Heatstroke-induced coagulopathy: Biomarkers, mechanistic insights, and patient management

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Summary

Heatstroke is increasingly becoming a significant concern due to global warming. Systemic inflammation and coagulopathy are the two major factors that provoke life-threatening organ dysfunction in heatstroke. Dysregulated thermo-control induces cellular injury, damage-associated molecular patterns release, hyperinflammation, and hypercoagulation with suppressed fibrinolysis to produce heatstroke-induced coagulopathy (HSIC). HSIC can progress to disseminated intravascular coagulation and multiorgan failure if severe enough. Platelet count, D-dimer, soluble thrombomodulin, and inflammation biomarkers such as interleukin-6 and histone H3 are promising markers for HSIC. In exertional heatstroke, the measurement of myoglobin is helpful to anticipate renal dysfunction. However, the optimal cutoff for each biomarker has not been determined. Except for initial cooling and hydration, effective therapy continues to be explored, and the use of antiinflammatory and anticoagulant therapies is under investigation. Despite the rapidly increasing risk, our knowledge is limited, and further study is warranted. In this review, we examine current information and what future efforts are needed to better understand and manage HSIC.

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Introduction

Global warming may increase the frequency of natural disasters such as devastating storms, floods, wildfires, and most directly, increases the prevalence of heat-related illness.[1] Heatstroke is a critical condition with high mortality characterized by an elevated core body temperature above 40.5 °C (> 105°F) accompanied by central nervous system dysfunction, and often complicated by other organ dysfunction including renal, hepatic, and hemostatic failures.[2] Li et al.[3] warned that "The historical ~1 °C of global-mean surface air temperature increase above preindustrial levels has already increased the population annually exposed to at least one day with wet bulb globe temperature (WBGT) exceeding 33 °C (the reference safety value for humans at rest) from 97 million to 275 million. Maintaining the current population distribution, this exposure is projected to increase to 508 million with 1.5 °C of warming, 789 million with 2.0 °C of warming, and 1.22 billion with 3.0 °C of warming." Although exposure to one day of WBGT exceeding 33 °C may not directly relate to the increased risk of heatstroke, continuous warming seemingly affects healthcare.

Kaewput et al.[4] used the National Inpatient Sample database of the US consisted of over 3000 inpatients with heatstroke and reported an increased inpatient prevalence of heatstroke between 2003 and 2014. They also reported that among inpatients with heatstroke, 20% required mechanical ventilation, and 2% received renal replacement therapy. Rhabdomyolysis was the most common complication, and renal failure was the most common end-organ failure followed by neurological, respiratory, metabolic, hematologic, circulatory, and hepatic systems, and the in-hospital mortality rate of heatstroke was 5%. As a result, heat-related worker illness and the associated mortality are increasing. In the last 25 years, more than 900 US workers died and nearly 80,000 were seriously affected by extreme heat exposure, according to Bureau of Labor Statistics (BLS) data. Accordingly, California enacted its heat standard in 2005, heat-related injuries declined by 30%, from 2001 to 2006–2018 period.[5]

In addition to the acute thermal disorder, silent but progressive heat-related health problems continue to attract attention. The increased death toll from chronic

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kidney disease (CKD) among agricultural workers in Africa, India, the Middle East, and Central America was reported, and a similar trend is noted in the subtropical areas.[6] Heat exposure, dehydration, and salt loss are the major factors of heat-induced CKD. Thermal tissue injury and temperature-induced oxidative stress further accelerate the development of CKD. In addition, circulating toxic substances, such as myoglobin due to rhabdomyolysis, damage kidneys even if it is subclinical and asymptomatic. The causes remain unclear but may involve a complex interplay of environmental exposures, infections, genetic factors, and heat.[7] Certainly, there are opposing opinions. Herath et al.[8] advocated that the extent of global warming over the last half-century was not sufficient to cause a drastic change on renal function in manual workers. In Mesoamerican sugarcane workers, serum creatinine levels have been reported to increase during the work shift with the vast majority demonstrating glomerular filtration rates of less than 60 mL/min; the repeated kidney damage leads to irreversible kidney dysfunction.[9]

Heatstroke is often accompanied by coagulation disorders with an incidence of disseminated intravascular coagulation (DIC) reported to be as high as 48%.[10,11] Coagulopathy is a complication of heatstroke but also involved in its pathogenesis. Hifumi et al.[12] reported that the hospital mortality of heatstroke patients was significantly associated with the presence of DIC (odds ratio [OR], 2.16; 95% confidence interval [CI], 1.09 −4.27; P = 0.028), and the mortality increased as the DIC score increased. Thus, it is important to learn about the relevance of coagulation disorders associated with heatstroke. This review discusses the etiology, diagnosis, and treatment of heatstroke-induced coagulopathy (HSIC).

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed, Scopus, and Web of Science from relevant articles using the search terms “COVID”, “vaccine”, “thrombosis” and “thrombocytopenia”. Abstracts and reports from meetings were not included. Only articles published in English between 1980 and 2021 were included.

Classification and epidemiology

Heatstroke is the most severe stage of heat-related illnesses that carries a high mortality. Multiple organs, such as the central nervous system, kidney, and liver, are damaged, and hemostatic disorders frequently occur. Heatstroke can be classified into two types depending on its cause. Classic (non-exertional) heatstroke occurs in hot environments, leading to increased body temperature while exertional heatstroke occurs in strenuous exercise. Although HSIC can occur in both types of heatstroke, it is more frequent in non-exertional heatstroke depending on the severity.[13] Exertional heatstroke prevalence continues to decrease by educational campaigns among athletes, instructors, and emergency medical providers. The overall incidence of heatstroke and heat exhaustion in 2020 was 0.36 and 1.26 per 1000 United States military soldiers/years, the lowest annual rates during the 2016–2020 period.[14] In contrast, the prevalence of non-exertional heatstroke has increased with global warming, especially among vulnerable populations, such as children left in sun-exposed confined vehicles and elderly people in homes without air conditioning during heatwaves. Impairments in the physiological responses for maintaining the homeostasis against heat exposure should contribute to the increased prevalence of heatstroke among senior citizens. Bobb et al.[15] claimed periods of heat exposure were associated with the increased risk of hospitalization for fluid and electrolyte disorders, renal failure, urinary tract infection, septicemia, and heatstroke in older adults. The incidence of heatstroke between June and September in Japan was 37.5 per 100,000 (95% CI, 36.8–38.2) in 2015–2017 and 74.4 (95% CI, 72.7–76.1) in 2018.[16]

