The coagulopathy of heat stroke: alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah

S. A. Al-Mashhadani, A. G. M. A. Gader, S. S. Al Harthi, D. Kangav, F. A. Shaheen and F. Bogus

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Haemostatic measurements were undertaken in 132 patients diagnosed with heat stroke during the pilgrimage to Makkah, in two successive summers of 1989–90. The control group comprised 49 patients, all pilgrims, with a wide range of clinical conditions, but without hyperpyrexia or deranged haemostasis. Heat stroke patients showed (i) significant prolongation of the prothrombin (PT), activated partial thromboplastin (aPTT) and thrombin times (TT) but normal reptilase time (RT); (ii) significant reduction in plasma levels of antithrombin III (AT-III), factor V, protcins C and S, plasminogen activator inhibitor (PAI) and platelet count; (iii) increase in plasma factor VIII, tissue plasminogen activator (t-PA) and serum FDP; (iv) no significant changes in plasma fibrinogen, plasminogen, α_2-antiplasmin and factors VII and X. Heat stroke patients were then grouped into those with and those without bleeding symptoms. Bleeders showed greater prolongation of the PT, aPTT and TT and significant reductions in fibrinogen, AT-III, factors V, VIII and X, plasminogen, α_2-antiplasmin and platelet count. Logistic regression and discriminant analysis showed that AT-III was the parameter associated most with heat stroke and reliable enough to predict its occurrence, whether or not bleeding occurred. The results indicate that activation of the haemostatic mechanism, consumptive in nature, regularly accompanies heat stroke and highlights the physiological role of AT-III in checking this activation process.

Key words: Heat stroke, coagulation, fibrinolysis, coagulation inhibitors.

Introduction

It is well established that heat stroke is accompanied by widespread cellular damage and extensive tissue dysfunction. A frequent complication of heat stroke is derangement of the haemostatic system which varies in severity from an increased bleeding tendency, for example, prolonged bleeding from venepuncture sites and/or petechial haemorrhages, to more severe bleeding from multiple sites often with fatal outcome.[1–21] These haemorrhages, mainly seen at post-mortem, were seen in the skin, mucous membranes and internal organs, such as lungs, heart, brain, gastrointestinal tract, kidneys, pleurae, conjunctivae and the pericardium.[1–5] The earliest investigators attributed these haemorrhages to (a) a combination of increased capillary permeability, thermal destruction of coagulation factors, thrombocytopenia and hypoprothrombinaemia secondary to liver damage,[3,6,7] (b) primary fibrinolysis,[4,7,8,12,15] and (c) more recently, there has been evidence for disseminated intravascular coagulation (DIC) being the primary event with thrombocytopenia, enhanced fibrinolysis and haemorrhagic diarhesis occurring as secondary phenomena.[9–14,16–21] In recent years, new techniques for assaying various components of the haemostatic system have become avail-

S. A. Al-Mashhadani is with the Department of Pathology, A. G. M. A. Gader is with the Department of Physiology, S. S. Al Harthi is with the Department of Medicine, and D. Kangav is with the Research Centre, College of Medicine and King Khalid University Hospital, and F. A. Shaheen and F. Bogus are with the Ministry of Health, Riyadh, Saudi Arabia. Address correspondence to Dr S. A. Al-Mashhadani, Division of Haematology (32), College of Medicine and King Khalid University Hospital, PO Box 2925, Riyadh 11461, Saudi Arabia. Tel: +966-1-4670011; Fax: +966-1-4672462.

able which are sensitive enough to more accurately reflect changes in haemostasis. In this study a wide range of haemostatic tests was performed, including components that have not previously been studied in heat stroke patients, such as proteins C and S and plasminogen activator inhibitor (PAI). The aims were to further characterize the haemostatic defect in these patients and to establish a pathognomic association between alterations in the levels of various haemostatic factors and the occurrence of bleeding complications.

