Serum immunoglobulin E response to myocardial infarction

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ABSTRACT Mast cells have been implicated in the pathogenesis of coronary heart disease. They can be activated by immunoglobulin (Ig) E-mediated mechanisms to release powerful mediators affecting local blood flow. We have determined systematically serum IgE concentrations in 100 patients with acute myocardial infarction. There was a consistent pattern of change in serum IgE, characterized by a significant increase on the third and fifth day, peak values on the seventh day, and a gradual decline to initial levels by the end of the third week after infarction. The increase in serum IgE shortly after myocardial infarction was similar to the increase in blood eosinophil count, but was in contrast to serum IgG levels. After infarction, patients with high initial IgE levels (>200 IU/ml) had a greater increase in IgE and less frequent severe complications than those whose initial IgE levels were below 200 IU/ml. In 16 subjects with acute coronary insufficiency without infarction serum IgE levels remained unchanged. It is suggested that in myocardial infarction circulating IgE sensitizes both mast cells of coronary arteries and eosinophils, invading ischemic myocardium; this facilitates release of chemical mediators. Patients with high IgE levels might be protected against complications of infarction because of a favorable ratio of locally released mediators and because of decreased platelet function.


MAST CELLS have been implicated in the pathogenesis of coronary heart disease.1,2 Their number in the adventitia of coronary arteries increases with the progression of atherosclerosis.3 Higher mast cell counts are seen in coronary arteries containing both fresh and organizing thrombi, and lower counts are observed in association with fully organized thrombi.3

Several stimuli can activate mast cells to release a wide variety of vasoactive compounds.4,5 The best-known mechanisms of activation involve immunoglobulins of the E class (IgE). They bind to specific receptors on the mast cell surface, thus priming the cells to release their mediators in response to challenge with a specific antigen.6 In vitro, an anti-IgE challenge of human heart tissue induces release of histamine and prostaglandin D2 (PGD2).7 We reasoned that if mast cells contributed to pathology of myocardial infarction, then the signals turning them on should be detectable in the blood. We therefore measured systematical-

ly serum IgE in patients hospitalized with recent myocardial infarction.

Patients and methods

We studied 116 consecutive patients with coronary heart disease who were admitted to the Intensive Care Unit because of acute coronary accidents. They were divided into two groups. The first consisted of 100 patients (79 men, 21 women, average age 56 years) with recent acute myocardial infarction. The second was formed by 16 patients (10 men and six women, average age 59 years) with acute coronary insufficiency without any evidence of recent myocardial infarction.

The diagnosis of acute myocardial infarction was based on a typical history of chest pain, changes in the standard 12-lead electrocardiogram, and serial elevation of serum enzymes. Seventeen patients had had at least one prior myocardial infarction. The patients were further divided into two subgroups, depending on presence or absence of very severe complications, i.e., cardiac arrest or cardiogenic shock. These complications were absent in 82 patients and present in the remaining 18. Of the latter, eight died, while 10 were successfully resuscitated.

Each patient was interviewed by one of us concerning any personal history of hay fever; allergic rhinitis or eczema; allergy to grasses, house dust, horses, cats, or dogs; or any history of hay fever, asthma, or eczema in parents, children, or siblings. The questionnaire also asked whether there had ever been any recurrent wheezing episodes or sneezing associated with a blocked nose and runny eyes that cleared up and did not develop into colds.

Serum IgE levels were determined in duplicate by use of a sandwich enzyme immunoassay (IgE FAST, Allergenetics, CA) on days 1, 3, 5, 7, 14, and 21. Since total IgE values follow
a log-normal distribution, \(^8\) all subsequent analyses were performed on a log-transformed scale (log IgE), and geometric mean values were used in the table. Serum IgG levels were assessed with use of Partigen (Behringwerke, West Germany) immunodiffusion plates in 10 patients. In the last 67 consecutive patients with myocardial infarction total eosinophil count was determined on the same days as IgE.