According to the Japanese cross-sectional survey, among 763 admitted patients with heat illness (non-exertional heatstroke 56.9% and exertional heatstroke 40.0%), the mortality was 4.6%. The median Japanese Association for Acute Medicine (JAAM) DIC score and Sequential Organ Failure Assessment (SOFA) score on admission were 1 (interquartile range [IQR], 0–2) and 4 (IQR, 2–6), respectively. JAAM-DIC was designed to detect acute DIC such as DIC in sepsis and trauma, with the diagnosis of DIC confirmed when the total score is four or more. Not surprisingly, these two indicators were associated with the patients’ outcome, and the areas under the receiver operating characteristic curves (AUC) to predict hospital mortality were 0.776 and 0.825, respectively. In this survey, 82.3% (632 cases) were defined as heatstroke, and 11.6% (73 cases) were diagnosed as having DIC. In the multivariate analysis, platelet count and Glasgow Coma Scale (GCS) were the independent predictors of mortality. Interestingly, there was no significant association between the body temperature at patient presentation and mortality or poor neurological outcome,[17] suggesting that the primary pathway to the deterioration may not be the direct heat-oriented injury but the sequential physical responses triggered by heat.

Mechanisms of organ dysfunction

Inflammation and coagulation are physiologic responses to injury. The connection between inflammation and coagulation that occurs in response to infectious diseases including bacterial sepsis and viral infections including COVID-19 occur also in HSIC.[18,19] In infections, mild hyperthermia improves outcomes by

diminishing viral replication, virion entry, and suppressing the genome transcription, resulting in the increased host defense against infection.[20] On the other hand, high fever damages host cellular and organ functions via the increased metabolic demands, dysregulated inflammation, and unbalanced hemostatic systems. It is assumed that rhabdomyocytes are especially susceptible to heat and heat-induced rhabdomyolysis, a common mechanism in non-infectious diseases such as malignant hyperthermia and heatstroke, with complex pathophysiologic mechanisms that underlay HSIC as described below.

Inflammatory responses

The magnitude of hyperthermia is considered the primary determinant of morbidity and mortality in heatstroke, although recent studies suggest a complex interplay of heat cytotoxicity, coagulation, and inflammation contributing to systemic injury[21] (Figure 1). The inflammatory consequences of heatstroke comprise humoral mediators including cytokines, chemokines, leukocytes, platelets, and endothelial cells and inflammatory activation may provoke multiorgan failure similar to other injuries. The inflammatory response produced by the thermal tissue injury is mediated by the molecular chaperone family of heat shock proteins, inflammasome, and varieties of pro- and antiinflammatory cytokines.[22–24] In infectious diseases, pathogen-associated molecular patterns elicit inflammatory reactions by binding to their specific receptors, pattern recognizing receptors. In heatstroke, not pathogen-derived but host cell-derived damage-associated molecular patterns (DAMPs) bind to the same receptor and upregulate inflammation through inflammasome formation.[25] Proinflammatory cytokines are important immune modifiers implicated in multiorgan failure, and experimental data demonstrated the increase of tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 in the non-exertional heatstroke model.[26] Heat injury also directly and indirectly induces cytotoxic effects via inflammation, leading to non-programmed necrosis and programmed cell death, i.e., apoptosis, necroptosis, and pyroptosis.[25,27] The necrotic and apoptotic cell death accompany activation in coagulation and inflammation, and the DAMPs such as DNA, histones, and high-mobility group box 1 protein (HMGB1) leaked from damaged or dead cells further propagate the systemic inflammation and coagulopathy.[23,28] These phenomena mimic those seen in sepsis that is often complicated with sepsis-induced coagulopathy.[18,29] Non-bacterial sepsis including viral hemorrhagic diseases and COVID-19 demonstrate coagulation disorders with similar mechanisms.[30] Non-infectious injury like trauma can also induce a similar type of coagulopathy where the thromboinflammatory interplay among neutrophils, platelets, and activated coagulation contributes to the microcirculatory injury.[31]

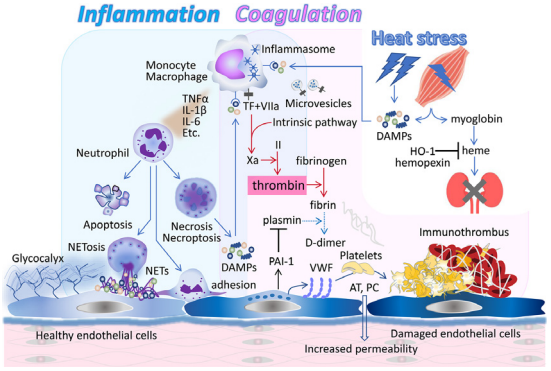

Figure 1. Pathophysiology of heatstroke

'Inflammation' and 'coagulation' are the two major factors that lead to detrimental organ dysfunction in heatstroke. Thermal tissue damage originated damage-associated molecular patterns (DAMPs) stimulates macrophage/monocyte to release cytokines (tumor necrosis factor α [TNFα], interleukin [IL]-1β, IL-6, etc.) via inflammasome production. At the same time, activated macrophages/monocyte express tissue factor (TF) and release microvesicles that initiate coagulation. The inflammatory cytokines activate neutrophils and induce various types of cell death such as apoptosis, necrosis/necroptosis, pyroptosis, and NETosis. Neutrophil extracellular traps (NETs) and adhesive neutrophil damage the endothelial cells and facilitate thrombosis. Extrinsic and intrinsic pathways collaboratively activate coagulation cascades that generate the critical mediator, 'thrombin.' Thrombin further activates both inflammation and coagulation and finally leading to the formation of 'inflammatory thrombus.' The endothelial damage results in decreased fibrinolysis via plasminogen activator inhibitor 1 (PAI-1) production and increased permeability and loss of natural anticoagulants such as antithrombin (AT) and protein C (PC). Damaged endothelial cell releases von Willebrand factor (VWF) that stimulates platelet aggregation. HO-1: heme oxygenase-1.

