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CLINICAL STUDIES

# Lack of Elevation of Platelet Factor IV in Plasma From Patients With Myocardial Infarction

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**Platelet factor IV and beta-thromboglobulin are protein constituents of platelet granules. Elevated levels of these proteins in plasma have been used as sensitive indicators of platelet degranulation. Clearance of platelet factor IV is much faster than that of beta-thromboglobulin after release of the proteins in vivo. Although increases of platelet factor IV have been observed in patients with infarction, the implication that they reflect pathogenetic phenomena such as coronary thrombosis has not been assessed explicitly. Accordingly, plasma samples obtained serially from 52 patients with acute myocardial infarction under rigorous conditions verified to minimize platelet degranulation in vitro were evaluated prospectively. Correlative studies were performed to detect left ventricular mural thrombus, and coronary thrombosis was assessed independently in selected patients with indium-111 platelet scintigraphy.**

**Platelet factor IV was normal at the time of admission in patients with infarction, averaging 6.3 ± 3.3 ng/ml, similar to values in 44 other patients with chest pain without subsequent infarction (5.7 ± 2.7 ng/ml) and in 25 normal subjects (4.3 ± 1.6 ng/ml). Platelet factor IV generally did not increase during hospitalization in patients with infarction despite recurrent chest pain, development of left ventricular thrombus or documented recurrent infarction. However, platelet factor IV increased consistently after invasive procedures, accounting for 104 of the total of 110 increases due to platelet activation in vivo as reflected by persistence of elevated levels of beta-thromboglobulin. Thus, platelet factor IV values generally remain normal despite acute myocardial infarction. Rare increases that occur reflect platelet degranulation in vitro due to sampling artifact or perturbations of platelets in vivo due to invasive procedures. They do not provide a definitive criterion of coronary thrombosis.**

Release into plasma of platelet factor IV and beta-thromboglobulin from platelet granules provides a sensitive index of platelet degranulation and activation in vivo (1–3). Increased platelet factor IV and other manifestations of platelet aggregation have been reported (4–12) to occur frequently in association with myocardial infarction. However, the relation of increased platelet factor IV to pathogenetic phenomena such as coronary thrombosis is not clear, nor is its temporal relation to clinical sequelae associated with myocardial infarction. Platelet factor IV values in plasma samples are prone to spurious elevation due to platelet degranulation in vitro, particularly when conventional sampling techniques are employed, or could increase in vivo in response to invasive procedures. Accordingly, the implication that increased platelet factor IV in patients with infarction reflects coronary thrombosis must be questioned.

The present study was designed to determine the extent to which increases in platelet factor IV reflect platelet activation in vitro as a result of inadequately controlled sampling and processing procedures, or degranulation in vivo due to invasive procedures. It was performed also to clarify whether the pattern of serial platelet factor IV values in patients with infarction can be used to implicate coronary thrombosis as a pathogenetic mechanism for initial or recurrent injury.

Because measurements of platelet factor IV in plasma samples become misleading when degranulation occurs in vitro, sampling and processing must be controlled rigorously (13,14). Beta-thromboglobulin released into the circulation has a half-life of 100 minutes compared with one too short to be measured for platelet factor IV (3). Thus, increases

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JACC Vol 4, No 4
October 1984.653–9

in platelet factor IV attributable to platelet degranulation in vivo can be differentiated from those due to degranulation in vitro by concomitantly observed and sustained increases in beta-thromboglobulin, that is, persistence of elevated levels of beta-thromboglobulin, but a normal level of platelet factor IV during the next sampling period. Interpretation of increases in platelet factor IV with reference to assay of beta-thromboglobulin is also useful because heparin in vivo does not cause an increase in plasma beta-thromboglobulin in contrast to platelet factor IV, which increases because of heparin-induced release of platelet factor IV from vascular endothelium (2,3).

## Methods

**Study patients.** Fifty-two patients admitted to the cardiac care unit at Barnes Hospital with documented acute myocardial infarction, 44 patients with chest pain without infarction and 25 normal subjects were studied. All patients gave informed consent for the protocol, which is part of a Specialized Center of Research protocol for blood sampling approved by the Human Experimentation Committee. Criteria for infarction included increased serum creatine kinase (CK)-MB isoenzyme (> 12 IU/liter) and characteristic, serial electrocardiographic changes. In hospitalized patients, blood samples were obtained for assay of platelet factor IV and CK-MB beginning at admission and three times daily until hospital discharge or for 14 days. Beta-thromboglobulin assays were performed in samples with elevated levels of platelet factor IV and in those collected two sampling periods before and two after the index sample.

