

# Clinico-pathological evaluation of Heat Stroke induced Disseminated Intravascular Coagulation

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We report a case of a 57-year-old man who presented with haemostatic disturbance due to exertion induced heat stroke while running a marathon competition. His haemostatic disturbances were diagnosed as severe disseminated intravascular coagulation (DIC). Appropriate supportive component transfusions were given, guided by rotational thromboelastometry (ROTEM) test. He died eventually due to respiratory arrest and multiorgan failure. The cause of death was ascertained as death due to heat stroke based on clinical history as well as characteristic pathophysiological features.

**Keywords:** Heat stroke, DIC, Rotational thromboelastometry

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## Introduction

Heat stroke (HS) is a rare fatal condition clinically defined by elevation of core body temperature (>40°C), marked central nervous system abnormalities, hepatic, renal dysfunction and coagulation disorder diagnosed as DIC.<sup>[1]</sup> The majority of DIC cases with multiple organ impairment occurs in class III heat illness.<sup>[2]</sup> The prognosis for DIC is found to be particularly poor with the impairment of 2 or more organs and patients often die within 2 days of hospital admission.<sup>[2]</sup> Severe traumatic brain injury (TBI) is often associated with haemocoagulative disorders. A ten times higher mortality rate is reported in patients

who present with coagulopathy (TBI) compare to patients who present with no coagulopathy.<sup>[3]</sup> In fact, histological features of heat stroke associated deaths pertaining to vascular endothelium and intestinal mucosa are mostly non-specific and diagnosis is usually lamented on pathognomonic changes of coagulation status following DIC.

Environmental factors such as high temperature, humidity, wind strength, strong sun exposure, excessive exercise and certain medications like anticholinergic are known to predispose exertional heat stroke<sup>[4]</sup>, predominantly in able-bodied

individuals. The elevation of body temperature results in systemic inflammatory changes that eventually lead to disturbances of the haemostasis. Those changes of haemostatic behaviour can be analyzed by serial rotational thromboelastometry tests. The tests are also helpful in selecting appropriate blood components for transfusion to stabilize haemostasis.<sup>[5]</sup> We evaluated severe haemostatic disturbance in a patient who died of heat stroke using ROTEM and other confounding coagulation investigations.

### Case report

A 57-year old man had collapsed with generalized tonic-clonic seizures while running a marathon race in Colombo, Sri Lanka on a sunny morning in April, when atmospheric temperature was 32°C. He was found to be on long-term anticholinergic drugs, Venlaflexin and Benzhexol for a psychiatric illness. He was brought to the emergency treatment unit (ETU) of a tertiary care hospital and then immediately transferred to a medical intensive care unit (MICU).

On admission, his rectal temperature was 41.1°C. Reduced responsiveness was noted according to the Glasgow coma scale (GCS) value 6/15. He had supraventricular tachycardia in the electrocardiogram (ECG) with a pulse rate of 180/min. Blood pressure was normal 110/70 mmHg at the time. Peripheral oxygen saturation was low (92 %). He was electively intubated and ventilated. He developed severe puncture site bleeding within 6-8 hours of initial symptoms however a non-contrast computerized tomography (NCCT) of the brain had excluded intracranial haemorrhage.

ROTEM performed at the time had shown absolute flat lines in the INTEM (intrinsically-activated test using Ellagic acid elastometry), EXTEM (extrinsically-activated test with tissue factor elastometry) and FIBTEM (fibrin-based extrinsically activated test with tissue factor and the platelet inhibitor cytochalasin elastometry) indicated a gross disturbance at first, second level coagulation and fibrinolytic pathways.<sup>[6]</sup> Assessment of primary coagulation profile consisted of prolongation of prothrombin time (PT) >100 seconds (9.5-13.5 sec) and activated partial thromboplastin time (APTT) >200 seconds (26-40 sec). The plasma fibrinogen level was undetectable <1g/L (1.5-4.5g/L) in oppose to high D

Dimer level 43940 ng/mL (<243ng/mL). The platelet count was low  $31 \times 10^3/\mu\text{L}$  ( $150-400 \times 10^3/\mu\text{L}$ ). A mild red cell fragmentation was noted in the blood picture. Haemoglobin level was 16.4 g/dL and there was marked neutrophil leukocytosis  $24.89 \times 10^3/\mu\text{L}$  ( $4-11 \times 10^3/\mu\text{L}$ ).