Materials and methods

Patients

This investigation continued through two successive pilgrimages (Haj) to Makkah, in the summers of 1989 and 1990. A team of doctors and technicians managed a total of 132 heat stroke patients (Table 1) in Jiad, Mina and Arafat Hospitals and the Heat Stroke Centres, in the Makkah region. All patients fulfilled the diagnostic criteria of heat stroke: rectal temperature of 40°C and above, dry, hot flushed skin and disturbances of consciousness varying from drowsiness to deep coma. Blood samples were collected and processed as appropriate for the various tests undertaken. These included complete haemogram and coagulation screening tests which were performed on site. All patients were sampled on their admission to hospital or the Heat Stroke Centre after establishing the diagnosis of heat stroke and before any therapeutic intervention including blood product replacement (FFP or platelet concentrates). Plasma was separated in the cold and stored frozen (−40°C) for more specialized assays to be undertaken in the Coagulation Laboratory in the College of Medicine, Riyadh. Record was made of the presence or absence of bleeding or any other complications as well as therapeutic interventions, particularly blood products and heparin anticoagulation.

Table 1. Demographic characteristics of heat stroke patients and controls

	Heat stroke patients	Controls
Sex		
Male	79 (59.2%)	40 (81.6%)
Female	53 (40.8%)	9 (18.4%)
Age		
Mean	59.4 years	54.0 years
Mean ± SD	59.4 ± 13.3 years	54.0 ± 20.2 years
Range	30–80 years	35–95 years
Rectal temp	42.0 ± 0.8	–
Range	(40–44.8)	
Bleeding		
Yes	41 (30.6%)	–
No	91 (69.4%)	
Nationality		
Arabs	76 (61.2%)	31 (63.3%)
Egyptians	31 (25.6%)	18 (36.7%)
Asians	32 (24.8%)	13 (26.5%)
Turks	7 (5.8%)	3 (6.1%)
Africans	10 (7.4%)	2 (4.1%)
Unknown	7 (5.8%)	–

Controls

Controls ($n = 48$) were recruited randomly from Haggis (pilgrims) who were exposed to the same environmental conditions, but who presented with ailments not related to heat stroke. Their physical data and clinical presentation on arrival to hospital are shown in Tables 1 and 2. Patients with heat exhaustion ($n = 11$) had rectal temperatures 39.5°C and a combination of water and salt depletion.

Laboratory assays

The following tests were performed: prothrombin time (PT), activated partial thromboplastin time (aPTT; Manchester Comparative Reagents, UK), thrombin time (TT; Park Davis Topical Thrombin), reptilase time (RT; Pentapharm, Switzerland) plasma fibrinogen (turbidometric method[22]), antithrombin III (AT-III) by chromogenic assay[23] with S-2238 (Coatest[TM], Kabi, Sweden), clotting factor VIII (FVIII:C by one-stage clotting assay[24]) and clotting factors V and VII.[25] The following factors were assayed by chromogenic substrates using commercially available kits according to the manufacturers' instructions: plasminogen and α_2-antiplasmin (Berichrom Kits, Behring, Germany), clotting factor X (Coatest Kits, Kabi, Sweden), protein C, protein S, PAI and tissue plasminogen activator (t-PA) (Diagnostica Stago, Paris, France). Platelet count was part of the complete haemogram which was performing by electronic counting (Coulter S+).

Statistical analysis

The data were entered into a personal computer using the Lotus 123[TM] program. Several statistical programs

Table 2. Controls: clinical presentation

Chest complaints	22
Chest infection	19
Pain	3
Gastrointestinal complaints (GIT)	9
Gastritis	5
Gastroenteritis	4
Heat exhaustion	11
Fever for investigation	2
Miscellaneous	4
Jaundice	2
Hypertension	1
Parkinsonism	1

were used for the data analysis. The StatPack Gold program was used to compute the mean, standard deviation and the range for all the interval variables. Programs 3D, 8D, AM, 7M and LR from the BMDP Statistical Package were used at various stages in the analysis. Program 3D was used for conducting the unpaired trimmed *t*-test for two independent groups with the groups of interest being heat stroke patients *vs* controls, and among the former, bleeders *vs* non-bleeders. Program 7M for discriminant analysis and LR for logistic regression were applied to the data for the cases dichotomized into the groups bleeders *vs* non-bleeders. The objective of the analysis was to determine the most significant coagulation factors that may help to predict occurrence of bleeding among heat stroke patients. This analysis was also supplemented with tests of statistical significance using either the Chi-squared test or Fisher's Exact test depending on the nature of the data for a particular variable.

