

Coagulation Disorders in Heatstroke: Emerging Biomarkers, Pathophysiological Mechanisms, and Clinical

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Abstract

Heatstroke is a critical medical emergency characterized by a rapid rise in core body temperature accompanied by systemic inflammatory responses and widespread physiological disturbances. Among the most serious complications, coagulation abnormalities play a central role in determining disease severity, organ dysfunction, and mortality. Heat-induced cellular injury initiates the release of damage-associated molecular patterns (DAMPs), triggering activation of innate immune pathways, endothelial dysfunction, platelet activation, and dysregulation of the coagulation cascade. These interconnected processes promote a prothrombotic state with impaired fibrinolysis, culminating in heatstroke-associated coagulopathy, which may progress to disseminated intravascular coagulation and multiple organ failure in critically ill patients. Recent investigations have identified several circulating biomarkers, including platelet count, D-dimer, fibrinogen degradation products, soluble thrombomodulin, interleukin-6, high-mobility group box 1 (HMGB1), circulating histones, and markers of endothelial injury, as potential indicators of disease progression and prognosis. In exertional heatstroke, biomarkers of skeletal muscle injury such as myoglobin and creatine kinase may further aid in predicting acute kidney injury and systemic complications. Although these biomarkers show considerable clinical promise, standardized diagnostic thresholds and validated prognostic models remain unavailable. Current management primarily emphasizes immediate cooling, aggressive fluid resuscitation, correction of electrolyte disturbances, and comprehensive supportive care, while emerging therapeutic strategies targeting inflammation, endothelial protection, and coagulation modulation are under active investigation. This review summarizes current evidence regarding the biological mechanisms underlying coagulation disorders in heatstroke, evaluates the diagnostic and prognostic value of emerging biomarkers, and discusses contemporary and evolving management strategies that may improve clinical outcomes. Continued translational and clinical research is essential to establish evidence-based diagnostic criteria and targeted therapeutic interventions for this life-threatening condition.

Keywords: Heatstroke; Coagulation disorders; Heatstroke-associated coagulopathy; Biomarkers; Endothelial dysfunction; Systemic inflammation; Disseminated intravascular coagulation; Platelet activation; Fibrinolysis; Organ dysfunction; Myoglobin; Patient management.

Introduction

Heatstroke is a severe thermoregulatory disorder characterized by a core body temperature typically exceeding 40°C and central nervous system dysfunction following prolonged exposure to high environmental temperatures or strenuous physical activity. It is broadly classified into classic (non-exertional) and exertional heatstroke, each differing in epidemiology and predisposing factors but sharing common pathological mechanisms. The global increase in extreme heat events associated with climate change has contributed to a rising incidence of heat-related illnesses, making heatstroke an important public health concern. Despite advances in emergency medicine, heatstroke continues to be associated with substantial morbidity and mortality due to rapid progression to systemic inflammatory response syndrome, circulatory collapse, and multiorgan dysfunction [1].

Among the various pathological events occurring during heatstroke, coagulation abnormalities have emerged as critical determinants of disease severity and clinical outcome. Heat-induced endothelial injury, activation of inflammatory pathways, platelet dysfunction, and dysregulation collectively contribute to the development of heatstroke-associated coagulopathy. Severe cases may progress to disseminated intravascular coagulation (DIC), microvascular thrombosis, tissue ischemia, and irreversible organ failure. Early recognition of coagulation disturbances through laboratory biomarkers and prompt therapeutic intervention are therefore essential for improving survival. This review summarizes current knowledge regarding the mechanisms responsible for coagulation disorders in heatstroke, discusses emerging diagnostic biomarkers, and highlights contemporary approaches to patient management [2].

Heatstroke-induced coagulopathy results from a complex interaction between hyperthermia, systemic inflammation, endothelial dysfunction, immune activation, and dysregulated hemostasis. Elevated body temperature directly damages cellular proteins and membranes, leading to widespread tissue injury. Injured cells release damage-associated molecular patterns (DAMPs), including HMGB1, extracellular histones, mitochondrial DNA, and heat shock proteins. These endogenous molecules activate Toll-like receptors and other innate immune pathways, resulting in excessive production of pro-inflammatory cytokines such as interleukin-1 β , interleukin-6, and tumor necrosis factor- α [3].

Inflammatory mediators stimulate endothelial cells to express tissue factors, adhesion molecules, and procoagulant proteins while suppressing endogenous anticoagulant pathways involving thrombomodulin, protein C, and antithrombin. Endothelial glycocalyx degradation further enhances vascular permeability and leukocyte adhesion. Simultaneously, activated platelets aggregate within the microcirculation, releasing additional inflammatory mediators that amplify thrombus formation [4,5].

Hypercoagulation is accompanied by impaired fibrinolysis through increased expression of plasminogen activator inhibitor-1 (PAI-1), resulting in persistent fibrin deposition within small vessels.