Because subcutaneous heparin is often given to patients with infarction, a sampling interval was selected to minimize potential effects of heparin on endothelial release of platelet factor IV. Heparin (5,000 units subcutaneously) was found to increase platelet factor IV for as long as 6 hours in three control studies (Fig. 1). Thus, for patients in this study, subcutaneous heparin was given on a 12 hourly schedule and samples for platelet factor IV were obtained at least 6 hours after a dose.

Patients with renal insufficiency (serum creatine kinase > 2.0 mg/dl), anemia (hematocrit < 37%), thrombocytopenia (platelets < 150,000/ml), age older than 80 years, poor venous access or cardiogenic shock were excluded. Results in patients with infarction (Group I, n = 52) were compared with those in patients with chest pain without documented antecedent or subsequent infarction (Group II, n = 44) and with those in a group of normal volunteers (Group III, n = 25) including 12 men and 13 women aged 25 to 48 years without known illness. None had received antiplatelet agents in the past 7 days or smoked a cigarette within 4 hours of blood drawing.

**Assay procedures.** Venous blood was obtained by specially trained technicians using antecubital or forearm venipuncture with a 20 gauge needle vacutainer system. Generally, tourniquets were avoided. Heparin locks were not utilized because they were found to elicit platelet degranulation in vitro (Fig. 2). Blood was never obtained proximal to an intravenous line. The initial 3 ml sample was discarded and the 9.4 ml sample drawn subsequently was collected in a 10 ml thrombotect tube (Abbott Laboratories) containing ethlenediaminetetra-acetic acid (EDTA) 2.5%, 2-chloradenosine 0.0025% and procaine hydrochloride 7% (weight per volume).

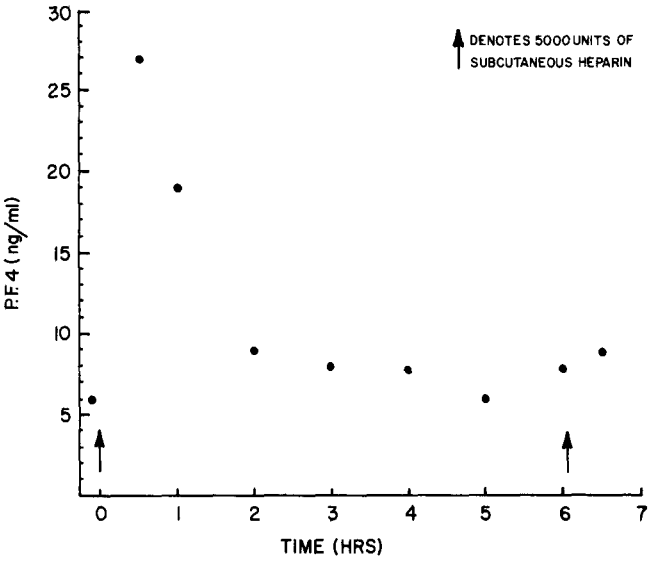
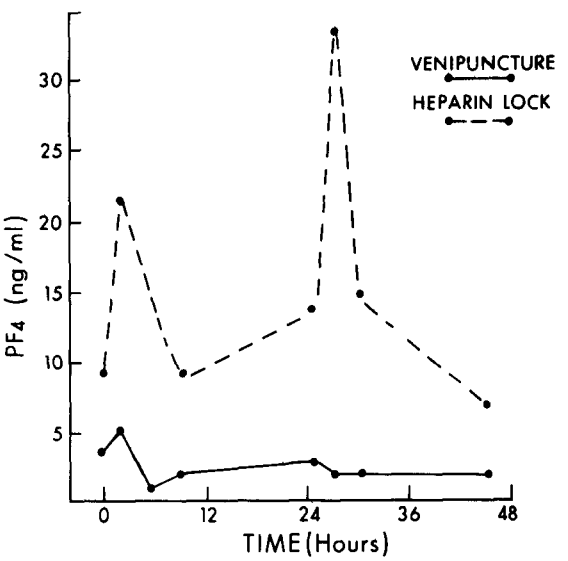



**Figure 1.** Effect of subcutaneous heparin on platelet factor IV (P.F.4) levels. Subcutaneous heparin (5,000 U) was administered at the intervals designated by **arrows**. Increases in platelet factor IV persisted for as long as 6 hours in some patients.