Results

The results were presented as follows. (1) Data obtained from all patients, on arrival for treatment were summarized and those relating to interval values were expressed as means ± SD and compared with controls (Table 3). (2) Since the study aimed to identify the haemostatic abnormalities associated with excessive bleeding in patients with heat stroke, the data were re-grouped and the results from bleeders compared with those in non bleeders (Table 4). In this study a patient was termed a bleeder if he exhibited mild bleeding, e.g. prolonged bleeding from venepuncture sites and petechial haemorrhages, to more severe bleeding, e.g. intractable bleeding from multiple sites such as gums, conjunctivae, haematuria and gastrointestinal bleeding (classic severe DIC). These bleeding symptoms were therefore taken as indicators of various degrees of derangement of haemostasis.

Effect of nationality, age and sex

Most heat stroke patients were Egyptians (25.6%; Table 1). It is also notable that most bleeders (29.3%) as well as controls (36.7%), who were selected randomly, were also Egyptians. This suggests that they succumb to the heat stress while performing the various HAJ rituals more than any other nationality. The number of Turks, Pakistanis and Iranians is always larger (> 100 000) than Egyptians (< 50 000), but they have lower morbidity than Egyptians. Neither age nor sex bore any relationship to the occurrence of bleeding in heat stroke patients. Since most of our patients were over 50 years of age (59.4 ± 10.4) the range of age groups was too narrow to allow age to be a discriminating factor in the occurrence of bleeding. As all patients were relatively old, this indicates that old age represents a special risk for the occurrence of heat stroke.

Table 3. Coagulation parameters in heat stroke patients and controls

	Patients ($X \pm SD$)	(*n*)	*vs* Control ($X \pm SD$)	(*n*)	*P* value (2-tail)
PT (%)	146.5 ± 99.5	(132)	112.8 ± 38.7	(46)	0.02*
PTT (%)	140.1 ± 93.2	(132)	110.7 ± 26.7	(46)	0.003*
TT (%)	114.9 ± 26.3	(130)	99.1 ± 21.6	(47)	0.0004*
RT (%)	120.4 ± 37.9	(130)	115.2 ± 49.0	(43)	NS
FIB (mg/dl)	259.8 ± 103.1	(128)	301.8 ± 152.3	(45)	NS
AT-III (%)	70.3 ± 22.5	(132)	84.5 ± 17.3	(48)	0.0001*
PLAS (%)	84.6 ± 23.0	(132)	88.2 ± 21.6	(49)	NS
ANTPLSM (%)	71.7 ± 26.7	(132)	74.2 ± 34.0	(48)	NS
t-PA (IU/ml)	1.2 ± 1.1	(48)	0.5 ± 0.6	(49)	0.023*
PAI (IU/ml)	10.8 ± 9.9	(43)	17.1 ± 15.0	(49)	0.003*
PROT C (%)	72.4 ± 24.4	(75)	84.2 ± 31.4	(49)	0.034*
PROT S (%)	97.0 ± 23.6	(70)	117.7 ± 27.7	(49)	0.000*
FVIII:C (%)	132.4 ± 61.1	(71)	84.9 ± 43.3	(47)	0.000*
FV (%)	60.7 ± 27.7	(68)	88.4 ± 26.5	(41)	0.02*
FVII (%)	78.7 ± 34.1	(71)	85.5 ± 18.8	(42)	NS
FX (%)	89.4 ± 30.8	(71)	98.5 ± 40.1	(43)	NS
Platelet ($\times 10^3$/mm^3)	211.8 ± 106.0	(132)	228.6 ± 66.1	NS	
FDP (μg/ml)	50.3 ± 91.6	(42)	Not done	–	

*Significant at 5% level of significance.

Coagulation screening tests

To facilitate comparison of the data on screening tests, the results were expressed as a percentage of the control plasma (test/control × 100). Patients showed significant prolongation of the PT, aPTT and TT but no significant alterations in reptilase time (Table 3).

