ORIGINAL ARTICLE

Increase in plasma sCD23 levels precedes immunoglobulin E elevation after coronary artery bypass graft surgery

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KEY WORDS

coronary artery bypass graft, immunoglobulin E, sCD23, surgery

ABSTRACT

INTRODUCTION Recent reports have confirmed an increase in plasma immunoglobulin E (IgE), which had been previously observed in clinical situations associated with tissue injury. Studies on the regulation of IgE levels have pointed to the role of low-affinity IgE receptor, i.e., sFcεRII (soluble CD23 [sCD23]).

OBJECTIVES The aim of the study was to assess the changes in the levels of this receptor in response to surgical injury during coronary artery bypass grafting.

PATIENTS AND METHODS The study group consisted of 33 patients (28 men and 5 women, aged 45–75 years). Blood samples were obtained from all patients before surgery and 24, 48, 72, and 120 hours after the surgery. The expression of FcεRII on B cells was measured using flow cytometry and plasma levels of sCD23 were determined by an enzyme-linked immunosorbent assay.

RESULTS We observed a significant increase in the total number of leukocytes and a significant decrease in the total number of lymphocytes with a simultaneous increase in the proportion of B cells ($P < 0.001$). At the same time, the percentage of CD23-positive B cells (CD19/23+) decreased significantly ($P < 0.001$) at 24 hours after surgery and remained low over the period of 72 hours. The plasma levels of sCD23 increased significantly ($P < 0.05$) at 24 hours after surgery and remained elevated until the end of follow-up. All the above changes in the immune status preceded an increase in plasma IgE levels ($P < 0.001$), which reached peak values on the fifth day after surgery (120 h).

CONCLUSIONS Surgical procedures are associated with a transient increase in plasma IgE levels, which is preceded by an increase in the level of sCD23 and a simultaneous decrease in the expression of CD23 on B cells. FcεRII (CD23) and sFcεRII (sCD23) may be involved in the regulation of IgE levels after trauma.

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INTRODUCTION Surgical trauma produces alterations in the hemodynamic, metabolic, and immune responses during the postoperative period. Current evidence indicates that early systemic inflammatory response observed after major surgery is followed by a compensatory anti-inflammatory response, which predisposes a patient to opportunistic infection, multiple organ dysfunction syndrome, and death.[1]

In 1996, we observed that surgical operations were accompanied by a characteristic, transient rise in immunoglobulin E (IgE) levels.[2] We hypothesized that immunoglobulin E (IgE) might be involved in acute-phase response.

In the current study, we sought to establish whether this transient rise in plasma IgE levels following cardiosurgical trauma was accompanied by changes in soluble low-affinity receptor for IgE, sFcεRII (sCD23). The results presented below suggest that rise in plasma IgE is preceded by an increase in sCD23.

PATIENTS AND METHODS In a prospective study, 33 patients (28 men and 5 women, aged 45–75 years) with symptomatic coronary artery

TABLE 1 Clinical characteristics of patients who underwent coronary artery bypass grafting

Patient	Sex	Age	Risk factors for atherosclerosis	Antiangina medications used chronically	Changes in medication in the postoperative period	Concomitant diseases (not connected with the cardiovascular system)
1	F	54	+	–	+	
2	F	67	+	+	–	
3	F	72	+	+	–	asthma
4	F	59	+	+	–	
5	F	63	+	+	–	
6	M	57	–	–	+	
7	M	68	+	+	–	
8	M	64	+	+	–	
9	M	59	+	+	–	
10	M	45	+	–	+	
11	M	47	+	–	+	peptic ulcer
12	M	58	+	+	–	
13	M	61	+	+	–	
14	M	67	+	+	–	
15	M	70	–	–	+	
16	M	75	+	+	–	depression
17	M	73	+	+	–	
18	M	71	+	+	–	
19	M	68	+	+	–	
20	M	59	+	+	–	
21	M	64	+	+	–	
22	M	68	–	–	+	
23	M	63	+	+	–	
24	M	66	+	+	–	gallstones
25	M	73	+	+	–	
26	M	54	–	–	+	
27	M	59	+	+	–	
28	M	58	+	+	–	
29	M	62	+	+	–	
30	M	68	+	+	–	glaucoma
31	M	73	+	+	–	
32	M	72	+	+	–	
33	M	67	–	–	+	

disease, underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass (TABLE 1).

The inclusion criteria were as follows: coronary artery disease confirmed by coronary angiography; scheduled CABG surgery. The exclusion criteria were as follows: renal insufficiency, liver failure, cancer, autoimmune diseases, treatment with glucocorticosteroids, and emergency procedure.

All patients signed written informed consent.