**Figure 2.** Elevations of platelet factor IV (PF4) in samples drawn through a heparin lock. Samples were drawn simultaneously through a heparin lock in one arm and venipuncture in the other.



After prompt mixing and transient storage on ice for 30 minutes, samples were centrifuged at 2,500 *g* in an AIEC HNS 11 centrifuge for 30 minutes. Any technical problems encountered during sampling, manifested by slow blood flow, interrupted flow or hemolysis, were recorded. After centrifugation, 1 ml of platelet-poor plasma was pipetted from a region 0.5 cm below the meniscus, placed in labeled polypropylene plastic tubes (platelet factor IV adheres to glass) and refrigerated at 2 to 4°C before radioimmunoassay for beta-thromboglobulin and platelet factor IV. Although platelet factor IV values (± standard deviation) increased only by 3.1 ± 3.5 ng/ml (n = 10) in samples stored for 4 days prolonged storage led to marked elevations. Accordingly, all samples were assayed within 4 days. Samples identified for assay of beta-thromboglobulin were stored at −70°C and analyzed within 1 month.

One milliliter of platelet-poor plasma was aspirated into a separate glass tube containing 20 μl of mercaptoethanol and used for assay of total CK and CK-MB isoenzyme as described previously (15,16). Values for total CK and CK-MB collected in the thrombotect solution were indistinguishable from those in separate samples drawn in the usual manner, that is, into media with ethyleneglycol-bis (β-amino ethyl ether) N,N′-tetraacetic acid (EGTA) (n = 20 comparisons for each). Platelet factor IV was measured by radioimmunoassay (Abbott Laboratories). Values of 10 ng/ml or greater were considered elevated. Standards with known concentrations of platelet factor IV were assayed with each set of patient samples to provide criteria for quality control. Beta-thromboglobulin was assayed conventionally by radioimmunoassy (Amersham, Inc.). Values of 52 ng/ml or greater were considered elevated.

**Detection of mural thrombus.** Two-dimensional echocardiograms (Advanced Technology Laboratories MK 300 C sector scanner with a 3.0 MHz mechanical transducer) were obtained every 3 days to detect mural thrombus in all patients with anterior transmural infarction (n = 51 echocardiograms, 13 patients). Apical two and four chamber projections including views with time-gain compensation set to provide visualization of structures at shallow depths were evaluated by three independent observers blinded to clinical or laboratory data. The presence of thrombi was determined with the use of Asinger's criteria (17).

**Detection of coronary thrombus with indium-111–labeled platelets.** In four patients with transmural infarction, scintigraphy was performed after administration of indium-111–labeled autologous platelets to detect coronary thrombi. Subtraction of blood pool activity, estimated with a dual isotope technique, was employed as previously described (12).

**Analysis of data.** Group comparisons of platelet factor IV and beta-thromboglobulin values were made with the use of an unpaired Student's *t* test. Serial values in samples from the same patient were compared with paired *t* tests.

**Table 1.** Platelet Factor IV Values in Patients Without Infarction (Group II)

| Day | No. of Patients | Platelet Factor IV (ng/ml) |
|---|---|---|
| 1 | 44 | 5.3 ± 3.2 |
| 2 | 26 | 5.6 ± 2.9 |
| 3 | 6 | 6.8 ± 4.0 |

Day 1 compared with day 2, p = 0.75; day 1 compared with day 3, p = 0.47; day 2 compared with day 3, p = 0.53. Data are reported as mean ± standard deviation.

Elevated values of platelet factor IV associated with normal beta-thromboglobulin in the sample obtained after the observed increase were considered to reflect degranulation in vitro rather than in vivo.

## Results

**Absence of infarction.** Platelet factor IV values (± standard deviation) in the 44 patients with chest pain without infarction (Group II) averaged 5.7 ± 2.7 ng/ml. No values exceeded 10 ng/ml. Values did not change from day to day (Table 1). Values in the 25 normal subjects (Group III) averaged 4.3 ± 1.6 ng/ml. No values exceeded 10 ng/ml. Corresponding beta-thromboglobulin values averaged 34.9 ± 9.4 ng/ml (n = 23). None exceeded 52 ng/ml.