Table 4. Coagulation parameters in bleeders *vs* non-bleeders

Haj Study	Bleeders ($X \pm SD$)	(*n*)	Non-bleeders ($X \pm SD$)	(*n*)	*P* value (2-tail)
PT (%)	191.4 ± 158.9	(39)	128.2 ± 51.9	(83)	0.0001*
PTT (%)	174.8 ± 109.9	(39)	120.9 ± 65.5	(83)	0.005*
TT (%)	123.7 ± 21.7	(38)	111.3 ± 27.7	(88)	0.004*
RT (%)	128.8 ± 32.7	(38)	116.9 ± 40.4	(85)	0.117
FIB (mg/dl)	179.9 ± 85.3	(37)	289.7 ± 91.4	(85)	0.000*
AT-III (%)	56.9 ± 21.4	(39)	75.4 ± 20.6	(88)	0.000*
PLASMNG (%)	73.2 ± 24.7	(39)	89.7 ± 20.8	(83)	0.002*
ANTPLSM (%)	53.3 ± 28.7	(39)	79.8 ± 30.8	(83)	0.002*
PROT C (%)	59.1 ± 21.2	(36)	76.9 ± 23.5	(49)	0.006*
PROT S (%)	93.8 ± 25.5	(33)	98.0 ± 23.8	(47)	0.372
FV (%)	41.3 ± 22.9	(32)	77.9 ± 19.0	(36)	0.000*
FVII (%)	71.4 ± 35.4	(32)	84.7 ± 32.2	(39)	0.073
FVIII:C (%)	105.3 ± 47.0	(32)	154.5 ± 62.9	(39)	0.003*
FX (%)	81.6 ± 30.1	(32)	95.7 ± 30.3	(39)	0.045*
PLATCNT ($\times 10^3$/mm^3)	160.3 ± 88.6	(39)	235.9 ± 107.1	(83)	0.001*
FDP (μg/ml)	69.5 ± 109.1	(20)	31.4 ± 66.6	(22)	0.156

*Significant at 5% level of significance.

Plasma fibrinogen

Although controls had a mean fibrinogen level (3.1 g/l) which was higher than that of the patients (2.6 g/l), this difference was not statistically significant. However when bleeders were compared with non bleeders (Table 4), the mean fibrinogen level in bleeders (1.8 g/l) was significantly lower than in non-bleeders (2.9 g/l; $P < 0.0001$).

Platelet count

The mean platelet count in patients was not significantly different from control values ($288 \pm 66 \times 10^9$/l). However, bleeders had significantly lower platelet counts than non-bleeders (Table 4). A very wide range of platelet counts was recorded in heat stroke patients ($33–605 \times 10^9$/l). Platelet counts of 150×10^9/l or less were taken to indicate thrombocytopenia and on this basis, a statistically significant association ($P < 0.005$) between thrombocytopenia and the risk of bleeding was noted; 88.9% of patients with platelet counts less than 150×10^9/l exhibited bleeding symptoms, compared with 26.1% in patients with platelet count above this level.

Antithrombin III (AT III)

The mean AT III level in heat stroke patients and the control group were 70.3 + 22.5% and 84.5 + 17.3%, respectively ($P < 0.0001$). When the association between AT-III levels and the occurrence of bleeding was studied in heat stroke patients, the mean AT-III levels was significantly lower in bleeders (56.9 ± 21.4%) than in non-bleeders (75.4 ± 20.6%; $P < 0.0001$).

Tests of fibrinolysis

There were no significant differences in the levels of plasminogen or α_2-antiplasmin between heat stroke patients and controls or between bleeders and non bleeders. However, PAI was lower in heat stroke patients (10.8 ± 0.9 IU/ml) than in controls (17.1 + 15.0; $P < 0.003$), while t-PA levels were higher in heat stroke patients. The number of PAI and t-PA measurements was too small for reliable analysis of the relationship between their levels and the occurrence of bleeding.

Proteins C and S

The mean levels of proteins C and S in heat stroke patients (72.4 ± 24.4 and 97.0 ± 23.6%, respectively) were lower than in controls (84.2 + 31.0 and 117.7 ± 27.7%, respectively). ($P = 0.034$ for protein C and $P < 0.0001$ for protein S). Despite these differences the values were within the normal reference range for both proteins (70–140%). Of these two proteins, only protein C exhibited a significant reduction in bleeders (59.1 ± 21.2%) compared with non bleeders (76.9 ± 23.5%).