Blood samples were taken before surgery and 24, 48, 72, and 120 hours after surgery.

FcεRII expression on CD19(+) B cells was measured by flow cytometry using fluorescein-labeled monoclonal antibodies. For the acquisition of data, flow cytometer – EPICS Coulter XL (Beckman Coulter, United States) was used. After initial gating of events, whose size and granulocity resemble those of lymphocytes, expression of CD23 antigen on the surface of CD19(+) B cells was analyzed.

Plasma sCD23 levels were measured by an enzyme-linked immunosorbent assay, using human CD23 ELISA kit (BD OptEIA, BD Biosciences, United States).

Statistical analysis was performed using the analysis of variance with a post-hoc Scheffe test. A $P < 0.05$ was considered statistically significant.

RESULTS We observed a significant increase in the total number of leukocytes (FIGURE 1A) and a significant decrease in the total number of lymphocytes (FIGURE 1B). Interestingly these chang-

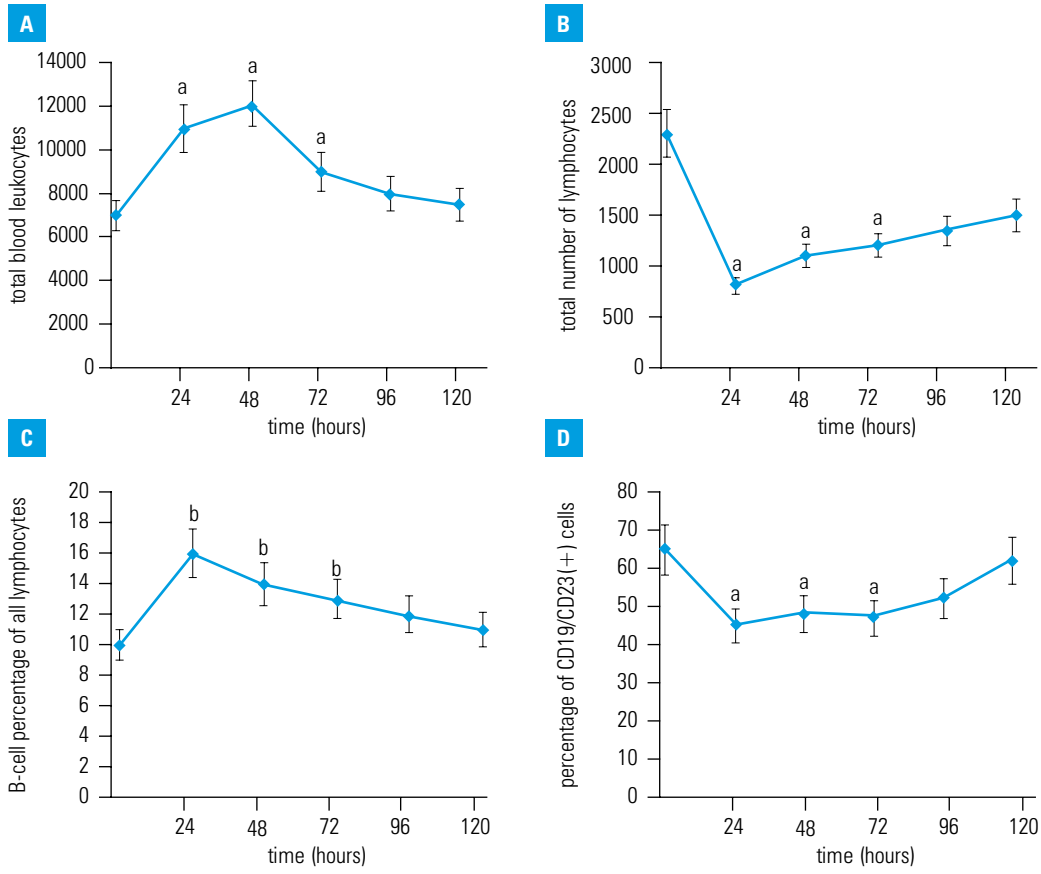

FIGURE 1

A Changes in the total number of peripheral blood leukocytes after CABG, expressed as mean ± SEM

B Changes in the total number of blood lymphocytes after CABG, expressed as mean ± SEM

C Changes of B cells as the percentage of all lymphocytes after CABG, expressed as mean ± SEM

D Changes of CD23-positive B cells (CD19/23+) as the percentage of all lymphocytes after CABG, expressed as mean ± SEM

a $P < 0.001$, compared with the initial level (0 h)

b $P < 0.05$, compared with the initial level (0 h)

Abbreviations: CABG – coronary artery bypass grafting, SEM – standard error of the mean

es were accompanied by a significant increase in the proportion of B cells ($P < 0.001$, FIGURE 1C).