**Myocardial infarction (Group I).** Clinical characteristics of the patients with infarction are summarized in Table 2. Platelet factor IV values in the samples initially obtained averaged 6.4 ± 3.3 ng/ml, similar to corresponding values in samples obtained initially in Groups II and III (5.7 ± 2.7 and 4.3 ± 1.6 ng/ml, respectively). Platelet factor IV values did not vary in relation to the interval between the

**Table 2.** Clinical Characteristics of Patients With Acute Myocardial Infarction (Group I)

| | No. of Patients (%) |
|---|---|
| No. | 52 |
| Mean age (yr) | 60; range 27 to 80 |
| Gender | |
| Male | 30 (58%) |
| Female | 22 (42%) |
| Distribution of infarction | |
| Transmural | 33 (63%) |
| Nontransmural | 19 (37%) |
| Location of infarction | |
| Anterior | 27 (52%) |
| Inferior | 22 (42%) |
| Lateral | 3 (6%) |
| Diabetes | 16 (31%) |
| Prior myocardial infarction | 13 (25%) |
| Prior coronary artery bypass surgery | 4 (8%) |

JACC Vol 4, No 4
October 1984 653–9

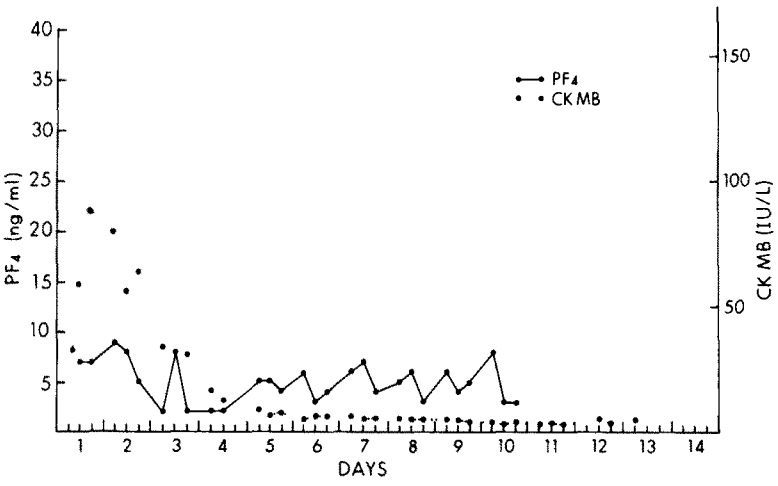



**Figure 3.** Platelet factor IV ($PF_4$) and creatine kinase MB isoenzyme (CK MB) values in a patient with uncomplicated inferior transmural myocardial infarction. Platelet factor IV values did not exceed the normal range (10 ng/ml).

onset of symptoms and the time of acquisition of the initial sample. Samples were obtained within the first 24 hours after the onset of symptoms in 90% of the patients. Values in the first sample for patients seen within 6 hours of the onset of symptoms (n = 14), within the first 12 hours (n = 24) and within the first 24 hours (n = 9) averaged 5.8 ± 3.4, 6.3 ± 2.9 and 6.4 ± 4.1 ng/ml, respectively.

*Platelet factor IV was assayed serially in all patients with infarction (35.9 ± 6.7 samples per patient) (Fig. 3).* No differences in the pattern or magnitude of values were seen in patients with transmural compared with nontransmural infarction, in those with anterior compared with inferior infarction, in those with and without prior infarction or bypass surgery, those with or without diabetes or in those with or without congestive heart failure (Table 3). The correlation between the mean level of platelet factor IV and peak CK-MB was poor (r = 0.05). Platelet factor IV values were not elevated in any sample obtained from the four