In exertional heatstroke, heavy muscle contraction associated with prolonged and strenuous physical stress together with or without external heat stress triggers thermoregulatory impairment and systemic inflammation. Although the thresholds are different depending on the genetic background,[32] the rhabdomyocytes are generally susceptible to heat injury and depletion of ATP. Excess heat production and energy loss cause activation of calcium-dependent neutral proteases and phospholipases, a mechanism that mimics the hyperactive calcium release channel-caused malignant hyperthermia.[33] As a result, there is eventual destruction of myofibrillar, cytoskeletal, and membrane proteins, followed by lysosomal digestion of fiber contents. Ultimately, the harmful substances including DAMPs and myoglobin spill out and induce multiple organ failures.[34] Myoglobin is cytotoxic, especially nephrotoxic through ferric oxide (Fe^{3+}) production, and levels over 8000 U/L were associated with the stage 2–3 acute kidney injury (AKI) in rhabdomyolysis.[35] In addition to this free iron-driven hydroxyl radical tubular damage,

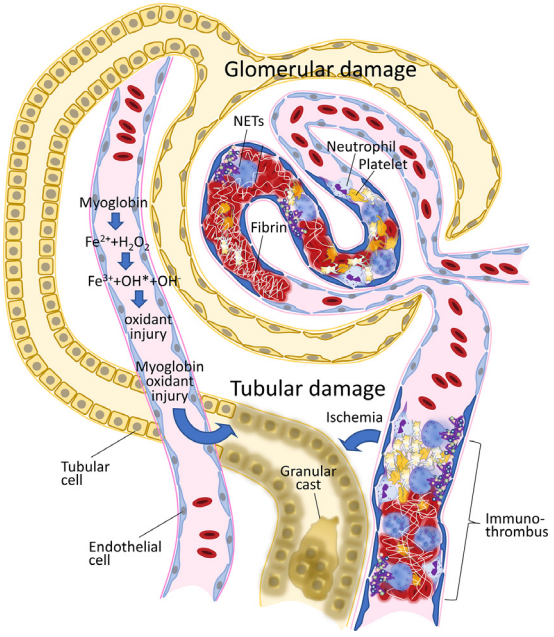

Figure 2. Mechanism of acute kidney injury in exertional heatstroke

In exertional heatstroke, activated inflammation and coagulation result in the formation of immunothrombus in the glomerulus. Neutrophil extracellular traps (NETs) ejection, activated platelets, damaged endothelial cells in addition to the activated coagulation systems play pivotal roles in thrombus formation. The obstruction of the renal artery leads to the ischemic change of the renal tubular system. Furthermore, myoglobin released from disrupted myocytes provides ferrous oxide (Fe^{2+}) and Fe^{2+} is oxidized to ferric oxide ($Fe3^{+}$), and finally generates hydroxyl radical. This oxidative potential is counteracted by physiological antioxidant molecules such as heme oxygenase 1 and hemopexin. However, massive myoglobin release leads to the increase of unquenched reactive oxygen species, and free radicals cause tubular cell injury. It has been suggested that heme and free iron –driven hydroxyl radicals are critical mediators of acute kidney injury in exertional heatstroke.

extracellular traps-mediated glomerular damage is suspected to play a significant role in kidney injury during heatstroke[36] (Figure 2).

Derangement of coagulation

Animal models of heatstroke provide important information. Diehl et al.[37] using a canine model of extracorporeal circulation of heated blood and reported thrombocytopenia, increased fibrin degradation products, prolonged clotting times, and evidence of spontaneous bleeding. Roberts et al.[38] used a baboon model of non-exertional heatstroke to examine inflammatory and hemostatic responses, and reported severe heatstroke elicited hypercytokinemia (IL-6), DIC, endothelial damage expressed by increased soluble thrombomodulin, and leukopenia with decreased neutrophils. The same group also reported hemostatic activation and fibrin formation with increased thrombin-antithrombin complexes and D-dimers due to activated tissue factor/factor VIIa pathway.[39] The pathological examination in these experiments noted microthrombosis with microbleeding, endothelial damage, and inflammatory cell migration, consistent with the coagulopathy of sepsis. Furthermore, immunohistology and ultrastructural analysis demonstrated increased apoptotic cells, tissue factor and phosphatidylserine expression, and leukocyte-platelet interactions. These findings support the idea that the organ damage in heatstroke is elicited through the mechanisms that mimic those of sepsis and other infectious diseases.

Heatstroke and DIC

DIC can be classified into hyperfibrinolytic, hypofibrinolytic, and balanced type, and the sepsis-induced coagulopathy and COVID-19-associated coagulopathy demonstrate hypo-fibrinolysis[40] (Figure 3). Hypofibrinolytic DIC often develops thrombotic complications due to excess production of plasminogen activator inhibitor 1 (PAI-1) presumably induced by endothelial damage, which is the natural response to the initial