Table 5. Haemostatic measurements in heat stroke patients with bleeding symptoms. A comparison between those with severe fatal DIC *vs* survivors

Variables	Bleeders				
	Severe (DIC) ($X \pm$ SEM)	(n)	Survivors ($X \pm$ SEM)	(n)	P value (2 tail)
PT (%)	226.3 ± 43.5	(21)	146.3 ± 11.1	(18)	0.031*
PTT (%)	197.7 ± 29.1	(21)	143.5 ± 13.6	(18)	0.02*
TT (%)	125.8 ± 4.4	(21)	117.9 ± 5.4	(18)	NS
RT (%)	126.6 ± 4.7	(21)	119.6 ± 7.7	(18)	NS
FIB (g/dl)	120.5 ± 6.9	(21)	267.1 ± 15.1	(17)	0.0000*
AT III (%)	46.7 ± 4.2	(21)	69.9 ± 3.6	(18)	0.001*
FDP (%)	87.3 ± 35.0	(12)	10.0 ± 2.1	(8)	0.01*
PLSMGN (%)	63.3 ± 4.2	(21)	83.9 ± 6.7	(18)	0.0023*
ANTPLSM (%)	70.5 ± 5.4	(21)	69.9 ± 5.5	(18)	NS
PROT C (%)	49.9 ± 4.6	(20)	83.3 ± 9.8	(13)	0.0043*
PROT S (%)	87.9 ± 3.0	(20)	132.7 ± 31.4	(16)	NS
FV (%)	33.1 ± 2.3	(20)	54.2 ± 9.8	(12)	NS
FVII (%)	58.1 ± 2.8	(20)	93.3 ± 15.4	(12)	0.05*
FVIII (%)	88.4 ± 6.3	(20)	142.7 ± 15.8	(12)	0.003*
FX (%)	81.6 ± 6.1	(20)	84.2 ± 13.8	(19)	NS
Platelet count ($\times 10^9$/mm^3)	151.1 ± 22.5	(21)	167.2 ± 20.5	(18)	0.001*

*Significant at 5% level of significance; NS, not significant.

Factors VIII, VII, V and X

The plasma levels of factors VII and X were not significantly different from controls. However, the levels of factor V were significantly lower in heat stroke patients. The levels of these clotting factors were still lower in bleeders than non-bleeders. In contrast, factor VIII levels were higher in patients than controls, but lower in bleeders than non bleeders.

Fatal DIC

Twenty-one patients out of 132 (18%) died from DIC. All patients were labelled as bleeders. The results of their haemostatic assays (Table 5) showed the expected severe derangement of haemostasis compared with survivors.

Discussion

The coagulopathy associated with heat stroke has been reported extensively in the literature and there is strong evidence that haemostatic failure and bleeding manifestations are a frequent complication in both severe and fatal heat stroke. Laboratory studies have confirmed disturbances of the blood coagulation mechanism in the form of prolongation of coagulation screening tests as well as consumption of coagulation and fibrinolytic factors.[1–21] In addition, reports of either individual patients[13,15,17,21] or series of

patients[9,13,14,18–20] have shown that a marked decrease in platelets is a common finding in heat stroke which was mostly but not always, accompanied by haemorrhagic complications.[3,8–10,14,15,18]

Significant prolongation of coagulation screening tests was seen in patients and to a lesser extent in controls, suggesting a generalized derangement of haemostasis. Individual factor assays showed that this haemostatic defect was primarily due to consumption of haemostatic factors, affecting various steps of the coagulation cascade, whether bleeding occurred or not (Table 4). However, as expected, heat stroke patients with bleeding had more severe haemostatic failure, with more marked prolongation of screening tests and diminution of haemostatic factor levels, than non-bleeders.

It must be remembered that deficiencies of a single haemostatic component or a group of deficiencies can result in bleeding symptoms. Forty-one patients (Table 4) were diagnosed as bleeders indicating clearly the very high prevalence (32.6%) of haemostatic failure associated with heat stroke. As mentioned earlier, bleeding can be mild (excessive bleeding from venepuncture sites) to severe (bleeding from multiple sites often with fatal outcome). This takes the form of a consumption coagulopathy of varying severity. It is noteworthy that bleeders had a multitude of abnormal haemostatic tests (Table 4): prolongation of coagulation screening tests, markedly reduced fibrinogen, AT III, plasminogen, α_2-antiplasmin, factors VIII, VII, V, protein C, platelet counts and PAI. In other words, there is overall derangement of various components of the haemostatic mechanism and some enhancement of fibrinolysis. Many earlier reports described varying diminution of the haemostatic variables, although none of these measured proteins C, S, PAI and α_2-antiplasmin.

