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Haemostatic variables in patients with unstable angina

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Abstract

To assess the contribution of thrombus formation in the pathogenesis of unstable angina, we employed the recently developed assays of small fragments which reflect the degree of activation of various components of the haemostatic system. Such haemostatic measurements were undertaken in patients with unstable angina ($n = 47$) from the time of their admission to the coronary care unit (CCU) at 8-h intervals in the first 24 h and then daily for a total of 5 days. The results obtained were compared with healthy control values. Patients exhibited lower ATIII, prolongation of the APTT and TT, but not PT or the reptilase time, which is a consequence of heparinization. There was significant elevation of fibrinogen, factor VIII:C, von Willebrand factor:antigen and von Willebrand factor:ristocetin cofactor throughout the study period. There was also evidence of thrombin generation as indicated by the elevated levels of fibrinopeptide A (FPA) and thrombin-antithrombin complexes. The platelet release proteins, β-thromboglobulin (BTG) and platelet factor 4 (PF4), were markedly elevated in the first 2 days and dropped gradually thereafter. The fibrinolytic inhibitor, plasminogen activator inhibitor (PAI), levels were elevated throughout. Proteins C and S, plasminogen and α_2-antiplasmin remained unchanged. It was concluded that in patients with unstable angina, there is significant activation of the clotting system and inhibition of fibrinolysis which confirms the existence of a tendency towards thrombus formation in patients with unstable angina.

Key words: Unstable angina; Haemostasis; Coagulation; Platelets

1. Introduction

Unstable angina is a heterogenous clinical entity provoked by a sudden increase of coronary artery obstruction leading to myocardial ischaemia but not infarction. Recently, several researchers using angiographic, angioscopic, pathological, biochemical and clinical data have demonstrated the importance of a dynamic thrombotic process leading to coronary obstruction, in the pathogenesis of unstable angina [1]. Both functional changes, in the form of increased vascular tone and spasm, as well as anatomical alterations such

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as plaque fissure/rupture, haemorrhage, platelet thrombus, in or around the atherosclerotic plaque seem to play an important role [2,3]. As a result of these revelations, current therapeutic interventions in unstable angina are directed at relieving the coronary spasm and preventing the progress of the potentially fatal thrombotic process [4,5].

Recently, measurements of small coagulation and fibrinolytic fragments, as well as the platelets, which release products in unstable angina, have become the subject of many studies [6–18]. These studies have yielded wide disagreements and inconsistencies: measured levels of the same haemostatic fragment exhibiting increase, no change or decrease being reported by different investigators. The causes of these discrepancies can be due to: (i) patient selection and exclusion criteria; (ii) timing and frequency of the blood samples varied widely — on admission, within hours or days after the onset of symptoms; (iii) type and number of drugs taken by patients; and (iv) technical differences due to special precautions exercised during blood collection, handling of blood samples and the assay techniques employed. Although it may prove difficult to standardise all these conditions, more frequent blood sampling in the first few days of admission will, no doubt, provide a closer picture of the fluctuation of haemostatic parameters and, thereby, the progress of the thrombotic event.

Coronary artery disease, which is considered a disease of Western industrialised countries, is being diagnosed with increasing frequency in Saudi Arabia and many studies are already underway investigating various aspects of this disease. Besides, the existence of racially determined differences in haemostatic variables has already been established in many studies, which attempted to define not only the haemostatic characteristics of populations but also the possible association between ethnic differences in the levels of these variables and the incidence of thromboembolic disease, especially ischaemic heart disease [19–25].

This study was therefore undertaken to monitor a wide range of haemostatic fragments in patients predominantly of Arab origin with unstable angina from the time of their admission to the hospital and then daily for a total of 5 days.

2. Patients and methods

Forty-seven patients with unstable angina were studied. Of these, 34 were males and 13 were females. Their ages ranged from 29 to 75 years (mean ± S.D., 51.8 ± 10.9); weights, 50.8–115.5 kg (mean ± S.D., 72.3 ± 13.8). Forty-one patients were Arabs (18, Saudis; 23, non-Saudis) and the rest ($n = 6$) were Asians (3, Pakistanis; 3, Indians). These patients were included in the study on their admission to the Coronary Care Unit (CCU), King Khalid University Hospital, Riyadh. The diagnosis of unstable angina was based on one of the following anginal symptoms: (i) typical history of crescendo angina; (ii) increased frequency and duration of previously diagnosed stable angina; (iii) new onset angina (all of these symptoms occurring within 4 weeks prior to admission to hospital and with or without transient ST segment changes in the ECG, and normal cardiac enzymes); and (iv) angina at rest.