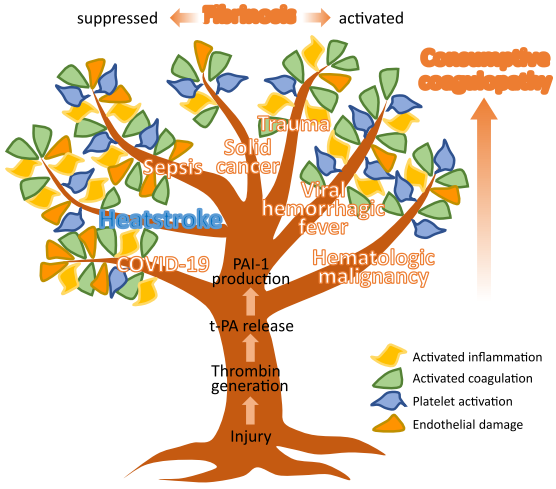

Figure 3. Classification of coagulopathy

Various diseases, including infectious to malignant diseases, accompany coagulopathy. Activated coagulation, inflammation, platelets, and endothelial damage are the main factors that induce thrombosis, and the contribution of each element varies depending on the underlying diseases. The common mechanisms are the initial thrombin generation caused by injuries followed by tissue plasminogen activator (t-PA) release. Plasminogen activator inhibitor 1 (PAI-1) production determines the fibrinolytic levels from hypo- to hyperfibrinolytic status. Heatstroke-induced coagulopathy is a type of hypofibrinolytic coagulopathy that can lead to the decompensated status, namely disseminated intravascular coagulation if severe enough.

release of tissue plasminogen activator mainly from endothelial cells.[29] Although the temporal fibrinolytic phase is also observed in HSIC, it is overridden by PAI-1 production. This type of dynamic change is commonly seen in trauma-induced coagulopathy and is understood as the universal result of injury. Consequently, increased level of PAI-1 is recognized in heatstroke, and the fibrinolytic state shifts to the hypofibrinolytic state with disease progress.[41] Above notion that HSIC is a hypofibrinolytic DIC is based primarily on the mechanisms of sepsis, COVID-19, and clinical cases of heatstroke, and may need further consideration.

DIC is commonly considered as 'consumptive coagulopathy' but, the original concept of DIC is 'systemic activation in coagulation', potentially with endothelial damage.[42] As described previously, the procoagulant reaction is a part of the host defense to a variety of insults, and it is recognized as a ubiquitous event. The phenotype differs depending on the underlying conditions, for example, COVID-19-associated coagulopathy does not usually fulfill the criteria of overt-DIC.[29] Platelet count, fibrinogen, and prothrombin time stay in the normal range in COVID-19; however, D-dimer and von Willebrand factor levels and mean platelet volume increase suggesting the presence of upregulated coagulation, endothelial damage, and platelet activation.[43] Similarly, even if the global coagulation markers do not change significantly, HSIC may be diagnosed by increased levels of sensitive coagulation biomarkers such as D-dimer, thrombin-antithrombin complex, and soluble thrombomodulin.[44]

Impairment of anticoagulant function

The impairment of anticoagulant function represented by low levels of antithrombin and protein C is recognized in sepsis, and their decreased levels are known to correlate with disease severity. These natural anticoagulants are consumed in response to the activated coagulation, suppressed production, and extravasation by increased permeability in sepsis.[45] Inflammation-induced endothelial damage leads to the cleavage of thrombomodulin and loss of antithrombin-bound glycocalyx. Similar mechanisms may exist in HSIC, with decreased protein C observed in the animal model of non-exertional heatstroke,[22,46] and reduction in plasma levels of antithrombin, proteins C and protein S reported in people during a pilgrimage to Mecca in response to the heat threat.[46] Since hepatic damage is commonly seen in HSIC, suppressed production may be more predominant compared to other causes.

Endothelial dysfunction

Endothelial damage is one of the key features in sepsis-induced coagulopathy and COVID-19-associated coagulopathy.[29] In such conditions, activated neutrophils release extracellular traps composed of procoagulant DNA and histones and form immunothrombus with aggregated platelets.[47] The damaged endothelial cell converts its usual antithrombotic state to the opposite side and facilitates intravascular clotting. In non-exertional heatstroke, the pathological examination in an animal model revealed the caspase-dependent endothelial cell apoptosis.[38,48] Tong et al.[49] have shown that the endothelial injury is expressed by increased circulating endothelial cells and elevated von Willebrand factor in a heatstroke model, and they suggested that the damage can be attributed to gut-derived septicemia. Similarly, Umemura et al.[50] reported the elevation of serum syndecan-1, one of the main components of the endothelial glycocalyx, in their non-exertional heatstroke model. In clinical studies, elevated circulating endothelial damage markers such as angiotensin-converting enzyme, soluble thrombomodulin, and von Willebrand factor have been reported.[51] Bouchama et al.[48] demonstrated increased levels of circulating intercellular adhesion molecule-1 (ICAM-1), endothelin, and von Willebrand factor along with the endothelial injury. Since the endothelial cell is not a simple barrier that separates blood and parenchymal cells but a vital interface that regulates the oxygenation, transportation, permeability, and thrombogenesis, endotheliopathy must play a critical role in the development of HSIC.

In exertional heatstroke, heme proteins i.e., myoglobin and free heme released into the circulation from rhabdomyocytes damage the vasculature. The mechanism of heme toxicity has not been clearly explained, but the involvement of lipid peroxidation causing mitochondrial damage in endothelial cells is suspected.[52] The described pathway can explain the glomerular endothelial damage seen in exertional heatstroke. It is known that microthrombi formation are commonly seen in hemolytic diseases such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. The heme-induced activation of coagulation system is suggested as a mechanism for the development of thrombotic events in these diseases.[53] Other than the direct heme toxicity, Okubo et al.[54] showed that myoglobin-derived heme activates platelets and stimulates extracellular trap release from macrophages that leads to AKI through intra-glomerular thrombosis in the rhabdomyolysis model. These findings suggest that endothelial damage is the primary mechanism in the development of AKI.