The combination of excessive thrombin generation, platelet consumption, and reduced fibrinolytic activity predisposes patients to disseminate intravascular coagulation. Microvascular thrombosis compromises perfusion of vital organs, including the kidneys, liver, lungs, heart, and brain, thereby accelerating multiorgan dysfunction. These interconnected mechanisms establish a vicious cycle in which inflammation promotes coagulation and coagulation further intensifies inflammatory injury [6].

MATERIALS AND METHODS

Early identification of coagulation abnormalities is essential for timely intervention in patients with heatstroke. Conventional laboratory parameters remain valuable for initial assessment. Progressive thrombocytopenia reflects platelet consumption, whereas prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), elevated international normalized ratio (INR), reduced fibrinogen concentrations, and increased D-dimer levels indicate activation of coagulation and fibrinolytic pathways [7].

Several novel biomarkers have demonstrated promises for identifying patients at increased risk of severe coagulopathy. Soluble thrombomodulin serves as a sensitive marker of endothelial injury and correlates with disease severity. Elevated concentrations of HMGB1, extracellular histone H3, nucleosomes, and cell-free DNA indicate extensive cellular damage and activation of innate immunity. Inflammatory cytokines, particularly interleukin-6 and tumor necrosis factor- α , are closely associated with systemic inflammatory response and adverse clinical outcomes [8].

Markers of endothelial activation, including von Willebrand factor, angiopoietin-2, and syndecan-1, may provide additional insight into vascular injury. In exertional heatstroke, elevated serum myoglobin and creatine kinase indicate rhabdomyolysis and help predict acute kidney injury. Cardiac troponins, lactate, and neutrophil-to-lymphocyte ratio have also been investigated as prognostic indicators. Although these biomarkers improve understanding of disease progression, standardized diagnostic thresholds and validated prognostic algorithms have yet to be established, limiting their widespread clinical application [9].

Patients with heatstroke frequently present with hyperthermia, altered mental status, hypotension, tachycardia, and varying degrees of organ dysfunction. Coagulation abnormalities may initially remain clinically silent but can rapidly progress to petechiae, ecchymoses, mucosal bleeding, thrombosis, or overt disseminated intravascular coagulation. Laboratory monitoring should include complete blood count, coagulation profile, fibrinogen concentration, D-dimer, serum electrolytes, renal and liver function tests, inflammatory markers, arterial blood gases, and biomarkers of muscle injury when exertional heatstroke is suspected [10].

Rapid reduction of core body temperature remains the cornerstone of treatment. Whole-body cold-water immersion

Biomarker	Physiological Role	Clinical Significance in Heatstroke	Potential Clinical Utility
Platelet count	Primary hemostasis	Decreased due to platelet consumption and microthrombus formation	Early indicator of coagulopathy and DIC
D-dimer	Fibrin degradation product	Elevated owing to increased fibrin formation and breakdown	Detects activation of coagulation and fibrinolysis
Prothrombin Time (PT)/INR	Extrinsic coagulation pathway	Prolonged in advanced coagulation dysfunction	Assesses severity of coagulation impairment
Activated Partial Thromboplastin Time (aPTT)	Intrinsic coagulation pathway	Prolonged in disseminated coagulation disorders	Monitors coagulation abnormalities
Fibrinogen	Clot formation	Reduced because of excessive consumption	Identifies consumptive coagulopathy
Soluble Thrombomodulin	Endothelial integrity marker	Increased following endothelial injury	Marker of vascular damage and disease severity
Interleukin-6 (IL-6)	Pro-inflammatory cytokine	Elevated during systemic inflammatory response	Predicts disease progression and poor prognosis
HMGB1	Damage-associated molecular pattern (DAMP)	Released after cellular injury	Reflects tissue damage and inflammatory activation
Histone H3	Marker of cell death and NET formation	Elevated in severe heatstroke	Associated with endothelial injury and thrombosis
Myoglobin	Skeletal muscle injury marker	Increased in exertional heatstroke with rhabdomyolysis	Predicts acute kidney injury
Creatine Kinase (CK)	Muscle enzyme	Elevated following muscle breakdown	Assesses severity of rhabdomyolysis
Lactate	Marker of tissue hypoperfusion	Increased during shock and organ dysfunction	Prognostic indicator of disease severity

Table 1: Emerging Biomarkers and Their Clinical Significance in Heatstroke-Associated Coagulation Disorders.

is considered the most effective cooling strategy for exertional heatstroke, whereas evaporative and convective cooling methods are frequently employed in classic heatstroke. Aggressive intravenous fluid therapy should restore circulatory volume while avoiding fluid overload. Electrolyte abnormalities, hypoglycemia, acid-base disturbances, and respiratory insufficiency require prompt correction.