Stool examination for parasites was performed in 39 patients with infarction, including eight of 16 with initial IgE levels greater than 200 IU.

The analyses were carried out by use of Statgraphics software (Statistical Graphics Corporation, USA, 1986) on an IBM personal computer.

The Wilcoxon sign test was used in analysis of IgE course, and the paired t test was used in analysis of the remaining variables. The level of significance was set at 5%.

Results

After logarithmic conversion IgE levels showed a log-normal distribution (figure 1). Mean serum IgE increased gradually after infarction, and was elevated significantly by the third day. It reached a peak by day 7, and was declining on day 14. By the end of the third week, mean IgE came close to the initial level, although some subjects continued to have increased levels. In three of eight patients who had determinations performed 50 days after the onset of infarction, IgE values were distinctly higher than on the first day after infarction. This behavior of IgE was in striking contrast to that of serum IgG, which showed a tendency to decrease in the first week, with a mild rise by the end of the third week. These trends, however, did not reach significance (p > .05, paired t test).

In patients with high initial IgE, severe complications of the infarction were less frequent (figure 2).

There were 16 subjects whose IgE on day 1 was 200 IU/ml or more. Only one of them had a severe complication (shock after complete atroventricular heart block in the course of anterior wall infarction), and he survived. On the other hand, severe complications occurred in 17 of 84 patients who had initial IgE less than 200 IU. Eight of them died. The IgE pattern in the two groups was similar. However, IgE increased, on average, by 60% in subjects with initial levels exceeding 200 IU/ml, as compared with a 20% increase in those who had initial levels below 200 IU/ml. Furthermore, in the former group the increase persisted longer (figure 3), i.e., until the end of the second week after infarction.

In 16 of 17 patients who had had at least one prior infarction, serum IgE on the first day of the present infarction was within the range of 39 to 186 IU/ml, and in one patient it was 899 IU/ml. The time course of IgE was similar to that in the patients who never had infarction before.

FIGURE 1. Distribution of natural log IgE on the first day of infarction in 100 patients. The curve is log-normal (mean = 4.35, SD = 1.08). Significance level determined by Kolmogorov-Smirnov one-sample test for goodness of fit = .999. The significance level for normal (Gaussian) distribution determined by the same test was 0.223.

FIGURE 2. Serum IgE levels (IU/ml) on the first day of myocardial infarction in 100 patients. ○ = free of severe complications defined as shock or/and cardiac arrest; ● = patient with severe complications who survived; ●+ = patient with severe complications terminating in death.
On the first day after infarction, half of the patients were eosinopenic (<20 cells/mm³), and only three had moderate eosinophilia (>300 cells/mm³). Blood eosinophil count increased quickly thereafter; it reached a plateau between days 5 and 7 and remained at this level, showing only minor fluctuations. In 15 of 67 patients studied, peak values moderately exceeded the upper limit of the range in our control laboratory (>300 cells/mm³). When reinfarction occurred in the third week, a second peak of eosinophils could be observed.

Statistical analysis revealed no significant correlation (p > .05) between individual serum IgE levels and eosinophil count for any period of blood sampling.

None of our patients had a recent history of atopic diseases and on physical examination none had symptoms suggesting such diseases. Three patients with myocardial infarction and one with acute coronary insufficiency gave a past history compatible with overt clinical manifestation of atopy. Seven patients with infarction had a positive family history of atopy. Stool examinations for parasites were negatives in all 39 patients.