Biomarkers and diagnosis

Heatstroke follows extreme hyperthermia and is complicated by organ dysfunction. However, body temperature does not necessarily correlate with the severity. Central nervous system, liver, and kidney injury are terminal organ dysfunction considerations that define the outcome. Similar to other diseases, early detection of injury

with sensitive biomarkers is needed. Currently, there are no established clinical tests that can adequately evaluate the severity of heatstroke. Although coagulation and inflammation biomarkers are promising since they are important in the pathogenesis, thermal changes influence coagulation tests, hyperthermia if severe can intensify the enzymatic activity of coagulation factors, potentially reflecting heat stress.[55] In the primate model of hyperthermia, increased prothrombin time, activated partial thromboplastin time, D-dimer, and plasma IL-6 levels are reported, with decreased platelets.[56]

During the heatwave of August 2003 in Paris, heatstroke patients developed thrombocytopenia and prolonged prothrombin time, changes that were more evident in non-survivors.[57] However, it may not be a good idea to use the existing DIC criteria such as ISTH overt DIC and JAAM criteria. Pan et al.[58] reported the platelet counts were significantly lower in non-survivors (60.8×10^9/L vs. 128.4×10^9/L, $P< 0.001$), and AUC for predicting death was 0.767 with the cutoff value of 86.5×10^9/L. In this study, sensitivity and specificity were not high enough, with 68.0% and 36.8%, respectively. AUC for prothrombin time in predicting death was better and 0.874 with the best cutoff value of 18.5 s, and the sensitivity and specificity were 76.9% and 20.0%, respectively. Therefore, more specific and reliable biomarkers are needed. Proctor et al.[44] demonstrated increased D-dimer and soluble thrombomodulin levels in a severe non-exertional heatstroke mouse model. Bouchama et al.[59] compared the levels of thrombin-antithrombin complex, fibrin monomers, plasmin-antiplasmin complex, and D-dimer between heatstroke and heat-illness at hospital presentation. The median values were 16.5 μg/L vs. 3.5 μg/L, $P< 0.001$; 16 nM vs. 2 nM, $P< 0.001$; 3300 μg/L vs. 255 μg/L, $P< 0.001$; and 0.72 vs. 0.15 μg/mL, $P< 0.01$ respectively. Regarding IL-6, the level was significantly higher in patients with heatstroke, and the median value was approximately 150 pg/mL.[60] Limitations of biomarkers in heatstroke are the lack of optimal cutoff, and a scoring system to determine the severity of non-exertional heatstroke using coagulation and inflammatory markers.

In exertional heatstroke, D-dimer, cytokines, and myoglobin can be the predictor of organ dysfunction. Wu et al.[61] analyzed the data from 187 hospitalized patients, of which 82 (43.9%) had AKI. Multivariate logistic analysis showed that lymphocyte, neutrophil, D-dimer, and myoglobin $\geq$ 1.0 μg/mL were the independent risk factors for AKI. Concerning cytokines and chemokines, IL-6, interferon-γ, soluble IL-2 receptor, and monocyte chemoattractant protein 1 were positively correlated with Simplified Acute Physiology Score. Meanwhile, no correlation between either cytokines or chemokines and body temperature was recognized.[62] Another study reported body temperature, Glasgow coma scale, pH, lactate, platelet count, prothrombin time, fibrinogen, troponin I, aspartate aminotransferase, total bilirubin, and creatinine are the useful markers in evaluating the prognosis.[63] Thus, the biomarkers that reflect organ dysfunction and metabolic changes seem to be important, as well as coagulation tests in exertional heatstroke.

In the case of sepsis, it had been complained that the timing of diagnosing DIC by overt DIC criteria is too late and the International Society on Thrombosis and Haemostasis introduced the new criteria namely Sepsis-induced coagulopathy for the detection of coagulation disorder in the earlier timing.[18] Similarly, the timing and duration of HSIC differ depending on the diagnostic criteria and we yet to know the optimal timing of interventions. The authorized criteria have not been available, and we need to establish the criteria for helping the physicians to diagnose and decide the treatment of HSIC.

Treatments

Cooling and hydration are the fundamental treatments for heatstroke. However, once the trigger of HSIC is initiated, additional therapy may also be beneficial to control the sequential events. Since inflammation and coagulation play significant roles in the pathophysiology of heatstroke, antiinflammatory and anticoagulant therapies are rational adjuncts for treatment to explore. In addition, in the case of exertional heatstroke, the management of toxic substances spilled out from the rhabdomyocytes is also expected.

Treatment for non-exertional heatstroke

The effect of anticoagulation in heatstroke remains uncertain. Heparins are the most commonly used anticoagulant, but not routinely used for the treatment of HSIC unless there is clinical manifestation of thrombosis. In the same manner, there is no evidence that show the efficacy of low-molecular-weight heparin for HSIC. A rat heatstroke model reported that the infusion of high dose (5–20 mg/kg) activated protein C decreased the level of tumor necrosis factor-α and improved hypotension, cerebral ischemia, and hypoxia and prolonged the survival time.[64] On the contrary, intravenous infusion of low-dose activated protein C (24 μg/kg/hr) did not suppress coagulation and fibrinolytic disorder, platelet consumption in the heatstroke model of baboons.[46] Thrombomodulin is known to have anticoagulant and antiinflammatory effects, and Hagiwara et al.[65] observed decreased cytokine levels and HMGB1 in a rat model of heat stress by the treatment with recombinant thrombomodulin. The same group also reported the effect of antithrombin concentrate in a similar model.[66] In another study, recombinant thrombomodulin has been shown to improve liver injury, coagulopathy, and mortality in a heatstroke model in mice.[67] However, further study is warranted that addresses the controversial

core issues such as patient selection, dose, timing, and duration.

An observational clinical study based on a Japanese nationwide inpatient database indicated the potential efficacy of antithrombin and thrombomodulin. In this study, 1606 heatstroke-associated DIC patients were evaluated. Of these, 556 (35%) were treated either with antithrombin concentrate or recombinant thrombomodulin. The result showed significantly decreased in-hospital mortality in the treated patients compared to the untreated patients (risk difference −6.5%; 95% CI, −12% to −1.4%).[68] However, the robust evidence is still lacking and whether we should consider anticoagulant therapy on HSIC is presently uncertain.