Liver and renal function tests were raised 2171 U/L of alanine transaminase (ALT) (<50 U/L), 1897 U/L of aspartate transaminase (AST) (<50 U/L) and 215  $\mu\text{mol/L}$  of serum creatinine level (60-120  $\mu\text{mol/L}$ ). There was metabolic acidosis on arterial blood gas analysis PH-7.12 (7.3-7.4). High level of serum creatinine phosphokinase 183 u/L (<171 u/L) with positive urine myoglobin indicated rhabdomyolysis.

According to the guidance provided by ROTEM and other coagulation investigations, six units of platelets, 15 mL/kg body weight of fresh frozen plasma (FFP) and 10 units of cryoprecipitate were transfused. Body cooling, neurological, cardiac, hepatic and renal management were done by appropriate teams.

After 24 hours of admission, bleeding manifestations at puncture sites were much settled in spite of deteriorating general condition GCS 7+ ET /15 and progressively worsening liver and renal functions. AST 2575 u/L and ALT 2950 u/L, serum creatinine level was 197  $\mu\text{mol/L}$ . The rectal temperature was 38.9°C. ROTEM revealed a partial improvement of the coagulopathy mainly in INTEM and EXTEM compared to FIBTEM indicated coagulation disturbance was predominantly in the fibrinolysis. Plasma fibrinogen level was still less than the critical level <1 g/dL and D Dimer level was high 33240 ng/mL. The Platelet count had improved to  $101 \times 10^3/\mu\text{L}$ . PT was 47.9 seconds and APTT was 33.3 seconds in the coagulation profile. Persisting mild red cell fragmentation in the blood picture was noted with a drop of haemoglobin from 16.4 g/dL to 10.3 g/dL. A standard dose of FFP and Cryoprecipitate were transfused.

After 48 hours of admission, his puncture site bleeding was settled. Rectal temperature was 36°C, further deteriorating liver, renal functions and GCS 3+ ET/15 were noted. ROTEM analysis revealed stable haemostasis except for mild prolongation of CFT (clot formation time) in the EXTEM. Platelet count was  $110 \times 10^3/\mu\text{L}$ , D Dimer level was high 30280 ng/mL and the plasma fibrinogen level was less than the critical level. Mild red cell fragmentation was still observed in the blood picture with neutrophil

leukocytosis. Haemoglobin level remained unchanged at 10.3 g/dL. According to coagulation studies at that time component transfusion was not recommended. The patient died in 48 hours of admission due to respiratory arrest. The cause of death was ascertained as death due to heat stroke based on circumstantial data, clinical features and characteristic pathophysiological changes.

### Discussion

Bouchama definition of heat stroke based on its pathophysiology state that the passive heat effect on leakage of endotoxin from intestinal mucosa and release of Interleukin1 (IL1) and Interleukin6 (IL6) from muscles into the systemic circulation results in excessive activation of leukocytes and endothelial cells.<sup>[1]</sup> Under physiological conditions the endothelial glycocalyx covers the endothelium as a negatively charged antiadhesive, anticoagulant surface layer to protect and maintain its vascular barrier function.<sup>[3]</sup> The direct heat effect, inflammatory response and cytokines injure the vascular endothelium and trigger the coagulopathy.

DIC is a clinicopathological syndrome characterized by activation of pathways leading to and regulating coagulation.<sup>[7]</sup> This results in a global deficiency of coagulation factors, generation of fibrin clots that may cause organ failure with concomitant consumption of platelets to result in clinical bleeding.<sup>[7]</sup> The coagulation abnormalities are reported to be quiet early in Heat Stroke<sup>[1]</sup>. Our patient had presented with severe puncture site bleeding and abnormalities of coagulation investigations within 6 to 8 hours of initial neurological symptoms. In fact, coagulation abnormalities are observed 25 minutes after tissue injury in trauma-induced coagulopathy.<sup>[3]</sup>

Analysis of whole blood in vitro haemostasis revealed absolute flat lines in the EXTEM and INTEM with prolonged PT and APTT provided evidence of severe degree coagulation factor consumption, leading to quantitative deficiency or inactivation of coagulation proteins due to heat effect.<sup>[7]</sup> Global coagulation protein deficiency must have been further aggravated by concomitant liver injury and acute shut down of protein production. Thrombocytopenia is a feature in about 98% of DIC cases with the platelet count  $<50 \times 10^3/\mu\text{L}$ .<sup>[7]</sup> Low platelet count of  $30 \times 10^3/\mu\text{L}$  correlated with platelet consumption in addition to platelet aggregation and reduced platelet release from megakaryocytes in the

