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Possible Interaction of Platelets and Adrenaline in the Early Phase of Myocardial Infarction*

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Summary. It is known that in most cases of transmural acute myocardial infarction a platelet clot originates within a coronary artery. In acute myocardial infarction patients increased levels of the plasma catecholamines adrenaline and noradrenaline as well as the platelet release proteins platelet factor 4 and β-thromboglobulin have been reported. In this study, significantly higher values were found of platelet factor 4 ($P < 0.0001$) and β-thromboglobulin ($P < 0.002$) in 17 acute myocardial infarction patients as compared to 17 control patients (on intensive care due to non-cardiac disorders), while the plasma levels of adrenaline and noradrenaline were not different. Positive correlations were obtained between the two catecholamines and the platelet products in the control group and between adrenaline and both platelet factor 4 ($r = 0.715$, $P < 0.01$) and β-thromboglobulin ($r = 0.547$, $P < 0.05$) in the acute myocardial infarction patients. The data suggest that a stimulation of the platelets by adrenaline may facilitate in vitro activation during sampling in patients with high catecholamine load. On the other hand, a "preactivation" of the platelets by an increase of adrenaline might be of significance for thrombus formation in acute myocardial infarction.

Key words: Acute myocardial infarction – Adrenaline – Platelet factor 4 – β-Thromboglobulin

Introduction

In the pathogenesis of acute myocardial infarction thrombotic occlusion of coronary arteries appears to be a decisive event [1]. The occurrence of sudden cardiac death is particularly associated with thrombi found at autopsy [2] in the coronary circulation. Elevated levels of the plasmatic coagulation factors VII, VIII, and fibrinogen [3] have been identified as risk factors. Of greater impor-

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tance, however, for the development of the coronary thrombosis are the blood platelets [4, 5].

A poor prognosis has been found to be related to an increased platelet release reaction after acute myocardial infarction [6]. Platelet aggregation is enhanced by catecholamines and can be induced by exercise [7] and stress [8]. The blood platelets themselves contain catecholamines [9] and may release them upon activation into the coronary circulation.

The plasma levels [10] and the urinary excretion of catecholamines [11, 12] are increased during acute myocardial infarction. As variations during antiarrhythmic therapy, elevated plasma levels [9], but lower urinary excretion [12], have been reported, while no consistent patterns were seen under heparin [12, 13]. A correlation of the prognosis and the degree of complications, such as arrhythmias has been observed with plasma levels [13–16] and the urinary excretion [17–20] of catecholamines, though not by all investigators [21].

It is an open question whether an interaction of platelets and catecholamines is of significance in the course of acute myocardial infarction. An adrenergic stimulation might be involved not only in coronary spasm but also in platelet activation leading to an obturating clot.

Conversely, a local release of catecholamines from platelets might contribute to coronary vasoconstriction and arrhythmias and lead furthermore to a more pronounced systemic adrenergic reaction [22].

To study the alterations of catecholamines in synopsis with the activation of platelets during acute myocardial infarction, the plasma levels of noradrenaline and adrenaline as well as platelet factor 4 and β-thromboglobulin were determined in 17 acute myocardial infarction patients and 17 control patients.

Patients and Methods

The study included 17 patients experiencing acute myocardial infarction, with onset of pain not more than 12 h before admission. The diagnosis was established according to the usual criteria, clinical picture, ECG changes, and creatine kinase (CK) elevation. The age of the 13 male and four female patients was between 34 and 78 years (mean 66 years). The infarction site was anterior in ten and posterior in seven cases, the peak CK levels (normal below 80 U/l) ranged from 160 U/l to 1185 U/l (mean 512 U/l). The first blood samples for determination of catecholamines and platelet proteins were obtained 1–12 h (mean 7.6 h) after onset of pain. Only after this procedure and the initial examination had been completed, did ten patients receive β-blocking agents, which have been shown to exert a favorable influence on survival after acute myocardial infarction [23]. The β-blocker (metoprolol, twice daily 50 mg) was given, if no contraindications were present: patients with sustained hypotension (three patients) and with bradycardia or arrhythmia necessitating other antiarrhythmic substances (four patients) were not treated with metoprolol. Patients with significantly impaired kidney function had been excluded from the study. From 14 of the 17 acute myocardial infarction patients further venous blood samples were obtained during the first four days twice per day: from 8.00 a.m. on day 1 to 4 p.m. on day 4 or from 4 p.m. on day 1 to 8 a.m. on day 5, depending on the time of admission. Furthermore, blood samples were obtained on the day of admission from a control group of 17 patients who had been admitted consecutively during the study period to the intensive care unit because of non-cardiac diseases. Patients who exhibited signs of acute myocardial infarction, pulmonary embolism, or deep vein thrombosis were not included into the control group. No further measures, such as age- and sex-matching, were carried out