In most of the patients, consumption of clotting and fibrinolytic factors with mild elevation of FDP levels suggested that a consumption coagulopathy was the predominant feature of severe heat stroke, with activated fibrinolysis occurring mainly as a secondary phenomenon. This is not unexpected, since fibrinolysis can be secondary to DIC, a consequence of small clots blocking the microcirculation leading to hypoxia, the release of tissue plasminogen activator and enhanced fibrinolysis. Besides no patient could be identified in whom the haemostatic derangement was characteristic of primary fibrinolysis.

Recently, Strother *et al.*,[26] studying cancer patients exposed to therapeutic hyperthermia where the core body temperature was raised to 41°C, found DIC, rather than primary fibrinolysis, to be a frequent complication of this form of therapy. Therefore, activation of the coagulation system seems to be the predominant and early consequence of the body exposure to high temperatures. This offers a reasonable explanation for the reduced AT-III concentrations in heat stroke patients whether they suffered bleeding complications or not.

In an effort to identify the mechanism(s) responsible for triggering the coagulopathy of heat stroke, evidence was recently presented[27] suggesting that direct activation of platelets by heat was the trigger for the clotting activation, a process which, if unchecked, may progress eventually to a consumption coagulopathy. It is noteworthy that derangement of haemostatic factors was not always associated with bleeding symptoms. The authors found a group of patients ($n = 15$) with markedly reduced platelet counts ($< 100 \times 10^9$/l) and no bleeding symptoms. This observation has been reported previously.[7,9,10,19] It can only be assumed that in such patients the platelet activation process did not progress beyond the initial stages of platelet activation and aggregation leading to their partial consumption. Since there was no associated activation of the clotting system, consumption coagulopathy and/or haemostatic failure did not occur. This is the most probable explanation of the thrombocytopenia seen in heat stroke in this and other studies.[7,9,13,19]

Discriminant analysis was used to determine which of the haemostatic test(s) mostly associated with heat stroke or bleeding symptoms. The results indicate that out of the many haemostatic measurements undertaken in this study, AT-III was the only parameter that showed marked reduction in heat stroke with or without bleeding, although reduction was more marked when bleeding complications dominated the clinical presentation. This observation confirms the established function of AT-III as a natural inhibitor of the coagulation system which becomes actively involved in the inhibition of not only thrombin, but also clotting factors X, VIII and XII, whenever coagulation is activated *in vivo*. In addition, this lends strong support to the earlier observation that heat stroke produces a hypercoagulable state[3] and to the authors' suggestion that the platelet activation trigger falls short of full-scale activation of the coagulation mechanism.

Earlier investigators gave prominence to primary fibrinolysis as the aetiological factor in the haemorrhagic complications in heat stroke patients.[4,7,8,12,15] This was based on post-mortem findings, since no intravascular clots could be detected in those heat stroke patients who die from a bleeding diathesis. Such a conclusion is not necessarily valid since post-mortem examination in patients with disseminated intravascular coagulation (DIC) often reveals no intravascular clots.[28]

On the basis of the results obtained in this study it

was concluded that derangement of the haemostatic mechanism frequently accompanies heat stroke. This may progress to a consumptive coagulopathy with serious bleeding. Only 18% of the heat stroke patients developed fatal DIC either on admission or shortly afterwards, making DIC an important cause of mortality in heat stroke patients. This should be considered by physicians managing heat stroke patients and necessitates the establishment of satisfactory coagulation laboratory facilities in all heat stroke centres. This will facilitate early detection of the haemostatic abnormalities so that the appropriate management can be started without delay.

Other than the consumption of clotting factors, this and other studies emphasized that platelet activation could be the real trigger to the coagulopathy of heat stroke. On this basis, the early administration of antiplatelet therapy should be considered as a preventive measure against the development of the DIC, as previously proposed in a similar situation,[29] and well before uncontrollable bleeding dominates the clinical picture.

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