There were no significant differences in L-selectin and CD11b expression between individual patients' neutrophils before and after streptokinase, or between patients and controls. (Previous studies in our laboratory on healthy individuals who had not received any medication, including aspirin, showed that virtually all neutrophils expressed L-selectin receptors.) Mean channel numbers, which represent the number of receptors expressed per cell, also showed no significant differences pre- or poststreptokinase or between the two groups (Table IIIb). In all cases when the neutrophils were stimulated in vitro with FMLP a marked decrease in the binding of Leu-8 was observed, reflecting the shedding of selectins from the cell membrane following neutrophil activation. Figure 1 shows a representative histogram of FACS analysis of neutrophils from a patient 6 h after treatment with streptokinase. On stimulation with FMLP, although the number of cells binding OKM1 was not changed, an increase in fluorescence intensity was observed indicating that FMLP stimulation increases the number of OKM1-binding receptors per cell. In contrast, FMLP stimulation decreased both the number of cells binding Leu-8 and the number of receptors for Leu-8 per cell.

Infusion of streptokinase after AMI resulted in a significant rise in circulating white cells 1 h post administration compared with values prior to ($p = 0.0098$) and 6 h after ($p = 0.0135$) streptokinase administration with no significant difference in the levels of circulating white blood cells between the pre- and 6 h poststreptokinase administration values (p values obtained using the analysis of variance statistical test) (Fig. 2).

Neutrophil aggregation (Fig. 3) and adhesion of neutrophils from streptokinase patients and controls to unstimulated (Fig. 4A) and thrombin stimulated (Fig. 4B) HUVECS showed no significant differences over time or between the groups studied.

TABLE I Patient population studied

	Streptokinase patients (n = 13)
Age	60 (40–66)
Sex	10 Male
	3 Female
Duration of pain at presentation	4 h (1–7)
Site of infarct	9 Inferior
	4 Anterolateral

Median values given with range in parentheses.

TABLE II Levels of circulating fibrin degradation products (μg/ml)

	0 h	1 h	6 h
Patients (n = 13)	0.6 (0.01–2.2)	255 (130–577)	300 (146–1762)

Median values given with range in parentheses.

TABLE III Neutrophil integrin and selectin expression

	0 h	1 h	6 h
A. Patients			
OKM1	89.7 (15.3)	89.9 (15.5)	96.7 (5.6)
OKM1 (after FMLP)	98.7 (2.9)	96.7 (5.0)	98.6 (3.3)
Leu-8	93.5 (10.0)	90.0 (8.9)	97.4 (2.8)
Leu-8 (after FMLP)	8.6 (5.0)	9.3 (9.2)	5.0 (3.2)
Control group			
OKM1	91.6 (9.3)	96.5 (4.5)	98.1 (2.0)
OKM1 (after FMLP)	99.4 (0.8)	97.4 (2.9)	95.2 (5.8)
Leu-8	87.9 (6.8)	93.5 (9.8)	96.4 (6.0)
Leu-8 (after FMLP)	9.2 (6.7)	13.9 (16.5)	9.8 (8.4)
B. Streptokinase patients			
OKM1	16 (7)	16.2 (9.5)	14.8 (8.7)
OKM1 (after FMLP)	40.2 (22.2)	31.4 (6.9)	35.2 (17.8)
Leu-8	22.7 (15.4)	15.4 (7.2)	17 (7.8)
Leu-8 (after FMLP)	8.2 (4.7)	5.8 (2.2)	8.4 (7.6)
Control group			
OKM1	13.9 (3.8)	13.3 (3.4)	11.3 (2.0)
OKM1 (after FMLP)	35.7 (5.5)	32.4 (2.9)	23.6 (5.3)
Leu-8	16.6 (9.6)	16.5 (6.9)	17.1 (9.1)
Leu-8 (after FMLP)	10.4 (1.4)	7.4 (2.6)	8.7 (3.0)

Binding of OKM1 (monoclonal antibody to CD11b) and Leu-8 (monoclonal antibody to L-selectin) to the surface of unstimulated and n-formyl-methionyl-leucyl-phenylalanine (FMLP)-stimulated neutrophils from patients and control subjects. Results are expressed as (A) percentage of cells binding antibody with standard deviation in parentheses and (B) mean channel number (representing the number of receptors expressed per cell) binding OKM1 and Leu-8 with standard deviation in parentheses.