in the control group; there were 11 male and six female patients (age 28–82 years, mean age: 61 years).

The patients all kept strict bed rest in the intensive care unit. The blood was drawn through heparin-perfused vein catheters at least 1 h after they had been inserted. The blood sampling in the further course was performed in each case at least 1 h after the last venipuncture or invasive procedures had been completed.

After discarding the first 5-ml portion blood, the samples were collected into precooled vacutainer tubes containing a solution of EGTA and glutathione for catecholamine determinations, EDTA for platelet factor 4 and EDTA plus theophylline for β-thromboglobulin assay. The tubes were cooled again in an ice-water bath immediately. The samples for catecholamine determination were centrifuged without delay, those for the platelet release proteins after 30 min incubation on ice. The determination of noradrenaline and adrenaline was performed with a radioenzymatic assay [24] using the CAT-A-KIT test combination (Upjohn Diagnostics, Kalamazoo, MI, USA), platelet factor 4 and β-thromboglobulin were measured by radioimmunoassay (platelet factor 4 RIA: Abbott, Chicago, IL, USA; β-thromboglobulin: Amersham Buchler, Amersham, UK).

The arithmetic means and the standard deviations (SD) of the values were calculated for both patient groups, differences were examined for significance by *t*-test. Furthermore, correlations between parameters were evaluated in each patient group.

Results

The platelet count decreased during the first 4 days of acute myocardial infarction from $229{,}000 \pm 62{,}000$ to $189{,}000 \pm 46{,}000/mm^3$, the decrease was just below the limit of significance.

The values found in the first samples of the myocardial infarction patients (obtained after a mean duration of 7.6 h after onset of pain) are compared with the results of the control group in Table 1. The mean plasma concentrations of platelet factor 4 and β-thromboglobulin were significantly higher in the patients with acute myocardial infarction, the catecholamines were not different.

In the 14 acute myocardial infarction patients studied continuously over the first 4 days, the plasma levels of both adrenaline (Fig. 1) and noradrenaline (data not shown) showed marked individual variations with slowly decreasing tendency. A particular time course of the levels or a circadian rhythm of release was not evident. The plasma levels ± SEM of platelet factor 4 decreased slightly from 82.4 ± 13.4 to 70.9 ± 15.1, those of β-thromboglobulin from 171.1 ± 19.1 to 151.2 ± 22.0.

Table 1. Mean plasma concentrations ± SEM, given in ng/ml, of PF4, βTG, A, and NA in the AMI and control patients, respectively

	PF4	βTG	A	NA
Controls ($n = 17$)	19.6 ± 4.0	92.8 ± 12.3	0.50 ± 0.21	1.16 ± 0.23
	$P < 0.0001$	$P < 0.002$	n.s.	n.s.
AMI ($n = 17$)	88.5 ± 11.8	169 ± 18.5	0.31 ± 0.05	1.09 ± 0.17

Abbreviations: SEM, standard error of means; PF4, platelet factor 4; βTG, β-thromboglobulin; A, adrenaline; NA, noradrenaline; AMI, acute myocardial infarction; n.s., not significant