Every patient with unstable angina received: (i) oral aspirin (325 mg daily), three patients had active peptic ulcer disease and they received persantin instead (75 mg, orally, three times per day); (ii) intravenous nitroglycerin (the dose was titrated against chest pain and blood pressure responses); (iii) intravenous heparin (the dose was adjusted to keep the APTT between 1.5 and 2 × the control), except the three patients who had active peptic ulcer disease. In addition, 40 patients also received Inderal (40 mg, orally, three times per day) and diltiazem (60 mg, orally, three times per day). If the chest pain did not subside within 24 h, patients were sent for urgent coronary angiography. Five patients had coronary angioplasty within 48 h of admission to hospital.

Positive coronary angiogram was established in 36 patients (41%, single vessel disease; 29%, two vessel disease and 30%, three vessel disease) and in the rest ($n = 11$) the diagnosis was based on positive stress thalliam test. Detailed medical history was recorded including the following coronary heart disease risk factors: diabetes mellitus only (DM), 8 patients (17%); hypertension only, 8 patients (17%); DM and hypertension, 12 patients (25.5%); smoking, 14 patients (29.8%).

The study protocol conforms to the ethical

guidelines of the 1975 Declaration of Helsinki, and accordingly, informed consent was obtained from each patient.

2.1. Blood samples

A total of seven blood samples were collected according to the following timing: first day, 3 samples (on admission and two more at 8-h intervals) and then daily from the second to the fifth day. Special tubes were used to fulfil the blood collection requirements for individual assays.

2.2. Controls

Healthy control values used in the analysis of the results were either the local laboratory reference data, which is obtained in healthy subjects, mainly blood donors, or, where reference values do not exist, data were obtained from age- and sex-matched healthy volunteers who were members of the acadamic and technical staff.

2.3. Laboratory tests

Coagulation screening tests. Prothrombin time (PT) and activated partial thromboplastin time (APTT) (Manchester Comparative Reagents, UK), thrombin time (TT) (Parke Davis Topical Thrombin, USA) and reptilase time (RT) (Stago Diagnostics, France) were performed by convential methods and the end-points were recorded in a Coagulometer (Amelung KC 4).

Coagulation factors. Plasma fibrinogen was assessed by the turbidometric method of Ellis and Stransky [26]; Factor VII:C by the one-stage assay according to Hardisty and Macpherson [27]; von Willebrand factor:antigen (vWF:Ag) by the method of Laurell [28]; von Willebrand factor:ristocetin cofactor (vWF: ricofactor) by the method of MacFarlane et al. [29].

Tests of thrombin generation. The tests used were thrombin-antithrombin complex (ATM) and fibrinopeptide A (FPA).

Platelet release proteins. The proteins used were platelet factor 4 (PF4), and β-thromboglobulin (BTG).

Tests of fibrinolysis. The tests used were plasminogen activator inhibitor (PAI), plasminogen and α-2-antiplasmin.

Coagulation inhibitors. The coagultion inhibitors were protein C, protein S and antithrombin III (ATIII).

The reagents for these tests were obtained from Diagnostica Stago (France) and the assays were performed according to the manufacture's instructions. The techniques employed were as follows:

(i) chromogenic: ATIII, protein C, FVIII:C, plasminogen, α_2-antiplasmin, PF4;
(ii) enzyme linked immunoassay (ELISA): PAI, BTG, FPA and ATM; and
(iii) immunological assays: vWF:Ag, protein S.

2.4. Statistical analysis

All the results were expressed as mean ± S.D. The differences between patients and controls were tested for significance using Student's *t*-test for unpaired data, and differences were considered significant when $P < 0.05$.

3. Results

3.1. Coagulation parameters (Table 1)

Since the standard management protocol involves heparinisation, there was the expected prolongation of the APTT and TT and no change in PT and RT. Significant elevation was observed in the plasma levels of fibrinogen, factor VIII:C, vWF:Ag and vWF:ristocetin cofactor throughout the study period.

3.2. Test of thrombin generation (Table 2)

The plasma levels of both FPA and ATM were elevated in the first 2–3 days after admission and decreased later; the highest levels were noted in the first 24 h.

3.3. Platelet function (Table 2)

Marked elevation of both BTG and PF4 levels were recorded in the first 2 days after admission and declined later.