Other than the anticoagulation, corticosteroids have been administered, although their efficacy has yet to be confirmed. In a baboon model of heatstroke, dexamethasone attenuated complement activation with increased arterial blood pressure, but the tissue injury and multiorgan system dysfunction were worse. A systematic review reported that corticosteroids administered before or at the onset of heat stress improved mortality and reduced organ dysfunction. The survival benefit was most significant when steroid administration preceded heat stress.[69] As for antipyretics, there is no evidence supporting the use of nonsteroidal antiinflammatory drugs in heatstroke.[70] Neural injury is a significant issue in heatstroke, and mesenchymal stem cell transplantation has been reported to improve neurological function, and its efficacy and molecular mechanisms have been intensively investigated.[71] Umemura et al.[50] examined the effects of the transplantation of bone marrow-derived mononuclear cells that secrete antiinflammatory proteins in a rat model. The treated animals demonstrated decreased tumor necrosis factor α, IL-6, and histone H3 and improved survival. The development of these types of new therapies is expected.

Treatment for exertional heatstroke

Initial thermo-control (rapid cooling), salt supplementation, and sufficient hydration to dilute circulating toxic substances and protect the kidney are the primary strategies for exertional heatstroke. Patients with core body temperatures decreased to 38 °C within 3 h of admission showed lower DIC rate and better survival than the patients with sustained hyperthermia over 3 h.[72] In addition to anticoagulation, administration of antithrombin concentrate can be used if the patient develops HSIC.[73] Difficulty developing an exertional heat stroke model, and the lack of prospective clinical studies to examine the effect of anticoagulation need to be further evaluated.

Other than the anticoagulation, since heme originated from the injured muscle promotes the organ damage, circumventing its toxicity may provide the organ protective effects. Heme oxygenase-1, also known as heat shock protein 32, is an inducible heme oxygenase that catabolizes heme. The effect of heme oxygenase-1 has been examined in animal models; however, a clinical trial has yet to be done.[74] Alternatively, hemopexin, another physiological heme-neutralizing protein may play a similar protective role, and its protective effects on vascular endothelial cells are reported.[75] Further research on the specific treatment targeting heme is needed.

Outstanding questions

- What are the major factors that facilitate the progression of organ damage in heatstroke?

Coagulation disorder and inflammation play important roles in the deterioration of organ damage via microcirculatory disturbance and cellular damage.

- Which biomarkers are expected to be useful for evaluating severity in heatstroke?

The platelet count, D-dimer, soluble thrombomodulin, and inflammation biomarkers such as interleukin-6 and histone H3 are promising markers for evaluating the severity of heatstroke.

Conclusions

Despite the hot summer, it was fortunate that the Tokyo Olympic Games held in midsummer 2021 ended without major medical complications; however, it is noteworthy that approximately 30% of the marathon runners withdrew during the race because of the intolerable heat. Global warming appears unavoidable, and the climatic circumstances will continue to change. Consequently, the heat-related events that occur in current tropical areas will likely be occurring in other zones in the future. The inflammatory and coagulopathic responses involved the pathogenesis of heatstroke, and their monitoring is helpful to evaluate the severity of heatstroke. Platelet count, D-dimer, and IL-6 are promising biomarkers for heatstroke. The establishment of diagnostic criteria using these new markers is expected. The specific inflammatory and anticoagulant therapies targeting HSIC are undergoing evaluation and are expected to mitigate the damage from heatstroke.

Declaration of interests

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Octapharma, and Leading Biosciences. ML has received grants and has participated in advisory boards of Novo-Nordisk, Eli Lilly, Asahi Kasei Pharmaceuticals America, and Johnson & Johnson. The other authors state that they have no conflicts of interest. JHL serves on the Steering Committees for Boehringer-Ingelheim, CSL Behring, Instrumentation Laboratories, Octapharma, and Leading Biosciences.

Contributors

Toshiaki Iba and Jerrold H. Levy wrote the draft. Jean Marie Connors and Marcel Levi reviewed and revised the manuscript. All authors read and approved the final manuscript.