**Table 3.** Relation of Platelet Factor IV to Clinical Variables

| Variable | No. | Mean Value of Platelet Factor IV (ng/ml) | p Value |
|---|---|---|---|
| Transmural infarction | 32 | 6.7 ± 3.1 | 0.18 |
| Nontransmural infarction | 20 | 5.7 ± 1.6 | |
| Diabetes | 16 | 5.4 ± 1.7 | 0.10 |
| No diabetes | 36 | 6.8 ± 2.9 | |
| Anterior myocardial infarction | 27 | 6.4 ± 2.7 | 0.90 |
| Inferior myocardial infarction | 22 | 6.5 ± 2.7 | |
| Prior myocardial infarction | 13 | 6.3 ± 2.1 | 0.87 |
| No prior myocardial infarction | 38 | 6.4 ± 2.8 | |
| Prior or concomitant antiplatelet agents | 22 | 6.7 ± 3.7 | 0.37 |
| No prior or concomitant antiplatelet agents | 30 | 6.1 ± 1.6 | |
| Prior bypass surgery | 4 | 6.4 ± 1.3 | 0.99 |
| No prior bypass surgery | 48 | 6.4 ± 2.7 | |
| Patients with anterior transmural myocardial infarction with mural thrombi | 7 | 6.8 ± 3.0 | 0.14 |
| Patients with anterior transmural myocardial infarction without mural thrombi | 6 | 5.1 ± 1.3 | |
| Values in patients during clinical heart failure (no invasive procedures) | 5 | 6.3 ± 1.5 | 0.15 |
| Values in patients without clinical heart failure | 30 | 5.3 ± 1.4 | |

**Table 4.** Increases in Platelet Factor IV

| | No. |
|---|---|
| Increases associated with heparin therapy | 48 |
| In vivo increases* | 110 |
| Associated with invasive procedures | 104 |
| Others (one patient with presumed thrombotic coronary occlusion and mural thrombus) | 6 |
| In vitro increases† | 86 |
| Total | 244 |

*Confirmed by beta-thromboglobulin; †not confirmed by beta-thromboglobulin.

patients studied scintigraphically with indium-111–labeled platelets despite scintigraphic detection of coronary thrombi in each.

*Elevated levels of platelet factor IV (> 10 ng/ml)* were rare, occurring in only 12% of all samples (244 of a total of 2,028 samples) (Table 4). Seventy-five of the observed increases were modest (11 to 24 ng/ml) and 169 more striking (> 25 ng/ml). In 48 samples from three patients given heparin by continuous infusion because of clinical indications (an example of the effects of heparin is shown in Fig. 4), platelet factor IV was elevated but beta-thromboglobulin remained within the normal range. Thus, the elevated levels of platelet factor IV appeared to be due to heparin-induced release of platelet factor IV from endothelium. Of the 196 increases in platelet factor IV in patients who were not treated with heparin, 110 were associated with persistent increases in beta-thromboglobulin. Such increases were considered to be due to platelet degranulation in vivo. They occurred in 5.4% of a total of 2,028 samples obtained. In 86 samples, elevations of both platelet factor IV and beta-thromboglobulin had returned to normal by the next sample. These samples met criteria for degranulation in vitro and appeared randomly distributed throughout the study group. The vast majority (66%) were greater than 25 ng/ml.

*Technical difficulties in sampling* were prospectively identified in 56% (48 instances) of the 86 samples that met criteria for degranulation in vitro by beta-thromboglobulin. Sampling problems were identified in an additional 103 samples without increases in platelet factor IV. In 83%, slow or interrupted blood flow occurred; in 8%, multiple venipunctures were required and in 9% a hemolyzed sample was noted after centrifugation despite a clean venipuncture and smooth uninterrupted flow.

**Invasive procedures (Table 5).** Seventeen patients underwent 19 invasive procedures (insertion of a Swan-Ganz catheter or a transvenous pacemaker electrode). Among the 15 patients with baseline platelet factor IV results available, platelet factor IV values increased in 14 after the procedure by an average of 8.6 ± 8.6 ng/ml. Among the 14 patients in whom baseline beta-thromboglobulin values were available, these values increased in 13 (Fig. 5). Elevated levels of platelet factor IV in association with invasive procedures represented 104 of the total of 110 increases attributable to platelet degranulation in vivo. They generally persisted until removal of the catheter or pacemaker electrode. Subsequently, platelet factor IV promptly returned to baseline while beta-thromboglobulin decreased more slowly in keeping with its longer biologic half-life.

**Recurrent chest pain (Fig. 6).** Recurrent chest pain in the absence of recurrent infarction occurred in 34 of the 52 patients (97 episodes). Platelet factor IV did not increase before or after such episodes.