bone marrow due to its susceptibility to heat.<sup>[1]</sup> Fibrinogen is an acute phase reactant which remains within the normal range for a long time despite ongoing consumption.<sup>[7]</sup> Thus severe hypofibrinogenemia and a flat line in the FIBTEM of ROTEM graph were indicative of a severe degree of DIC. Further Fibrinogen level can be reduced as a part of consumptive coagulopathy in addition to coexisting liver damage. And fibrinogen levels are particularly reduced in HS associated with acidosis.<sup>[3]</sup> Enhanced thrombin formation and fibrinolytic activity are measured as fibrin degradation products (FDP). The measurement of D Dimer is related to plasmin degraded fibrin. A high level of D Dimer was not only evidence of severe fibrinolysis but their accumulation due to liver and renal failure as FDP and D Dimer are metabolized in the liver and excreted via kidneys. The red cell fragmentation was mild and constituted  $<10\%$  of red cells in the blood picture but it provided confirmatory evidence of DIC.<sup>[7]</sup>

International Society on Thrombosis and Haemostasis (ISTH) diagnostic scoring system provides an objective measurement of DIC and our patient who presented with DIC considering HS as a prerequisite underlying condition fulfilled criteria for overt DIC.<sup>[8]</sup> The cornerstone of the treatment of DIC is the treatment of underlying heat-induced vascular endothelial injury in par with the management of neurological, cardiac, hepatic and renal damage. Therefore, the clinical approach of the management was based on strategies pertaining to the management of DIC. Up to date, there is no universally accepted definition for heat stroke to understand its manifestations with regard to the management.

The primary indication for judicious component transfusion in DIC is the presence of bleeding manifestations. Hence component transfusion of any kind should not be based on the abnormalities of laboratory investigations alone. The presence of severe puncture site bleeding, severe impairment of in vitro haemostasis in the EXTEM, INTEM of the ROTEM and prolonged PT, APTT, justified transfusion of FFP. Severe impairment of FIBTEM and critically low level of plasma fibrinogen was treated with cryoprecipitate. Thrombocytopenia was corrected with platelet transfusion and maintained the platelet count above  $50 \times 10^3/\mu\text{L}$ .

In a situation where fluid overload is a problem, use of factor concentrates such as prothrombin complex concentrates (PCC), and fibrinogen concentrates can be recommended in place of FFP and cryoprecipitate.<sup>[9]</sup> However, unlike FFP and cryoprecipitate these factor concentrates contain only selected coagulation factors, thus global factor deficiency in DIC is corrected partially. Fortunately, fluid overload had not been an issue in our patient whose blood pressure remained normal and had no signs of oedema or pleural effusion.

The dynamically changing scenario of the patient's clinical status and laboratory investigations were monitored daily by repeated coagulation investigations such as ROTEM, PT, APTT, Plasma fibrinogen level, platelet count and examination of the blood picture for red cell fragmentation.

There was no place of anticoagulation in this patient with severe bleeding due to DIC at presentation or later in the follow-up. The only place of anticoagulation recommended in DIC is when there are severe arterial or venous thrombo-embolism, severe purpura fulminans and associated vascular skin infarctions or acral ischemia.<sup>[7]</sup> The use of protein C concentrates and tissue factor pathway inhibitor in patients with severe sepsis are also discouraged due to the uncertainty of their efficacy and concerns of high bleeding risk.<sup>[10]</sup> There are few reported cases of using anticoagulants such as recombinant thrombomodulin and anti-thrombin III concentrates in the coagulopathy of heat stroke, based on their negative feedback regulator effect on coagulation and inhibition of cytokines and HMGB1 (High mobility group box 1) proteins responsible for vascular endothelial cell damage.<sup>[1, 11]</sup> However, there are no proper guidelines available for the management of DIC in HS patients may be due to an inadequate number of heat stroke victims studied so far.<sup>[1]</sup>

### Conclusions

Heat stroke is a rare but potentially fatal condition, which constitutes a severe form of coagulopathy similar to overt DIC activated through damaged intestinal mucosa and vascular endothelium. The risk of the fatal outcome in heat stroke is several times higher when internal organ damage is associated with DIC. Serial testing of *in vitro* haemostatic status by ROTEM is useful to diagnose and study the dynamically changing scenario of heat stroke associated coagulopathy and its manifestations. In

circumstances with no independent reliable eyewitnesses, the presence of heatstroke induced sequential changes of coagulation that cascade shortly after the injury can be used by the forensic pathologist to ascertain the cause of death as heat stroke.

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