Discussion

Activated neutrophils are recognized as mediators of reperfusion injury in experimental infarction.[13] We observed, as have other workers,[14] an increase in the number of circulating neutrophils following streptokinase therapy. Previous investigation has shown a rise in circulating levels of neutrophil elastase and neutrophil elastase-derived fibrinopeptide Bß(30–43) after streptokinase infusion implying the presence of activated cells.[14] Neutrophil-mediated tissue damage arises as a consequence of upregulation of neutrophil adhesive properties in

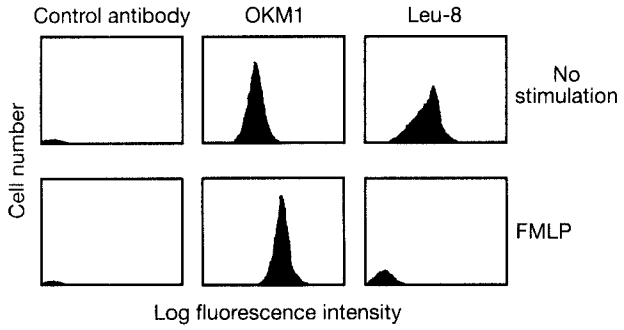

FIG. 1 Expression of CD11b and L-selectin on nonstimulated and FMLP (concentration 10^{-8}M) stimulated neutrophils from a patient with acute myocardial infarction (AMI) 6 h after treatment with streptokinase. Neutrophils were stained with either a negative control, OKM1 (a monoclonal antibody to CD11b), or Leu-8 (a monoclonal antibody to L-selectin), and GAM-FITC second antibody.

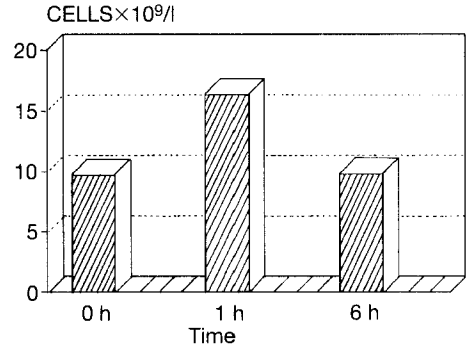

FIG. 2 Concentration of circulating white blood cells in patients with AMI pre- and 1 and 6 h poststreptokinase administration. There is a significant rise in circulating white blood cells at 1 h poststreptokinase administration compared with prestreptokinase ($p = 0.0098$) and 6 h poststreptokinase ($p = 0.0135$). (Analysis of variance.)

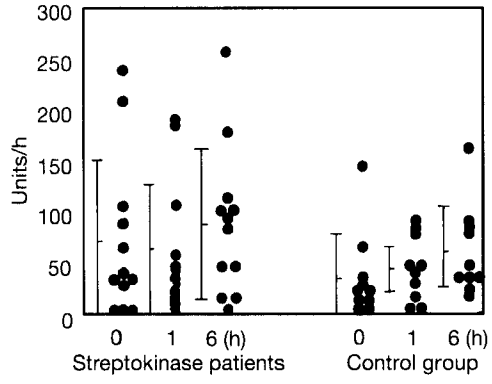

FIG. 3 Neutrophil aggregation measured in patients with AMI pre- and 1 and 6 h poststreptokinase therapy (n = 12) and in control subjects at matched time intervals (n = 10). Individual results for patients and controls are represented by solid circles, with mean and standard deviation of the mean represented by solid lines and bars. There are no significant differences within or between groups.