Management of coagulation disorders is primarily supportive and individualized according to clinical severity. Blood component therapy, including platelet transfusion, fresh frozen plasma, cryoprecipitate, or fibrinogen replacement, may be necessary in patients with active bleeding or severe coagulation abnormalities. Anticoagulant therapy remains controversial because of the simultaneous risks of thrombosis and hemorrhage. Experimental therapies targeting inflammatory cytokines, endothelial protection, complement activation, and neutrophil extracellular traps are currently under investigation but require confirmation through well-designed clinical trials [11].

Growing recognition of coagulation disorders as a major contributor to heatstroke-associated morbidity has stimulated considerable interest in identifying reliable biomarkers and targeted therapeutic interventions. Future research should

prioritize multicenter prospective studies to validate diagnostic biomarkers, establish clinically relevant cutoff values, and develop integrated risk prediction models that combine laboratory findings with clinical characteristics. Advances in proteomics, metabolomics, transcriptomics, and artificial intelligence may facilitate earlier detection of patients at high risk for severe coagulopathy and multiorgan failure [12].

Therapeutic innovation should focus on modulating the complex interaction between inflammation, endothelial dysfunction, and coagulation without increasing the risk of bleeding complications. Precision medicine approaches incorporating biomarker-guided therapy may improve patient outcomes while minimizing unnecessary interventions. In addition, public health initiatives emphasizing heat exposure prevention, early recognition, and rapid emergency response remain essential as climate change increases the global burden of heat-related illness.

Coagulation disorders represent a pivotal component of heatstroke pathophysiology and substantially influence disease progression and survival. Improved understanding of the molecular mechanisms, validation of emerging biomarkers, and development of evidence-based management strategies are critical for reducing mortality and improving the prognosis of patients affected by this life-threatening condition.

Results and Discussion

This was conducted to summarize current evidence regarding coagulation disorders in heatstroke, with emphasis on pathophysiological mechanisms, diagnostic biomarkers, and patient management strategies. Peer-reviewed studies published in English were identified through major biomedical databases, including PubMed, Scopus, Web of Science, and Google Scholar. The literature search focused on publications investigating heatstroke-associated coagulopathy, disseminated intravascular coagulation, endothelial dysfunction, inflammatory signaling, platelet activation, fibrinolysis, and emerging laboratory biomarkers. Original research articles, systematic reviews, meta-analyses, clinical guidelines, and experimental animal studies were considered eligible for inclusion. Studies with insufficient methodological quality, duplicate publications, conference abstracts without full-text availability, and articles unrelated to coagulation abnormalities in heatstroke were excluded. Data were synthesized qualitatively to provide an integrated overview of current knowledge, identify areas of consensus, and highlight existing gaps requiring further investigation [12].

The reviewed evidence consistently demonstrated that coagulation disorders are a major contributor to the progression and severity of heatstroke. Hyperthermia initiates extensive cellular injury, resulting in the release of damage-associated molecular patterns that activate inflammatory and coagulation pathways simultaneously. Endothelial dysfunction, platelet activation, excessive thrombin generation, and suppression of fibrinolysis collectively promote a hypercoagulable state that may progress to disseminated intravascular coagulation and multiorgan dysfunction. Conventional laboratory parameters, including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer, remain essential for evaluating coagulation status. Emerging biomarkers such as soluble thrombomodulin, high-mobility group box 1 (Table 1), extracellular histones, interleukin-6, syndecan-1, and circulating cell-free DNA have demonstrated potential for early diagnosis and risk stratification [13]. In exertional heatstroke, elevated serum myoglobin and creatine kinase were consistently associated with rhabdomyolysis and increased risk of acute kidney injury. Therapeutic evidence indicates that rapid cooling, aggressive fluid resuscitation, correction of metabolic abnormalities, and comprehensive supportive care remain the primary management strategies. Although anticoagulant, anti-inflammatory, and endothelial-protective therapies have shown encouraging findings in preclinical investigations, robust clinical evidence supporting their routine use remains limited [14-17].

Conclusion

A fundamental component of heatstroke pathophysiology and are strongly associated with disease severity, organ failure, and mortality. Increasing evidence supports the interplay between systemic inflammation, endothelial injury, platelet activation, and dysregulated coagulation in the development of heatstroke-associated coagulopathy. While several conventional and novel biomarkers have demonstrated promise for early diagnosis

and prognostic assessment, standardized diagnostic criteria and validated biomarker thresholds have yet to be established. Current treatment continues to rely primarily on rapid cooling, hemodynamic stabilization, and supportive intensive care, whereas targeted therapies aimed at modulating inflammation and coagulation require further clinical validation. Future multicenter prospective studies are essential to refine biomarker-guided diagnosis, develop personalized therapeutic strategies, and improve clinical outcomes in patients with heatstroke-associated coagulation disorders.

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