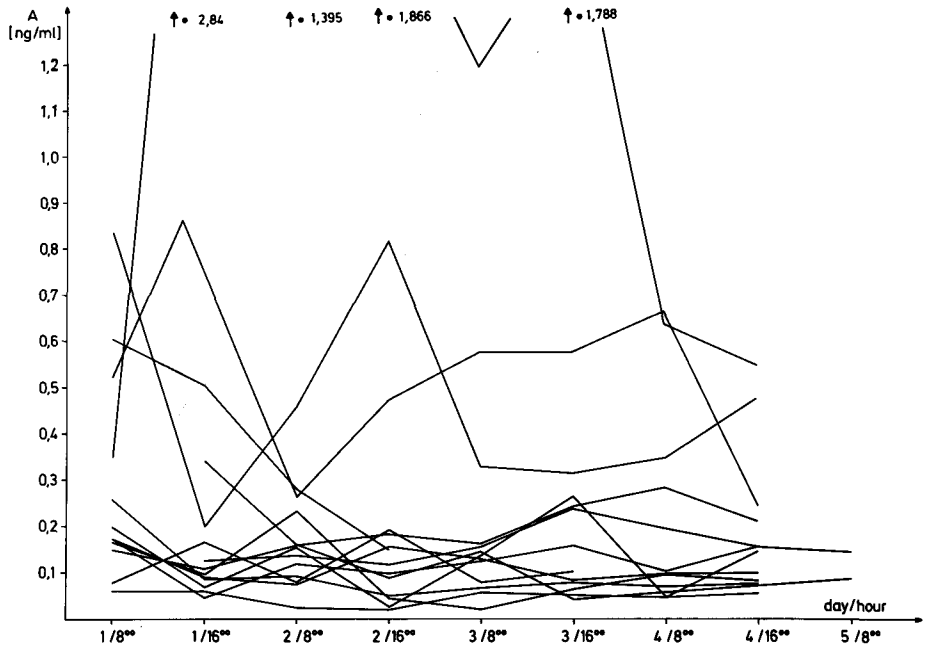

Fig. 1. Course of adrenaline *(A)* plasma concentrations in 14 acute myocardial infarction patients during the first 4 days. The *arrows* and *values above* indicate exceedingly high levels found in one of the patients

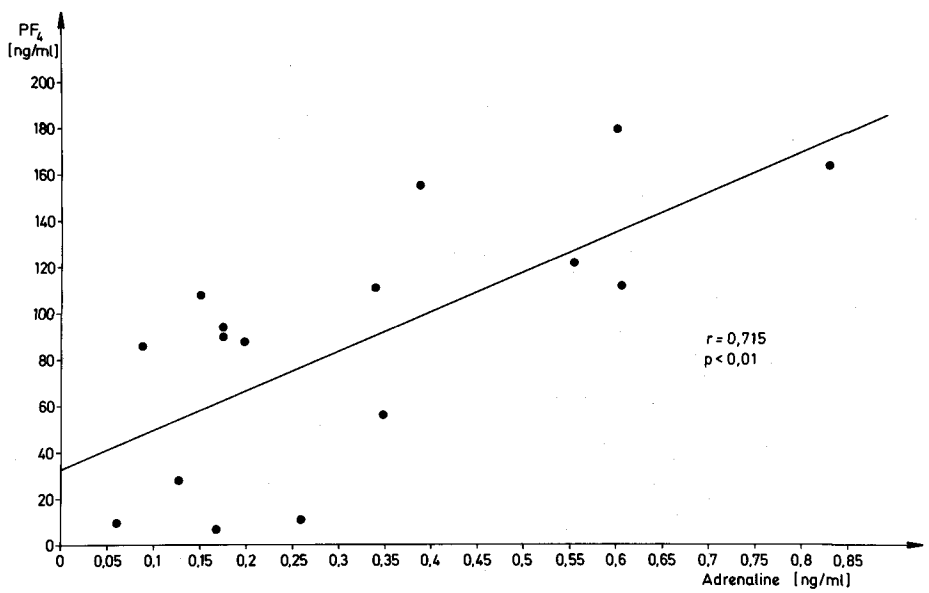

Fig. 2. Correlation between adrenaline and platelet factor 4 (PF4) in the acute myocardial infarction patients, in the first samples drawn 1–12 h (mean 7.6 h) after onset of pain