At the same time, the percentage of CD23-positive B cells (CD19/23+) decreased significantly 24 hours after surgery and remained low for 72 hours ($P < 0.001$, FIGURE 1D).

On the contrary, the plasma level of sCD23 increased significantly 24 hours after surgery and remained elevated throughout the whole follow-up ($P < 0.05$, FIGURE 2A).

All these changes in the immune status preceded an increase in plasma IgE levels, which reached the peak value by the fifth day after surgery (120 h) ($P < 0.001$, FIGURE 2B).

DISCUSSION IgE is one of the 5 classes of antibodies known in humans.[3-5] It constitutes a minuscule fraction of total antibody count in human serum, but its action is powerfully amplified by the activation of 2 types of receptors to which it binds. The high-affinity receptor (FcεRI) on mast cells and basophils is responsible for immediate hypersensitivity reactions; when 2 adjacent cell-bound IgE molecules are cross-linked by an antigen, various mediators are released by the activated cells. The low-affinity receptor (FcεRII or CD23), expressed by a broad range of cells, including B cells, eosinophils, monocytes, and platelets, is responsible for the IgE-dependent cytotoxic activities of inflammatory cells and it plays a role in antigen presentation to T cells.[6]

How can we explain the results of our study? The systemic response to all types of tissue injury, including surgical operations, is inflammation. During this process, the number of leukocytes rapidly increases. However, the number of total lymphocytes decreases due to the action of endogenous glucocorticoids (GCs). B cells, however, remain relatively high because the action of GCs and catecholamines leads to a "switch" from T helper type 1 (Th1, cellular) to T helper type 2 (Th2, humoral) response. An increase in interleukin 4 (IL-4) causes activation of immunoglobulin-produced B lymphocytes. The phenomenon of a decreased expression of CD23 on B-cell surface (mCD23) with a simultaneous increase in sCD23 in plasma can be explained by the so called shedding of this receptor under the influence of GCs[7] and IL-4. Moreover, during tissue injury, an increased number of neutrophils release proteases, which also contribute to the shedding.

In 1988, we observed[8] that acute myocardial infarction[9-11] was associated with the immune response characterized by a consistent pattern of change in plasma IgE. We wondered whether this response was specific for myocardial infarction or whether it reflected a more general phenomenon. Several years later, we carried out a large prospective study on patients undergoing various surgical procedures, including coronary artery bypass grafting.[2] It occurred that surgical operations were accompanied by a characteristic, transient rise in plasma IgE levels. At that time, we thought that IgE might be involved in acute-phase response to tissue injury.[12-14] Other publications also confirmed our observations concerning the unusual behavior of IgE.[15-21]

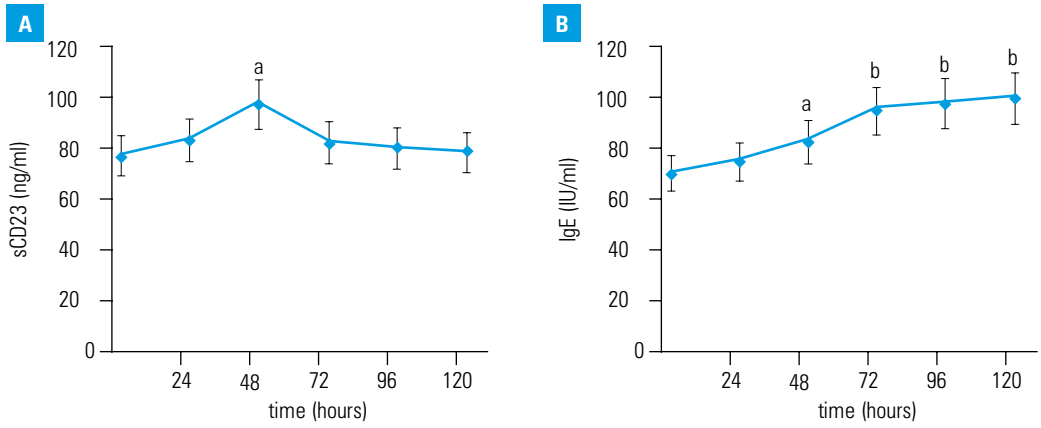

FIGURE 2

A Changes in plasma sCD23 concentration after CABG, expressed as mean ± SEM

B Changes in plasma IgE concentration after CABG, expressed as mean ± SEM

Abbreviations: IgE – immunoglobulin E, sCD23 – soluble CD23, others – see **FIGURE 1**

The phenomenon was finally explained by Decker et al.[22] Surgical stress induces a shift in Th1/Th2 lymphocyte balance (increased Th2 response and decreased Th1 response). Exaggerated Th2 response causes transient overproduction of IgE through the rise of IL-4.