3.4. Fibrinolytic tests (Table 3)

PAI exhibited marked elevation throughout. There were insignificant fluctuations of plasminogen and α_2-antiplasmin.

Table 1
Coagulation parameters in unstable angina

	Day 1			Day 2	Day 3	Day 4	Day 5	Control
	Group A	Group B	Group C					
PT (s)	15.4 ± 8.7 (26)	15.3 ± 4.5 (26)	14.1 ± 2.5 (25)	13.5 ± 2.3 (26)	13.4 ± 2.2 (26)	13.3 ± 2.3 (25)	13.5 ± 2.7 (21)	15.1 ± 1.0 (48)
APTT (s)	50.8 ± 12.8 (26)	85.4 ± 45.9 (26)[a]	86.5 ± 39.7 (25)[a]	66.3 ± 25.7 (26)[a]	56.5 ± 24.8 (26)	59.5 ± 31.9 (25)	59.4 ± 35.1 (21)	47.5 ± 3.3 (48)
TT (s)	18.6 ± 7.9 (26)	35.4 ± 9.0 (26)[a]	29.0 ± 6.1 (25)[a]	19.8 ± 12.5 (26)[a]	21.4 ± 14.9 (26)	23.0 ± 17.6 (25)	25.3 ± 24.0 (21)	15.0 ± 4.0 (48)
RT (s)	16.6 ± 9.3 (26)	16.3 ± 3.4 (26)	17.1 ± 8.7 (25)	17.8 ± 2.6 (26)	16.6 ± 2.8 (26)	16.2 ± 2.5 (25)	17.2 ± 8.7 (21)	15.9 ± 1.6 (61)
FIB (mg %)	357 ± 148 (26)[a]	370 ± 142 (26)[a]	410 ± 154 (25)[a]	399 ± 168 (26)[a]	393 ± 167 (26)[a]	428 ± 134 (25)[b]	427 ± 196 (21)[a]	288.0 ± 76.6 R
FVIII:C (%)	160 ± 83 (26)[a]	158 ± 90 (26)[a]	153 ± 73 (26)[a]	170 ± 70 (26)[a]	165 ± 61 (26)[a]	192 ± 128 (25)[a]	169 ± 63.4 (21)[a]	110.4 ± 40.4 R
RICOF (%)	142 ± 70 (26)[a]	128 ± 58 (26)	138 ± 80 (26)[a]	152 ± 79 (26)[a]	152 ± 84 (26)[a]	145 ± 58 (25)[a]	142 ± 50 (21)[a]	114.3 ± 49.9 R
vWF:Ag (%)	171 ± 76 (26)[a]	168 ± 75 (26)[a]	177 ± 74 (26)[a]	184 ± 86 (26)[a]	192 ± 75 (26)[a]	192 ± 94 (25)[a]	187 ± 99.8 (21)[a]	113.7 ± 46.1 R

All values are mean ± S.D. with number in parenthesis. A, B and C, 8-h samples in day 1.
Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; RT, reptilase time; FIB, fibrinogen; RICOF, vWF, ristocetin cofactor; FVIII:C, factor VIII clotting; vWF:Ag, von Willebrand factor- antigen; R, laboratory reference values.
[a] $P < 0.05$.
[b] $P < 0.001$.

Table 2
Platelet release proteins (BTG and PF4) and parameters of thrombin generation (FPA and ATM) in unstable angina

	Day1			Day 2	Day 3	Day 4	Day 5	Control
	Group A	Group B	Group C					
BTG (IU/ml)	65.6 ± 17.2 (23)[a]	62.1 ± 17.2 (22)[a]	58.2 ± 13.9 (22)[a]	49.3 ± 12.1 (24)[b]	34.6 ± 14.5 (21)	32.2 ± 14.6 (19)	38.9 ± 15.8 (19)	44.9 ± 8.8 (44)
PF4 (IU/ml)	22.5 ± 6.0 (23)[a]	21.5 ± 5.8 (22)[a]	20.3 ± 5.8 (22)[a]	16.5 ± 5.3 (22)[a]	12.9 ± 6.7 (22)[a]	7.6 ± 4.2 (19)	7.5 ± 5.1 (19)	4.5 ± 3.5 (47)
FPA (ng/ml)	13.9 ± 10.8 (23)[a]	12.7 ± 9.7 (23)[a]	14.1 ± 10.5 (22)[a]	7.9 ± 5.8 (22)[a]	4.3 ± 4.0 (22)[b]	4.7 ± 4.5 (19)	2.2 ± 1.4 (19)	2.2 ± 1.6 (46)
ATM (ng/ml)	27.3 ± 14.8 (23)[b]	22.8 ± 10.7 (22)[b]	21.9 ± 10.5 (22)[b]	20.2 ± 12.7 (23)[b]	14.0 ± 8.4 (22)	11.7 ± 6.9 (19)	16.0 ± 10.9 (19)	13.0 ± 7.6 (46)