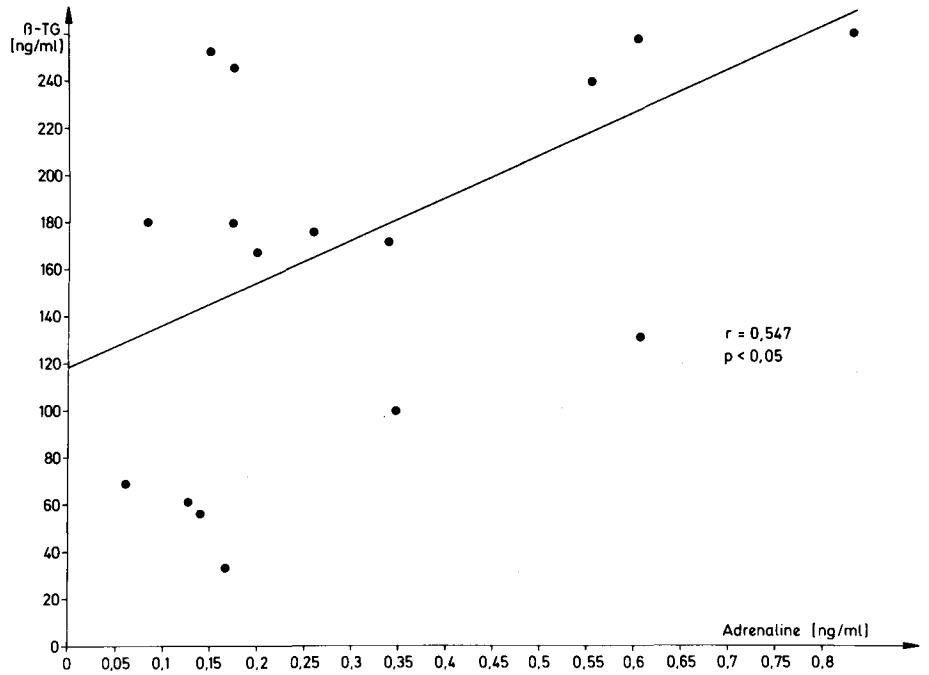

Fig. 3. Correlation between adrenaline and β-thromboglobulin (β-TG) in the acute myocardial infarction patients, in the first samples

Table 2. Correlations between catecholamines and platelet release proteins

	A/PF4	A/βTG	NA/PF4	NA/βTG
Controls ($n = 17$)	$r = 0.754$	$r = 0.779$	$r = 0.580$	$r = 0.664$
	$P < 0.001$	$P < 0.001$	$P < 0.02$	$P < 0.01$
AMI ($n = 17$)	$r = 0.715$	$r = 0.547$	$r = 0.089$	$r = 0.118$
	$P < 0.01$	$P < 0.05$	n.s.	n.s.

For *abbreviations* see Table 1

In the first samples, a positive correlation was found between adrenaline and platelet factor 4 (Fig. 2) and adrenaline and β-thromboglobulin (Fig. 3) in the acute myocardial infarction patients. These samples had been obtained 1 to 12 h (mean 7.6 h) after onset of pain, before any of the patients received metoprolol. At this time no correlations emerged between noradrenaline, and the platelet release proteins. In the further course, the plasma concentrations of adrenaline and both platelet factor 4 and β-thromboglobulin obtained in 14 acute myocardial infarction patients (nine of them on the β-blocker) did not correlate significantly. In the control group significant correlations were present between all parameters, as shown in Table 2.

The peak CK levels were found in the first samples of eight of the 14 patients who were studied continuously over 4 days. Among these 14 patients, the peak CK levels were obtained in the same samples as the highest noradrenaline values in five patients, and in the same samples as the highest adrenaline values in seven patients. It has to be considered, however, that in contrast to the CK levels no clear-cut "peaks" were found of the adrenaline (Fig. 1) and noradrenaline concentrations. In calculating the correlations between CK levels and both catecholamines, no significant results were obtained.

Discussion

It is generally held that the blood platelets play a major role in the pathogenesis of coronary heart disease and acute myocardial infarction [4, 5]. In accordance with other investigators [25], we found a moderate decrease of the platelet count during the first 4 days of acute myocardial infarction. The platelet release products platelet factor 4 and β-thromboglobulin are widely used to monitor in vivo platelet activation. The determination of β-thromboglobulin has been found to be more sensitive for detecting α-granule release [26]. The collection of blood through heparin-bonded catheters, as used in this study, was performed also by other authors [27] who did not find elevated platelet factor 4 and β-thromboglobulin levels.