**Left ventricular thrombus.** Thirteen patients with anterior transmural infarction were evaluated with serial two-dimensional echocardiography. A left ventricular thrombus was documented in seven. In six, neither platelet factor IV values in initial samples (6.8 ± 3.0 ng/ml) nor subsequent values increased before or after formation of the thrombus detectable by echocardiography (Fig. 4). Thus, the pattern and magnitude of levels of platelet factor IV were identical among patients with and without ventricular thrombus. The

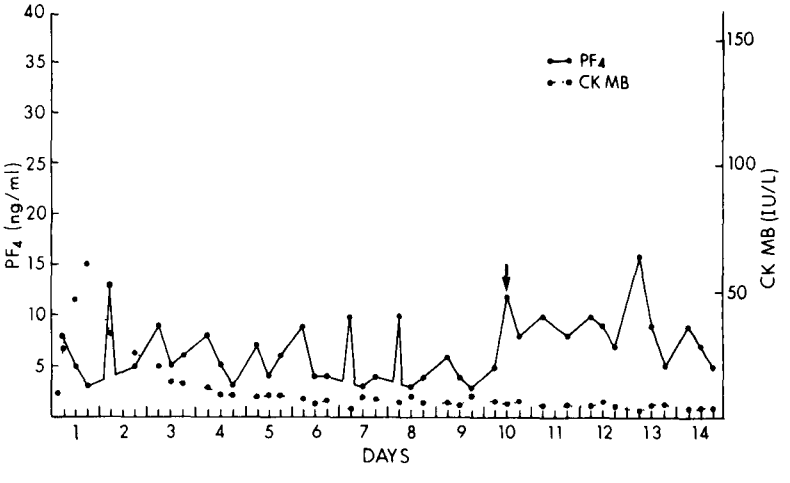



**Figure 4.** Platelet factor IV ($PF_4$) and creatine kinase MB isoenzyme (CK MB) values in a patient with anterior myocardial infarction who developed an apical thrombus. Heparin was given at the time designated by the **arrow**, resulting in increases in platelet factor IV. Beta-thromboglobulin remained normal; it also remained normal in the sample on day 2 after platelet factor IV had increased modestly in a sample compromised by technical difficulties.

JACC Vol 4, No 4
October 1984 653–9

**Table 5.** Platelet Factor IV and Beta-Thromboglobulin Values Associated With Invasive Procedures

| | Platelet Factor IV (ng/ml) | | Beta-Thromboglobulin (ng/ml) | |
|---|---|---|---|---|
| Mean value before procedure | 8.2 ± 4.7 | $p < 0.001$ | 48 ± 26 7 | $p = 0.034$ |
| Mean value during procedure | 16.8 ± 9.9 | | 125 ± 155 | |

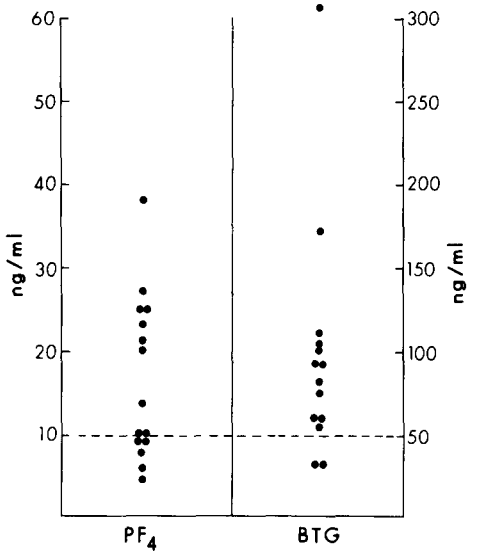
seventh patient with mural thrombus manifested markedly elevated platelet factor IV levels and persistently elevated levels of beta-thromboglobulin. She was a 27 year old woman who had used oral contraceptive agents before sustaining an anterior myocardial infarction. Coronary arteriography 2 weeks after the episode delineated a recanalized left anterior descending coronary artery, but no coronary atherosclerosis.

**Recurrent infarction (Fig. 6).** Eight patients had early recurrent infarction (10 recurrences) reflected by reelevation of CK-MB, three patients with initial transmural and five patients with initial nontransmural infarction. Platelet factor IV did not increase before or after any of these episodes.

## Discussion

Results of this study indicate that platelet factor IV generally does not increase in association with acute myocardial infarction. Elevated levels did not presage complications

**Figure 5.** Platelet factor IV ($PF_4$) and beta-thromboglobulin (BTG) after invasive procedures. In 14 of 15 samples, values increased after the procedure by a mean of 8.5 ± 8.6 ng/ml. The **dashed line** indicates the upper limit of normal.



