Review Article Open Access

Hyperthermia-Induced Coagulopathy: Understanding Platelet Activation and Management in Heat-Related Illness

Received date: 12th June 2024
Review date: 19th August 2024
Accepted date: 20th September 2024

Waqas Ahmed, *BS, M. Phil*
PhD Scholar, Department of Translational Medicine, Shenzhen University, China

*Corresponding Author: Waqas Ahmed (**w_ahmed099@gmail.com**)

Cite this article:
Ahmed S. Hyperthermia-Induced Coagulopathy: Understanding Platelet Activation and Management in Heat-Related Illness. AJMAHS. 2024; 2(3):20-28

ABSTRACT

Heat-related illnesses have become widespread, and they pose a high concern at the wake of global warming. They cause systemic inflammation and coagulopathy by the activation and injury of leukocytes, platelets, and vascular endothelial cells. Hyperthermia, a state of elevated body temperature, will have direct effects on platelet function and possibly cause cell injury. More importantly, platelet activation is induced by heat stress through the induction of coagulation, enhanced inflammation, and increased expression of cytokines and heat shock proteins. Interactions between leukocytes and endothelial cells are significantly affected in hot conditions, and these affect how platelets are regulated. Heat-induced coagulopathy often evolves into DIC, and DIC may result in multiple organ failure, thereby exacerbating bleeding. For this reason, it is crucial to measure platelet numbers, prothrombin time (PT), and DIC scores, along with the markers of organ dysfunction including Glasgow Coma Scale, creatinine, and bilirubin level. Despite the burgeoning menace, therapeutics targeting platelets remain scant, and there is no well-established treatment in use thus far. This review briefly discusses the latest insights regarding the function of platelets in pathophysiology, diagnostic analysis, and therapy of heat-associated illnesses.

Keywords: Coagulation, hyperthermia, platelets, inflammation, organ failure.

INTRODUCTION

What once were the early spring landscapes, the rich autumn colors, and beautifully seasonal changes from warm to cool are all rapidly being erased. Over the past 190 years, every state in the U.S. has warmed by significant degrees, and what once was understood as the four distinct seasons are increasingly losing their crisp definition. The average annual temperatures across states have been rising far beyond 1.5 °C, thus altering both the visual beauty of the seasonal change and the environmental conditions that depend on which a living organism survives upon [1]. This warming trend imposes severe threats to health, with the Centers for Disease Control and Prevention warning that "climate change, combined with other natural and human-made stressors, impacts human health in various ways. Some current health risks will worsen, and new threats will arise"

Consequently, along with coagulopathy, heat-related illness cases are increasing as climate continues to change. Severe cases were also associated with DIC, with an incidence rate of 48%[2,3]. Furthermore, DIC associated with heatstroke is a predictor for organ failure and mortality[4]. While the exact mechanisms of coagulopathy in heatstroke are not clearly outlined, it is generally realized that inflammation, disruption of blood clotting, damage to vascular endothelial cells, and activation of leukocytes and platelets play pivotal roles[5,6]. The review will be focused on understanding the pathophysiology of heat-related illnesses with emphasis on platelet activation.

2. Temperature Effect on Platelets

Such an influence of hyperthermia on the activation of platelets has yet to be studied. Preliminary *ex vivo* research reveals that high temperatures can well inhibit the activity of platelets. For example, Rao et al. reported that if PRP from donors with normal status was placed for one hour into a temperature environment below 43°C there was no change in

the level of structure of the platelets or in their reaction to agonists[7]. But, platelets heated at 43°C for 60 minutes were no longer aggregable. Likewise, Gader et al. calculated the outcome of heat on PRP, heating samples between 38-45°C and then triggering accumulation with adenosine diphosphate (ADP)[8]. According to authors, the aggregated volume enhanced as the temperature was raised up to 43°C then went to peak level at 44°C. This signifies that aggregation increases with heat up to some point when the function deteriorates.

Contrarily, Al-Mashhadani et al. have studied the PRP from 34 heatstroke patients and showed that aggregation of platelets due to adrenaline, collagen, arachidonic acid, and ristocetin were substantially reduced[9]. Aggregation due to ADP was variable; it increased in 12 and decreased in 16 subjects, while being within normal limits in 6, indicating inconstancy of the platelet response in the cases of heatstroke. As for the platelet morphology, White another study has indicated that high temperatures caused the platelets to lose their normal discoid shape, swell in irregular manners, and move the organelles towards the center, where they frequently fused[10]. Platelet structure and function seem closely related to heat tolerance. Accordingly, the camels' platelets, that are relatively smaller than in humans, have demonstrated higher heat resistances. Differently, the camel platelets structural lack an open canalicular system and have bigger alpha granules that may explain their more tolerance to heat[11].

Al Ghumlas et al. found that human platelets exposed to temperatures between 43°C to 45°C had structural changes that impaired their ability to aggregate and spread while camel platelets were not affected[12]. Besides, Wang et al. investigated PRP at 40 and 42°C, and they discovered that heat exposure would activate platelet apoptosis through mechanisms such as mitochondrial membrane depolarization, caspase-3 mediated cleavage of gelsolin, and phosphatidylserine exposure[13]. The dysfunction of heat-exposed platelets has been presumed to happen from cytoskeletal protein disruption that is critical for pseudopod formation, shape changes, and adhesion molecules expression, like glycoprotein (GP) IIb-IIIa[8]. The temperatures of 43°C or higher severely impair platelet function and decrease the capacity of platelets to aggregate, contributing to coagulopathy in the heatstroke.