All values are mean ± S.D. with number in parentheses. A, B and C, 8-h samples in day 1.
Abbreviations: BTG, beta-thromboglobulin; PF4: platelet factor 4; FPA, fibrinopeptide A; ATM, thrombin-antithrombin complexes.
[a] $P < 0.05$.
[b] $P < 0.001$.

Table 3
Fibrinolytic parameters in unstable angina

	Day 1			Day 2	Day 3	Day 4	Day 5	Control
	Group A	Group B	Group C					
PAI (AU/ml)	15.4 ± 9.3 (26)[a]	15.1 ± 13.0 (26)[a]	16.6 ± 11 (25)[a]	17.5 ± 9.2 (26)[a]	16.2 ± 43.5 (26)[a]	16.8 ± 9.3 (25)[a]	18.1 ± 11.4 (26)[a]	6.3 ± 3.1 (41)
PLSMGN(%)	100 ± 18.3 (24)	88 ± 26.9 (24)	95 ± 25.8 (24)	93.5 ± 22.2 (23)	94.4 ± 20.5 (23)	97 ± 19.4 (22)	98.6 ± 24 (21)	105.4 ± 17.6 R
ANTPLS(%)	84.2 ± 16.7 (24)	80.1 ± 18.5 (24)	84 ± 17.6 (24)	85.9 ± 14.4 (23)	82.5 ± 16.1 (24)	82.4 ± 16.8 (23)	94.5 ± 18.0 (22)	97.3 ± 13.7 R

All values are mean ± S.D. with number in parentheses. A, B and C, 8-h samples in day 1. *Abbreviations*: PAI, plasminogen activator inhibitor; PLSMGN, plasminogen; ANTPLS, α_2-antiplasmin; R, laboratory reference values.
[a] $P < 0.05$.

Table 4
Coagulation inhibitors in unstable angina

	Day 1			Day 2	Day 3	Day 4	Day 5	Control
	Group A	Group B	Group C					
ATIII (%)	89 ± 13 (26)[a]	75 ± 14 (26)[a]	77.7 ± 14.3 (26)[a]	73 ± 16.4 (26)[a]	72 ± 16.9 (26)[a]	73 ± 13.1 (25)[a]	77 ± 12.7 (26)[a]	100.1 ± 13.4 R
PROT C (%)	107 ± 24 (26)	104 ± 30 (26)	103 ± 24.3 (25)	100 ± 22 (25)	102 ± 21.6 (25)	109 ± 26 (25)	11 ± 23 (26)	95.9 ± 27.3 (49)
PROT S (%)	102 ± 23 (26)	102 ± 23 (26)	104 ± 17.8 (26)	107 ± 22 (26)	109 ± 20.1 (26)	111 ± 23 (25)	116 ± 23 (26)	99.6 ± 22.3 (49)

A, B and C, 8-h samples in day 1. All values are Mean ± SD with number in parentheses. *Abbreviations*: ATIII, antithrombin III; PROT C, protein C; PROT S, protein S; R, laboratory reference values.
[a] $P < 0.05$.

3.5. Coagulation inhibitors (Table 4)

Significant decrease of ATIII levels were noted throughout the study periods; proteins C and S levels remained stable.

4. Discussion

In this study, laboratory measurements were undertaken of the plasma levels of small fragments reflecting the degree of activation of various components of the haemostatic system. It was hoped that this may shed some light on the possible involvement of perturbations of this system in the pathogenesis of unstable angina. Unlike most previous studies, these measurements were performed more frequently in the first 24 h following the onset of the anginal attack, and less frequently (daily) thereafter. Elevated levels of most fragments were noted in the first 24–48 h after admission to hospital.