**Discussion**

The present study demonstrates that acute myocardial infarction is associated with a consistent pattern of change in serum levels of IgE. There is an early increase, followed by sustained elevation and a drop to initial levels by the end of the third week. In some patients, however, IgE elevation persists, which might explain why in a recent population-based study higher IgE values were noted in 23 men (but not in 13 women) who survived myocardial infarction as compared with levels in subjects with no disease.9 The IgE pattern shows a striking difference from that of other major serum immunoglobulins. After myocardial infarction, IgA and IgM concentrations do not change while IgG levels fall over a period of 5 to 7 days and subsequently by the third week rise.10 Similar IgG trends were recorded in our patients, although they did not reach statistical significance, as has been noted by other authors.11

IgE concentrations on the first day after infarction were spread over a wide range of values in our patients. A marked skew was also apparent. Such IgE distribution reflects that observed in general populations.12 Sixteen percent of our patients had high (>200 IU/ml) IgE levels on admission. A comparable percentage has been reported in epidemiologic studies of general populations,12,13 including a study in Poland.14 High IgE levels are commonly related to atopy, parasitic infestations, and the acute phase of certain viral infections.13,15,16 These causes were unlikely to be present in our patients. The frequency of atopy appeared to be rather low, since only three of 100 patients had a past history of overt clinical symptoms compatible with atopy. IgE overproduction per se does not lead to the clinical manifestation of atopy unless other factors, such as upper respiratory tract viral infection, are present.13 However, the low frequency of atopy, as judged by the questionnaire results, could have resulted from the relative insensitivity of this method, which according to some authors17 identiﬁes at best 30% of atopic subjects. Furthermore, epidemiologic surveys conclude that atopic diseases affect 15% to 25% of the general population.12,13,18,19 However, our patients were of the age when frequency of these diseases decreases in the population. To assess frequency of atopy in patients with myocardial infarction, the same questionnaire should be applied to patients hospitalized for other reasons, and the study should be supplemented...
TABLE 1
Behavior of serum IgE, IgG, and eosinophil count in patients with acute myocardial infarction (MI) or acute coronary insufficiency (ACI)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnosis</th>
<th>Subjects</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>MI</td>
<td>All patients</td>
<td>76 ± 8</td>
<td>92 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84 ± 10</td>
<td>63 ± 11</td>
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<td></td>
<td></td>
<td>(n=100)</td>
<td>(n=93)</td>
<td>(n=82)</td>
<td>(n=89)</td>
<td>(n=88)</td>
<td>(n=53)</td>
<td>(n=53)</td>
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<tr>
<td>IgE</td>
<td>MI</td>
<td>Initial IgE ≥ 200 IU/ml</td>
<td>440 ± 44</td>
<td>545 ± 106&lt;sup&gt;a&lt;/sup&gt;</td>
<td>676 ± 108&lt;sup&gt;a&lt;/sup&gt;</td>
<td>687 ± 110&lt;sup&gt;a&lt;/sup&gt;</td>
<td>559 ± 100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>572 ± 132</td>
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<td></td>
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<td>(n=16)</td>
<td>(n=16)</td>
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<td>(n=16)</td>
<td>(n=16)</td>
<td>(n=9)</td>
<td>(n=9)</td>
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<tr>
<td>IgE</td>
<td>MI</td>
<td>Initial IgE &lt; 200 IU/ml</td>
<td>55 ± 4</td>
<td>62 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66 ± 6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>65 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55 ± 5</td>
<td>48 ± 6</td>
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<td>(n=73)</td>
<td>(n=72)</td>
<td>(n=44)</td>
<td>(n=44)</td>
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<tr>
<td>IgG</td>
<td>MI</td>
<td>All patients</td>
<td>2.19 ± 0.15</td>
<td>2.12 ± 0.16</td>
<td>2.09 ± 0.15</td>
<td>2.06 ± 0.14</td>
<td>2.19 ± 0.16</td>
<td>2.46 ± 0.26</td>
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<td>(n=10)</td>
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<td>(n=5)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>MI</td>
<td>All patients</td>
<td>49 ± 11</td>
<td>100 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>170 ± 19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>176 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>189 ± 17&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>(n=57)</td>
<td>(n=58)</td>
<td>(n=33)</td>
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<tr>
<td>IgE</td>
<td>ACI</td>
<td>All patients</td>
<td>52 ± 16</td>
<td>47 ± 14</td>
<td>56 ± 17</td>
<td>50 ± 15</td>
<td>52 ± 16</td>
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<td>(n=13)</td>
<td>(n=16)</td>
<td>(n=14)</td>
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</table>