In contrast to other reports [28, 29], in this study β-thromboglobulin as well as platelet factor 4 levels were found to be significantly higher in acute myocardial infarction patients than in control patients who had been admitted to the intensive care unit due to non-cardiac diseases. The catecholamine plasma concentrations were also above the normal range in acute myocardial infarction patients, but not higher than in the control group. As has been shown by others already [9], there was a continuous elevation of noradrenaline and adrenaline without specific pattern or circadian variations.

The aim of this study was to look for a correlation between the catecholamine release and the platelet activation during acute myocardial infarction. Positive correlations were present in the control group between all parameters. The strongest correlation was found between adrenaline and the platelet release proteins. Significant correlations were also demonstrable in the acute myocardial infarction patients between adrenaline and both platelet factor 4 and β-thromboglobulin. To explain these correlations two hypotheses may be discussed:

(1) Platelets contain catecholamines, adrenaline 76 times and noradrenaline 632 times the plasma concentration, stored in the dense bodies [9]. Upon platelet activation, as monitored by the β-thromboglobulin and platelet factor 4 increase, catecholamines may be released into the blood stream and increase the catecholamine plasma concentration directly or via an adrenergic reflex stimulation [22]. Adrenaline and not noradrenaline correlates with the platelet proteins, though noradrenaline is much more concentrated in platelets, since noradrenaline is rapidly metabolized in the pulmonary vessels [30] in contrast to adrenaline.

(2) An adrenergic stimulus occurs, during which adrenaline may induce platelet release to some degree. The plasma catecholamines are increased in close association to the onset of pain in acute myocardial infarction patients [31].

The second explanation is supported by the results of Straton et al. [32], who found a correlation between adrenaline increase during exercise and both platelet factor 4 and β-thromboglobulin levels. These authors did not observe any relation between these alterations and pain in patients with ischemic heart disease.

In an animal experiment inducing myocardial damage by adrenaline infusion, no relation to platelet activation has been observed [33]. However, there might be some release of platelet proteins induced by adrenaline, but not a sufficiently strong activation of the thrombocytes to produce a clot in arterial vessels, which are not seriously altered by atherosclerosis. This might be the explanation for our finding that the platelet factor 4 and β-thromboglobulin levels were much higher in the acute myocardial infarction patients, though the adrenaline concentration was not different from that of the control group. The correlations between adrenaline and platelet factor 4 and β-thromboglobulin were abolished in the further course of our acute myocardial infarction patients, probably due to the influence of adrenoceptor blockade [34].

In the present study, the peak CK levels coincided in seven of 14 patients with the highest adrenaline concentrations. This may point to a synchronicity of myocardial damage and adrenaline load in part of the patients, which would be compatible with the assumption that adrenaline is involved in the platelet stimulation contributing to coronary thrombus formation. There was, however, no direct correlation of the levels of catecholamines to the infarct size, as assessed by the CK levels.

There is a controversy as regards the elevation of β-thromboglobulin and platelet factor 4 in acute myocardial infarction. It has been affirmed that increased levels of these release products in acute myocardial infarction are merely due to incorrect sampling or invasive procedures [28]. It is remarkable, however, that in other studies [35, 36] the acute myocardial infarction patients exhibited clearly higher levels than comparably treated and examined control patients, as is the case in our study. This discrepancy might be due to an adrenergic "prestimulation" of the platelets of acute myocardial infarction patients which could facilitate thrombosis as well as an enhanced susceptibility for activation during sampling. Measures, such as careful sedation, β-blocking agents, and avoiding stress factors, such as invasive diagnostic procedures [27], may be of significance.

A major obstacle to the investigation of the events within the coronary artery during acute myocardial infarction is the difficulty of monitoring the amount of released substances directly in the vicinity of the thrombosed vessel. A catheterization of the venous vessels draining the coronary circulation in the often clinically dramatic situation of acute myocardial infarction is still problematic. Nevertheless, a more detailed analysis of the link between catecholamines and platelets in the very early phase of acute myocardial infarction seems worthwhile.

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