The results gave evidence of in vivo platelet activation, as indicated by the marked elevation in the plasma levels of the platelet release proteins BTG and PF4 in the first 24 h of the onset of anginal pain. Previous reports on the levels of these proteins varied widely from no change [6–8] to significant elevation [10]. Confirmative evidence of platelet activation in patients with unstable angina comes from the recently reported increased excretion of thromboxane metabolites [2,30]. In one of these studies [30], enhanced thromboxane (A_2, TXA_2) synthesis was frequently associated with angiographic evidence of intracoronary thrombus formation. It is reasonable, therefore, to conclude that in the chain of events triggered by plaque rupture and subsequent exposure of subintimal thrombogenic material, the generation of thromboxane represents an amplification factor, inducing and sustaining platelet activation and aggregation [31]. It is also possible that substances such as serotonin, adenosine diphosphate (ADP) and platelet activating factor (PAF), released from activated platelets, contribute further to thrombus formation and vasoreaction [32]. Lastly, strong indirect evidence that platelet constituents, namely TXA_2, play a significant pathogenic role in unstable angina comes from the well-established beneficial effect of aspirin on the survival and cardiac events in patients with unstable angina [33,34].

Evidence of intracoronary thrombosis in patients with unstable angina was provided by the recent study of Cowley et al. [46], who found angiographic appearance consistent with intracoronary thrombi in 58% of patients with unstable angina, when investigated very soon after episodes of chest pain. Other investigators employed the recently available assays of small haemostatic fragments which provide indirect evidence of in vivo thrombin generation, such as fibrinopeptide A (FPA) and thrombin-antithrombin complexes (ATM), on the pretext that such measurements may serve non-invasively to identify patients in whom activation of the clotting system and thrombus formation is underway.

The present study, in line with previous reports [7,9,35,36] has shown significantly elevated levels of FPA in patients with unstable angina. In an earlier study the levels of FPA were found to be similar to those measured in patients with acute myocardial infarction and were significantly higher than corresponding levels in patients with stable angina and normal control subjects [35]. The highest plasma levels of FPA were obtained in a sample collected a short time (1 h) after an episode of chest pain [9]. In the present study, the repeated blood sampling was designed to commence as close as possible to the onset of anginal pain, so as to obtain a detailed picture of the fluctuations of the various measured parameters. Peak FPA levels were detected in the first 24 h of the onset of pain and then levels declined gradually over the following 4–5 days. Elevated levels of FPA were found to be more common in patients with ST segment depression in the electrocardiogram in whom evidence of intracoronary thrombus was detected angiographically [36]. Such an association could not be established in the current study. Therefore, the body of laboratory evidence also supports the involvement of thrombin generation and clot formation in the pathogenesis of unstable angina. The recently employed assay for thrombin-anti-

thrombin complexes has not been studied widely and the limited reported evidence [37] is in agreement with our findings and gives further evidence that generation of thrombin is a prominent laboratory finding accompanying unstable angina.

The level of the serine inhibitor antithrombin III (ATIII) was found to be reduced below reference values throughout the observation period and this can readily be explained by the continuous heparinization in these patients during their stay in hospital; this is a well-established observation [38,39].

This study gave evidence of acute phase reaction and haemostatic response to tissue injury as evidenced by the elevated levels of clotting factor VIII, fibrinogen and von Willebrand factor:antigen as well as ristocetin cofactor activity. The latter is of particular interest since it is considered an expression of vascular endothelial damage in ischaemic heart disease including unstable angina [10,12,40,41] and its involvement in the pathogenesis of these diseases is quite possible.

The plasma levels of the other haemostatic inhibitory factors, proteins C and S, showed minimal changes and this suggests no significant contribution of these factors to unstable angina. A recent study reported elevated levels of protein C:antigen in patients of unstable angina [42].

The implication of reduced fibrinolysis in the pathogenesis of unstable angina has been highlighted in many previous studies. Our finding of elevated PAI levels in unstable angina confirms those findings [43–45]. The levels of t-PA were reported to be unaffected in unstable angina [43]. The fluctuations in the levels of PAI are of particular interest since a close association was found between elevated levels of PAI and myocardial infarction in young patients [44]. Our patients were not followed for long enough to seek confirmation of this observation.

In conclusion, this study gives strong evidence of active involvement of various components of the haemostatic system — platelets, clotting and fibrinolytic mechanisms — in the pathogenesis of unstable angina. It would be of great interest if some of these patients could be followed longitudinally to see which of the measured parameters can be used to predict those patients who progress to myocardial infarction. Lastly, the study gives strong basis to the currently (widely) employed antiplatelet and thrombolytic drug therapy in the management of unstable angina.

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