IgE presented in IU/ml as geometric mean ± error expressed as the product of geometric mean and SE of log IgE. IgG in g/dl (arithmetic mean ± SE), and eosinophil count in thousands per mm<sup>3</sup> (arithmetic mean ± SE).

<sup>a</sup>p < .05; analysis of IgE by Wilcoxon sign test, and of IgG and eosinophils by paired t test.

by assessment of skin tests and tests with specific IgE directed against common aeroallergens.

The increase in serum IgE was similar to that in blood eosinophil count. This is interesting, since eosinophils are equipped with specific IgE receptors, and low eosinophil counts are paralleled by depressed blood basophil counts on the first day of myocardial infarction. Some authors have suggested that eosinophils and their products might adversely affect the course of myocardial infarction. Eosinophil cationic protein, known for its cytotoxic properties, has been observed in increased concentrations in serum of patients with acute myocardial infarction. At autopsy, the number of eosinophils in the area of myocardial necrosis in the presence of cardiac rupture was reported to be greater than that in the presence of acute transmural rupture. In our subjects, eosinophilia did not seem to carry additional risk. In fact, all 15 of our patients whose eosinophil count exceeded 300 cells/mm<sup>3</sup> by the end of the first week had an uncomplicated course.

The early rise in serum IgE after myocardial infarction could be a part of the increased humoral immune response against the proteins released from the necrotic heart tissue. It is tempting to speculate that in patients with myocardial infarction circulating IgE sensitizes mast cells of coronary arteries and facilitates the release of chemical mediators. Eosinophils bearing IgE receptors on their surface and present at the infarction zone constitute another hypothetical source of mediators. Indeed, increased blood histamine levels were detected in some patients with acute myocardial infarction. Histamine constricts or dilates human coronary arteries depending on the size of the vessel and its structural changes. Mast cells also produce PGD<sub>2</sub> and sulfidopeptide leukotrienes, which are powerful vasoconstrictors of human arteries. On the other hand, they release heparin, which exerts powerful anticoagulant effects through activation of antithrombin III, and PGD<sub>2</sub>, which inhibits platelet aggregation. This complex interplay of the mediators at the target site might affect cardiac function and the course of infarction.

Our observations seem to suggest that in patients with very high initial levels of serum IgE (those exceeding 200 IU/ml), complications are rare and the course of infarction is benign. Perhaps the net effect of the mediators released from mast cells at the vicinity of necrotic myocardium is favorable for local blood flow conditions. Depressed platelet function might be another beneficial factor. Indeed, subjects with high IgE are characterized by a prolonged bleeding time and impaired platelet aggregability. This mild hemostatic imbalance, similar to the one caused by aspirin ingestion, might explain why death from myocardial infarction in patients with atopic bronchial asthma appears to be rare. We would like to point out, however, that in patients with acute myocardial infarction the high levels of IgE and low complication rate observed by us are only two associated events, and any causative relationship at this time is totally speculative.

Several great 19th century physicians, including Laënnec, Osler, and Trousseau, believed that asthma, distressing as it was, carried a prospect of freedom from other diseases and longevity. While deaths due
to acute asthmatic attacks continue to occur and are a subject of recent concern, at autopsy there is little evidence of accompanying coronary or heart muscle pathology, except for the rare focal necrosis that is distinctly different from myocardial infarction and related to overdosage of sympathomimetics. Could it be that IgE overproduction, a characteristic feature of the most common type of asthma, protects against fatal myocardial infarction? The present study raises such a possibility, although it does not provide a conclusive answer to this question.

References
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