In the present study, we tried to establish whether this rise of IgE was associated with plasma changes of sCD23. Our results showed that the rise in plasma IgE was preceded by an increase in sCD23. Moreover, there was a simultaneous decrease in the expression of CD23 on B cells, shown as a decrease in the mean fluorescence of CD23 on these cells.

Our study had the following limitations: there was a relatively small number of patients and there was no control group.

At least 2 signals have been shown to be necessary for the induction of immunoglobulin isotype switching in B cells. The first signal is given either by soluble IL-4 or IL-13, but alone is insufficient to trigger the secretion of IgE.[23] The second signal is provided by a physical interaction between B cells and activated T cells, basophils, and mast cells.[24,25]

The results from our study showed that B cells are probably the main source of sCD23. Our finding of decreased expression of CD23 on B cells, while the synthesis of IL-4 is increased, can be explained by enhanced shedding of CD23 from B cells, which in turn could be caused by an increased level of proteases derived from polymorphonuclear leukocytes. Among the numerous pairs of surface adhesion molecules, the CD23/CD21 pair seems to play the key role in the generation of IgE. CD23 interacts with CD21 on B cells, preferentially driving IgE production. Increased activity of sCD23, which we observed in our study, could be responsible for subsequent IgE synthesis.

On the other hand, sCD23 has multiple IgE-independent biological activities. It has been suggested that sCD23 is a proinflammatory cytokine that may play an important role in the control of the immune response via the enhancement of interferon-γ (IFN-γ) production.[26] sCD23 enhances the IL-2-induced IFN-γ production about 80-fold and response to IL-12 about 10-fold. Moreover, IL-12 and IFN-γ are typical Th1 cytokines. Thus, sCD23 action in restoring an altered balance between Th1 and Th2 response after trauma could constitute another mechanism, but this issue requires further investigation.

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ARTYKUŁ ORYGINALNY

Zwiększenie stężenia osoczowego sCD23 poprzedza wzrost stężenia immunoglobuliny E po zabiegu pomostowania aortalno-wieńcowego

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SŁOWA KLUCZOWE

chirurgia, immunoglobulina E, pomostowanie aortalno-wieńcowe, sCD23

STRESZCZENIE

WPROWADZENIE Ostatnie doniesienia potwierdzają stwierdzane wcześniej zwiększenie poziomu immunoglobuliny E (IgE) w sytuacjach klinicznych związanych z urazem tkankowym. W trakcie badań nad mechanizmami regulacji syntezy IgE pewną rolę zaczęto przypisywać receptorowi IgE o niskim powinowactwie – sFcεRII (*soluble* CD23 – sCD23).

CELE Celem badania była ocena zmian poziomu tego receptora w warunkach urazu chirurgicznego w czasie pomostowania aortalno-wieńcowego.

PACJENCI I METODY Badaną grupę stanowiło 33 chorych (28 mężczyzn i 5 kobiet, w wieku od 45 do 75 lat). U wszystkich chorych pobierano próbki krwi przed operacją i kolejno 24, 48, 72 i 120 h po operacji. Oznaczano ekspresję receptora FcεRII na limfocytach B za pomocą fluorocytometrii przepływowej oraz mierzono osoczowe stężenie rozpuszczalnej formy receptora CD23 (sCD23) za pomocą testu immunoenzymatycznego.

WYNIKI Stwierdzono znamienne statystycznie zwiększenie liczby leukocytów, ze zmniejszeniem limfocytozy względnej i równoczesnym zwiększeniem proporcji limfocytów B (P <0,001). Jednocześnie nastąpiło zmniejszenie odsetka limfocytów B z ekspresją receptora CD23 na powierzchni (CD19/23+) (P <0,001) 24 h po zabiegu i pozostawało one obniżone do 72. godziny. Osoczowe stężenie sCD23 wzrastało znamiennie (P <0,05) 24 h po zabiegu i pozostawało zwiększone do końca obserwacji. Wszystkie powyższe zmiany immunologiczne poprzedziły wzrost stężenia osoczowego IgE (P <0,001), ze szczytem w 5. dobie po zabiegu (120 h).

WNIOSKI Zabiegi chirurgiczne są związane z przejściowym wzrostem poziomu osoczowego IgE, który z kolei jest poprzedzony zwiększeniem poziomu sCD23 i równoczesnym spadkiem ekspresji CD23 na limfocytach B. FcεRII (CD23) oraz sFcεRII (sCD23) mogą być związane z regulacją poziomu IgE po urazie.

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