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References

1 Allan RP, Barlow M, Byrne MP, et al. Advances in understanding large-scale responses of the water cycle to climate change. *Ann N Y Acad Sci*. 2020;1472:49–75.
2 Bouchama A, Knochel JP. Heat stroke. *N Engl J Med*. 2002;346:1978–1988.
3 Li D, Yuan J, Kopp RE. Escalating global exposure to compound heat-humidity extremes with warming. *Environ Res Lett*. 2020;15:064003.
4 Kaewput W, Thongprayoon C, Petnak T, et al. Inpatient burden and mortality of heatstroke in the United States. *Int J Clin Pract*. 2021;75:e13837.
5 Kuehn BM. Why farmworkers need more than new laws for protection from heat-related illness. *JAMA*. 2021. https://doi.org/10.1001/jama.2021.15454. Sep 8.
6 Sorensen C, Garcia-Trabanino R. A new era of climate medicine - addressing heat-triggered renal disease. *N Engl J Med*. 2019;381:693–696.
7 Johnson RJ, Wesseling C, Newman LS. Chronic kidney disease of unknown cause in agricultural communities. Reply. *N Engl J Med*. 2019;381:689.
8 Herath C, Jayasumana C, De Silva PMCS, et al. Kidney diseases in agricultural communities: a case against heat-stress nephropathy. *Kidney Int Rep*. 2017;3:271–280.
9 Roncal-Jimenez C, García-Trabanino R, Barregard L, et al. Heat stress nephropathy from exercise-induced uric acid crystalluria: a perspective on mesoamerican nephropathy. *Am J Kidney Dis*. 2016;67:20–30.
10 Hemmelgarn C, Gannon K. Heatstroke: thermoregulation, pathophysiology, and predisposing factors. *Compend Contin Educ Vet*. 2013;35:E4.
11 Huisse MG, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: the link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. *Crit Care Med*. 2008;36:2288–2295.
12 Hifumi T, Kondo Y, Shimazaki J, et al. Prognostic significance of disseminated intravascular coagulation in patients with heat stroke in a nationwide registry. *J Crit Care*. 2018;44:306–311.
13 Sithinamsuwan P, Piyavechviratana K, Kitthaweesin T, et al. Exertional heatstroke: early recognition and outcome with aggressive combined cooling—a 12-year experience. *Mil Med*. 2009;174:496–502.
14 Update: heat illness, active component, U.S. Armed Forces, 2020. *MSMR*. 2021;28:10–15.
15 Bobb JF, Obermeyer Z, Wang Y, Dominici F. Cause-specific risk of hospital admission related to extreme heat in older adults. *JAMA*. 2014;312:2659–2667.
16 Ogata S, Takegami M, Ozaki T, et al. Heatstroke predictions by machine learning, weather information, and an all-population registry for 12-hour heatstroke alerts. *Nat Commun*. 2021;12:4575.
17 Shimazaki J, Hifumi T, Shimizu K, et al. Clinical characteristics, prognostic factors, and outcomes of heat-related illness (Heatstroke Study 2017-2018). *Acute Med Surg*. 2020;7:e516.
18 Iba T, Connors JM, Nagaoka I, Levy JH. Recent advances in the research and management of sepsis-associated DIC. *Int J Hematol*. 2021;113:24–33.
19 Levy JH, Iba T, Olson LB, et al. COVID-19: thrombosis, thromboinflammation, and anticoagulation considerations. *Int J Lab Hematol*. 2021;43(Suppl 1):29–35.
20 Belon L, Skidmore P, Mehra R, Walter E. Effect of a fever in viral infections - the 'Goldilocks' phenomenon? *World J Clin Cases*. 2021;9:296–307.
21 Leon LR, Helwig BG. Heat stroke: role of the systemic inflammatory response. *J Appl Physiol*. 2010;109:1980–1988.
22 Yan YE, Zhao YQ, Wang H, Fan M. Pathophysiological factors underlying heatstroke. *Med Hypotheses*. 2006;67:609–617.
23 Dehbi M, Baturcam E, Eldali A, et al. Hsp-72, a candidate prognostic indicator of heatstroke. *Cell Stress Chaperones*. 2010;15:593–603.
24 Zhang ZT, Gu XL, Zhao X, et al. NLRP3 ablation enhances tolerance in heat stroke pathology by inhibiting IL-1β-mediated neuroinflammation. *J Neuroinflamm*. 2021;18:128.
25 Geng Y, Ma Q, Liu YN, et al. Heatstroke induces liver injury via IL-1β and HMGB1-induced pyroptosis. *J Hepatol*. 2015;63:622–633.
26 Lin XJ, Li YL, Mei GP, et al. Activated protein C can be used as a prophylactic as well as a therapeutic agent for heat stroke in rodents. *Shock*. 2009;32:524–529.
27 Li Y, Zhu X, Wang G, et al. Proteomic analysis of extracellular vesicles released from heat-stroked hepatocytes reveals promotion of programmed cell death pathway. *Biomed Pharmacother*. 2020;129: 110489.
28 Hirose T, Hamaguchi S, Matsumoto N, et al. Presence of neutrophil extracellular traps and citrullinated histone H3 in the bloodstream of critically ill patients. *PLoS ONE*. 2014;9: e111755.
29 Iba T, Warkentin TE, Connors JM, Levy JH. Therapeutic strategies in patients with coagulopathy and disseminated intravascular coagulation: awareness of the phase-dependent characteristics. *Minerva Med*. 2021. https://doi.org/10.23736/S0026-4806.21.07469-3.
30 Iba T, Levy JH, Levi M. Viral-induced inflammatory coagulation disorders: preparing for another epidemic. *Thromb Haemost*. 2021. https://doi.org/10.1055/a-1562-7599.
31 Moore HB, Gando S, Iba T, et al. Defining trauma-induced coagulopathy with respect to future implications for patient management: communication from the SSC of the ISTH. *J Thromb Haemost*. 2020;18:740–747.
32 Scalco RS, Snoeck M, Quinlivan R, et al. Exertional rhabdomyolysis: physiological response or manifestation of an underlying myopathy? *BMJ Open Sport Exerc Med*. 2016;2: e000151.
33 Yamazawa T, Kobayashi T, Kurebayashi N, et al. A novel RyR1-selective inhibitor prevents and rescues sudden death in mouse models of malignant hyperthermia and heat stroke. *Nat Commun*. 2021;12:4293.
34 Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med*. 2009;361:62–72.
35 Candela N, Silva S, Georges B, et al. Short- and long-term renal outcomes following severe rhabdomyolysis: a French multicenter retrospective study of 387 patients. *Ann Intensive Care*. 2020;10:27.
36 Bruchim Y, Ginsburg I, Segev G, et al. Serum histones as biomarkers of the severity of heatstroke in dogs. *Cell Stress Chaperones*. 2017;22:903–910.
37 Bruchim Y, Kelmer E, Cohen A, et al. Hemostatic abnormalities in dogs with naturally occurring heatstroke. *J Vet Emerg Crit Care*. 2017;27:315–324.
38 Roberts GT, Ghebeh H, Chishti MA, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol*. 2008;28:1130–1136.
39 Bouchama A, Al-Mohanna F, Assad L, et al. Tissue factor/factor VIIa pathway mediates coagulation activation in induced-heat stroke in the baboon. *Crit Care Med*. 2012;40:1229–1236.
40 Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. *J Intensive Care*. 2014;2:20.
41 Matsumoto H, Takeba J, Umakoshi K, et al. Successful treatment for disseminated intravascular coagulation (DIC) corresponding to phenotype changes in a heat stroke patient. *J Intensive Care*. 2019;7:2.

42 Taylor FB, Toh CH, Hoots WK, et al. Scientific subcommittee on disseminated intravascular coagulation (DIC) of the international society on thrombosis and haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86:1327–1330.

43 Comer SP, Cullivan S, Szklanna PB, et al. COVID-19 induces a hyperactive phenotype in circulating platelets. *PLoS Biol*. 2021;19: e3001109.

