BAYLOR
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Department of Pathology
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December 4, 1985

Dr. Philip Migliore
Chairman
The Moran Foundation
Department of Pathology
Baylor College of Medicine

Dear Dr. Migliore,

Enclosed, please find our Progress Report on our study related to Complement Activation Associated with Acute Myocardial Infarction. (2-85-0016)

Sincerely,

William Bennett M.D.

William Bennett, M.D.
Fellow in Cardiology

WB:jrb

Enclosure (1)

Revised Corrected Copy

PROGRESS REPORT

We have studied seven patients according to our protocol. These patients were enrolled in the Thrombolysis Myocardial Infarction study (TIMI). No significant changes in sequential white cell count, platelet count, total C_3 or C_4 levels were observed. There was no evidence of degranulation of neutrophils in these seven patients. However, we did note marked changes in the degree of complement anaphylatoxin generated in certain patients. Three patients in this study had patent coronary arteries at the time of initial cardiac catherization. These patients were not given tissue plasminogen activator. Their average C_{3a} values were 208 (range 104-560). (Normal levels of C_{3a} range from 44-116 ng/ml.) C_4a levels in these patients had a mean of 278 (range 140-540) with a normal expected level of 36-680. C_{5a} averaged 10.3 in this group of patients with a range of $< 4 - 14.8$. Normal levels of C_{5a} are < 10.

In marked distinction to minimally elevated values in the above group of patients, the levels of anaphylatoxins in three patients after receiving tissue plasminogen activator were markedly elevated. The earliest determination of anaphylatoxins were made as soon as 5 minutes after administration of tissue plasminogen activator and the final measurements were obtained approximately 2 hours after initiation of tissue plasminogen activator infusion. The C_{3a} mean value in this group of patients was 2,398 (range 500-5,000). C_4a was elevated to a mean of 3,281 (range 60-6,200). C_{5a} levels averaged 68.7 (range 14.8-212).

One patient initially had 100% obstruction of the left anterior descending coronary artery. His initial complement levels were as follows: C_{3a} 208, C_4a 152, C_{5a} 11.2. This patient received intravenous nitroglycerin with resultant reperfusion of the vessel. (This patient apparently had severe coronary artery spasm.) He did not receive tissue plasminogen activator. Within 1 minute after reperfusion the C_4a level increased to 4,200 with a C_{3a} level of < 40 and a

C_5a level of 92. Seventeen minutes later the C_3a level remain at < 40 and the C_4a level had decreased to 1,600 with a C_5a value of 40.

The above data while not conclusive due to the very small number of patients studied, suggest:

1. The infusion of tissue plasminogen activator causes a marked rise in activated products of complement. This is not an unexpected finding since Ratanoff in the 1960's and others have described activation of the complement system via generation of plasmin. The possible deleterious effects of complement activation associated with tissue plasminogen activator therapy is unknown.
2. Immediately after reperfusion of ischemic myocardium there may be elevation of the complement anaphylatoxins due to reperfusion *per se*.

We believe these initial findings in this small pilot group of patients warrant the study of additional patients. We will conduct *in vitro* studies on plasma and serum to determine the degree to which tissue plasminogen activator activates the complement via plasmin generation. Complement activation associated with reperfusion therapy of ischemic myocardium may also result in some harmful effects. The therapeutic implications of these findings is that if it were possible to neutralize the complement system, reperfusion therapy and the use of tissue plasminogen activator might result in improved clinical results.

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RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR INDUCES COMPLEMENT ACTIVATION.

WR Bennett*, R Bolli, A Raizner**, C Pratt, P Migliore*, Young, D Yawn*, R Roberts**, Baylor College of Medicine, Houston, TX.

Tissue plasminogen activator (rt-PA) is undergoing intense investigation in patients with acute myocardial infarction (AMI) subsequent to initial trials showing it to be an effective thrombolytic agent. Since rt-PA converts plasminogen to plasmin, an activator of complement (C_1), we tested the hypothesis that rt-PA induces complement activation. Seven patients with AMI underwent coronary angiography within 9 h of onset of symptoms; 3 received rt-PA (80-100 mg i.v.) and 4 did not. Blood samples collected in EDTA, on the average 15 min before and 45 min after initiating rt-PA were immediately put on ice, as were samples during comparable intervals in controls (Group I). Serum complement levels were assessed by radioimmunoassay for components C_3a, C_4a and C_5a. In patients receiving rt-PA all samples were obtained before reperfusion was detected by angiography.

($\bar{X}$ ± SEM) (¶P < .05 vs Group I)	C_3a	C_4a	C_5a
Normal Range (ng/ml)	144-166	136-680	14-14.8
Group I (n=4) (no rt-PA)	263±61	427±106	11.2±0.6
Group II (n=3) Before rt-PA	295±85	409±46	11.8±2.7
After rt-PA	597±125¶	2088±392¶	42.3±21.6

In the absence of rt-PA, C_3a was slightly increased but C_4a and C_5a were normal. Thus, rt-PA causes a rapid, striking increase in components of the complement system. Serum complement levels may be a useful means of detecting activity of rt-PA and the level of activity may reflect the extent of thrombolysis.

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