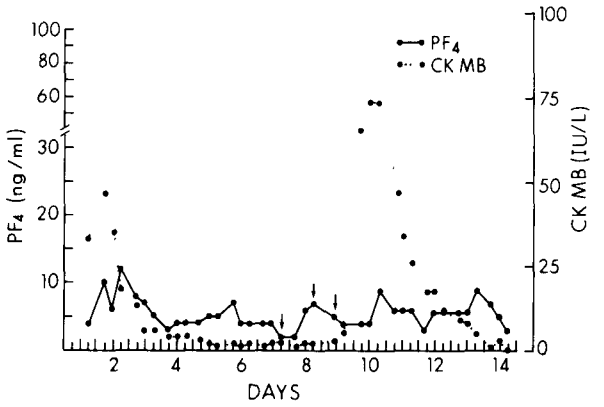




**Figure 6.** Values of platelet factor IV ($PF_4$) in a patient with nontransmural myocardial infarction, chest pain and subsequent early recurrent infarction. Increases in platelet factor IV did not occur before, during or after episodes of chest pain (**arrows**) or in association with recurrent injury on days 9 and 10 (when creatine kinase MB [CK MB] became elevated).

potentially attributable to thrombosis and associated platelet aggregation, such as recurrent chest pain, mural thrombus or recurrent infarction. Those increases attributable to platelet degranulation in vivo were modest and generally occurred after invasive procedures. Because such increases were accompanied by increases in beta-thromboglobulin, it is unlikely that they were due to heparin used in conjunction with the procedures. Although patients who require Swan-Ganz catheterization or pacemaker placement are, as a rule, in less stable condition than others, increases occurred only after the invasive procedures, suggesting they were related to the procedure itself rather than to more severe infarction.

**Comparison with previous data.** Our results are similar to those of Pumphrey and Dawes (18), who evaluated serial levels of beta-thromboglobulin in patients with acute myocardial infarction, and those of other investigators (13, 14), who emphasized the need for meticulous sampling procedures. Platelet factor IV values were not affected by treatment with antiplatelet agents (aspirin, dipyridamole or sulfinpyrazone), an observation consistent with results of recent pharmacologic studies (19). Many reports (4–8) of elevated levels of platelet factor IV in association with infarction have been based on analysis of isolated or infrequently drawn samples. Differences in components used in the anticoagulant/antiaggregant media may have accounted for increases in platelet factor IV in some studies. Such differences could affect samples from patients with acute infarction compared with normal subjects differentially if their platelets were more sensitive to conditions in vitro of suboptimal anticoagulation or antiaggregation. These factors have been extensively reviewed by others (20).

**Present study.** To clarify apparent disparities among results of previous studies and to assess the potential utility of platelet factor IV as a criterion of coronary thrombosis,

we designed the present study according to several considerations including early initiation of sampling, serial sampling, differentiation of platelet degranulation in vitro and in vivo, prospective recording of unavoidable sampling difficulties potentially affecting platelet factor IV values, avoidance of misinterpretation due to heparin-induced release of platelet factor IV from endothelium and avoidance of artifact induced by inadequately rigorous sampling or processing procedures.

After invasive procedures, beta-thromboglobulin remained elevated, whereas platelet factor IV returned promptly to a normal value, supporting the use of persistent increases in beta-thromboglobulin to confirm degranulation in vitro. Many of these increases were detected by careful monitoring of the sampling procedure; however, the sensitivity and specificity of careful monitoring alone would not have identified samples with and without degranulation in vitro. If beta-thromboglobulin had not been measured, 86 increases in platelet factor IV attributed to platelet degranulation in vitro might have been attributed spuriously to platelet degraulation in vivo. Even if our criteria utilizing beta-thromboglobulin erroneously excluded a few true increases in platelet factor IV, no pattern to these additional values could be detected.

**Clinical implications.** Our findings indicate that elevation of platelet factor IV is not a common antecedent or concomitant condition of acute myocardial infarction. The few increases in platelet factor IV that are encountered are most often associated with invasive procedures or platelet degranulation in vitro. Thus, elucidation of coronary thrombosis and the contributions of platelet aggregation to precipitation of myocardial infarction or its complications will probably require assessment of regional platelet deposition (12) or the development of more sensitive systemic indexes of platelet activation in vivo.

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