44 Proctor EA, Dineen SM, Van Nostrand SC, et al. Coagulopathy signature precedes and predicts severity of end-organ heat stroke pathology in a mouse model. *J Thromb Haemost*. 2020;18:1900–1910.

45 Iba T, Kidokoro A, Fukunaga M, et al. Association between the severity of sepsis and the changes in hemostatic molecular markers and vascular endothelial damage markers. *Shock*. 2005;23:25–29.

46 al-Mashhadani SA, Gader AG, al Harthi SS, et al. The coagulopathy of heat stroke: alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah. *Blood Coagul Fibrinolysis*. 1994;5:731–736.

47 Ng H, Havervall S, Rosell A, et al. Circulating markers of neutrophil extracellular traps are of prognostic value in patients with COVID-19. *Arterioscler Thromb Vasc Biol*. 2021;41:988–994.

48 Bouchama A, Hammami MM, Haq A, et al. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med*. 1996;24:1173–1178.

49 Tong H, Wan P, Zhang X, et al. Vascular endothelial cell injury partly induced by mesenteric lymph in heat stroke. *Inflammation*. 2014;37:27–34.

50 Umemura Y, Ogura H, Matsuura H, et al. Bone marrow-derived mononuclear cell therapy can attenuate systemic inflammation in rat heatstroke. *Scand J Trauma Resusc Emerg Med*. 2018;26:97.

51 Shieh SD, Shiang JC, Lin YF, et al. Circulating angiotensin-converting enzyme, von Willebrand factor antigen and thrombomodulin in exertional heat stroke. *Clin Sci*. 1995;89:261–265.

52 Higdon AN, Benavides GA, Chacko BK, et al. Hemin causes mitochondrial dysfunction in endothelial cells through promoting lipid peroxidation: the protective role of autophagy. *Am J Physiol Heart Circ Physiol*. 2012;302:H1394–H1409.

53 Hopp MT, Imhof D. Linking labile heme with thrombosis. *J Clin Med*. 2021;10:427.

54 Okubo K, Kurosawa M, Kamiya M, et al. Macrophage extracellular trap formation promoted by platelet activation is a key mediator of rhabdomyolysis-induced acute kidney injury. *Nat Med*. 2018;24:232–238.

55 Levi M. Hemostasis and thrombosis in extreme temperatures (hypo- and hyperthermia). *Semin Thromb Hemost*. 2018;44:651–655.

56 Bouchama A, Roberts G, Al Mohanna F, et al. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. *J Appl Physiol*. 2005;98:697–705.

57 Mégarbane B, Résière D, Shabafrouz K, et al. Descriptive study of the patients admitted to an intensive care unit during the heat wave of August 2003 in France. *Presse Med*. 2003;32:1690–1698.

58 Pan ZG, Shao Y, Liu YN, et al. Relationship between early coagulability parameters at admission and outcome in patients with severe heatstroke. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2013;25:725–728.

59 Bouchama A, Bridey F, Hammami MM, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost*. 1996;76:909–915.

60 Hammami MM, Bouchama A, Al-Sedairy S, et al. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med*. 1997;25:1314–1319.

61 Wu M, Wang C, Liu Z, et al. Clinical characteristics and risk factors associated with acute kidney injury inpatient with exertional heatstroke: an over 10-year intensive care survey. *Front Med*. 2021;8: 678434.

62 Lu KC, Wang JY, Lin SH, et al. Role of circulating cytokines and chemokines in exertional heatstroke. *Crit Care Med*. 2004;32:399–403.

63 Yang MM, Wang L, Zhang Y, et al. Establishment and effectiveness evaluation of a scoring system for exertional heat stroke by retrospective analysis. *Mil Med Res*. 2020;7:40.

64 Chen CM, Hou CC, Cheng KC, et al. Activated protein C therapy in a rat heat stroke model. *Crit Care Med*. 2006;34:1960–1966.

65 Hagiwara S, Iwasaka H, Goto K, et al. Recombinant thrombomodulin prevents heatstroke by inhibition of high-mobility group box 1 protein in sera of rats. *Shock*. 2010;34:402–406.

66 Hagiwara S, Iwasaka H, Shingu C, et al. High-dose antithrombin III prevents heat stroke by attenuating systemic inflammation in rats. *Inflamm Res*. 2010;59:511–518.

67 Kawasaki T, Okamoto K, Kawasaki C, Sata T. Thrombomodulin improved liver injury, coagulopathy, and mortality in an experimental heatstroke model in mice. *Anesth Analg*. 2014;118:956–963.

68 Ohbe H, Isogai S, Jo T, et al. Treatment with antithrombin or thrombomodulin and mortality from heatstroke-induced disseminated intravascular coagulation: a nationwide observational study. *Semin Thromb Hemost*. 2019;45:760–766.

69 Walter E, Gibson OR. The efficacy of steroids in reducing morbidity and mortality from extreme hyperthermia and heatstroke-a systematic review. *Pharmacol Res Perspect*. 2020;8:e00626.

70 Lott C, Truhlář A, Alfonzo A, et al. European resuscitation council guidelines 2021: cardiac arrest in special circumstances. *Resuscitation*. 2021;161:152–219.

71 Hsuan YC, Lin CH, Chang CP, et al. Mesenchymal stem cell-based treatments for stroke, neural trauma, and heat stroke. *Brain Behav*. 2016;6:e00526.

72 Sithinamsuwan P, Piyavechviratana K, Kitthaweesin T, et al. Exertional heatstroke: early recognition and outcome with aggressive combined cooling—a 12-year experience. *Mil Med*. 2009;174:496–502.

73 Pechlaner Ch, Kaneider NC, Djanani A, et al. Antithrombin and near-fatal exertional heat stroke. *Acta Med Austriaca*. 2002;29:107–111.

74 Wen YT, Liu TT, Lin YF, et al. Heatstroke effect on brain heme oxygenase-1 in rats. *Int J Med Sci*. 2015;12:737–741.