particular upregulation of the activity of the β_2 integrin, CD11b/CD18, binding to endothelial ICAM-1.[15, 16] This interaction occurs following initial neutrophil L-selectin interaction with endothelial cells.[17, 18] The L-selectins are present on leukocytes and participate in neutrophil recruitment via leukocyte rolling. This rolling is necessary before firm attachment to the endothelium, a process dependent on the β_2 integrins.[18, 19] L-selectins appear to be exquisitely sensitive to proteolytic cleavage and are shed following major cell activation.[18] In our study, the level of L-selectin on circulating patient neutrophils indicated these cells pre- and poststreptokinase therapy to be unstimulated but sensitive to stimulation with the chemotactic peptide FMLP, as observed through the loss of L-selectin following stimulation with a chemotactic peptide. No important differences in integrin/selectin levels on circulating neutrophils have been observed in a rabbit ischemia and reperfusion model.[20] The lack of difference that we find in aggregation and adherence to endothelial cells by

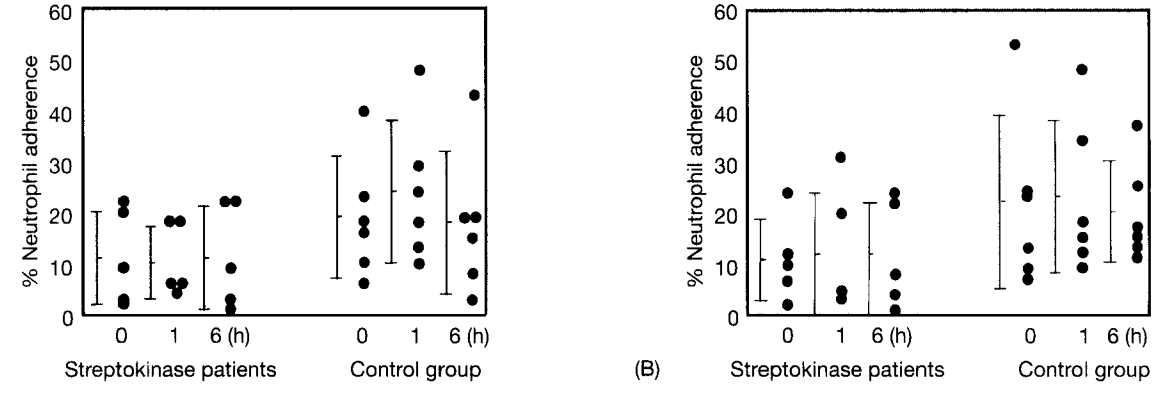

FIG. 4 (A) Neutrophil adherence to endothelium in patients with AMI pre- and 1 and 6 h poststreptokinase therapy (n = 5) and in control subjects at matched time intervals (n = 6). Individual results for patients and controls are represented by solid circles, with mean and standard deviation of the mean represented by solid lines and bars. There are no significant differences within or between the groups studied. (B) Neutrophil adherence to thrombin-activated endothelium in patients with AMI pre- and 1 and 6 h poststreptokinase therapy (n = 5) and in control subjects at matched time intervals (n = 6). Individual results for patients and controls are represented by solid circles, with mean and standard deviation of the mean represented by solid lines and bars. There are no significant differences within or between the groups studied.

neutrophils from patients with AMI and neutrophils from those in the control group further indicates circulating cells from patients with AMI to be unactivated.

Fibrin(ogen) degradation products (FDPs), in particular D and E, generated during thrombolysis, have been shown to inhibit neutrophil oxidative metabolism[6] and the interaction of neutrophils with the endothelium[5] through their ability to bind to the CD11b/CD18 receptor with specific regions in the fibrinogen molecule.[21, 22] Although serum levels of FDPs were raised in the patients studied, these products did not appear to be associated with the neutrophils isolated from these patients, as adherence of these cells to endothelial cells was no different from that of neutrophils from the control group. However the FDPs generated as a result of streptokinase therapy could well be playing a localized role at the site of coronary occlusion.

Conclusion

The overall conclusion from the results obtained from this study is that circulating neutrophils from patients with acute myocardial infarction who are treated with streptokinase are not activated. The assays used in this investigation sampled cells in the peripheral circulation and may not reflect the picture in the coronary vasculature. The active neutrophils may be preferentially trapped in the coronary circulation, whereas the neutrophils in the peripheral vessels appear to have normal functional characteristics. A more realistic reflection of the in vivo situation by using endothelium subject to ischemia and neutrophils from the coronary circulation is necessary to elucidate more clearly the effects of thrombolytic therapy on neutrophils at the site of pathology.

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