3. Regulators of Heat-Induced Platelets

3.1. Heat Shock Proteins (HSPs)

It has been proven that an exposure to heat tension can excite aggregation of platelets by the activation of HSPs as these play a big role in the structure and function of the platelet. Also, in terms of intracellular HSP27, research by Polanowska-Grabowska et al. indicates its involvement in the regulation of actin polymerization[14]. It is a critical process in platelet shape transformation and subsequent aggregation. Being evolutionarily conserved as critical mediators of cellular defense against various stresses, including thermal challenges, HSPs are located both inside and outside the cells and act as key regulators of platelet function[15]. Suzuki et al. targeted the particular role of HSP72, during thrombi formation and found that HSP72 added to platelet activators like low concentrations of ADP and collagen stimulated platelet aggregation, effect, which were impaired by the presence of anti-HSP72 antibodies[16]. Additionally, inhibition of HSP70 in platelets and was demonstrated to interfere with both platelet aggregation and granule secretion[17]. Jackson et al. described that inhibition of HSP40, HSP70, and HSP90 was also accompanied by a decrease in the level of GP IIb/IIIa and an attenuation of shape changes induced by fibrinogen in platelets; inhibition of HSP40 or HSP90 impaired aggregation selectively[18]. These results demonstrate that HSPs are indeed implicated in platelet activation. Yet, HSPs are generally associated with thermotolerance because HSPs are molecular chaperones. For example, in camels, they believed HSPs assist these animals in coping with extreme heat[19]. A small HSP known as HSP20 is highly induced under heat stress and known to be protective of cardiac function and capable of augmenting platelet aggregation[20]. Nawa et al. showed that the dissociated form of HSP20 inhibited receptor-mediated calcium influx and prevented platelet aggregation[21]. McLemore et al., reported recombinant HSP20 to have reduced vasospasm and platelet aggregation[22]. Varied action of differential HSPs on thermal stress indicated that some enhance the activation of platelets, whereas others repress. Thus, the net effect of platelets under thermal stress may

depend upon the balance between these opposing HSP actions.

Another interesting intracellular function of HSPs is the inhibition of apoptosis in monocytes. In an *in vitro* study, it was shown that monocytes could phagocytose platelets, and HSP70 from platelets mediated the inhibition of monocyte apoptosis through downregulation of caspase-9 and caspase-3. Of particular importance, neither supernatants of platelets nor granule contents influenced monocyte senescence, indicating the protective effect is specifically linked to intracellular HSP70[23].

3.2. Cytokines and the Molecular Configurations

Multiple cytokines of the inflammation, i.e., interferon-γ, interleukin-6 (IL-6), tumor necrosis factor (TNF) α, and interleukin-1β, are created due to stress of heat. Once initiated, other responses of inflammations are triggered, including fever, increased white blood cell count, and activation of leukocytes, endothelial cells, and platelets. This chain affects both the innate immune system and coagulation cascade[3]. The over-exuberant inflammatory response may lead to damage-associated molecular patterns (DAMPs) release by cells enduring apoptosis or other forms of cell death, such as pyroptosis[27]. These include some key DAMPs, such as HSP72 and high mobility group protein B1 (HMGB1) secreted from cells in dying state, which interact with pattern recognition receptors (PRRs) and Toll-like receptors 4 (TLR-4)[28]. The binding of such ligands to PRRs initiates transduction of signaling pathways that activate NF-κB, which modulates responses of inflammation. There is accumulating evidence that heme released from rhabdomyolysis, an event in exertional heatstroke, activates platelets through the engagement of GP VI and C-type lectin-like receptor-2 (CLEC-2), which are both hemin receptors in the exertional heatstroke[29]. Such inflammatory pathways started by heat cause a additional amplification of inflammatory responses and injury in cells[27]. Some heat shock proteins (HSPs) also inhibit these inflammatory processes and are identified as RAMPs[30].

Apart from hemostatic functions, platelets takes part in tissue reorganization and remodeling of tissues by providing inflammatory responses and activation of immune reactions in heat-associated illnesses. The activated platelets likewise participate in controlling apoptosis after tissue injury and maintaining endothelial integrity for overall biological hemostasis[31]. Thus, platelets play an important part in modulating inflammation and supporting recovery in heat-associated disorders.

4. Cellular Integration in Heat-Associated Illness

The cells in vascular endothelium are sensitive to the heat and cause blood vessels to enter a condition of thrombosis. This is mainly through the release of procoagulant factors, such as von Willebrand factor (vWF) and factor VIII. This causes the impairment of anticoagulant function and augments the expression of adhesion molecules[32]. According to Bouchama et al., vWF, endothelin-1, and endothelial cell-derived intercellular adhesion molecule-1, were significantly raised in patients with heatstroke before the cooling intervention[33]. Angiotensin-converting enzyme (ACE), soluble S-selectin, and thrombomodulin levels in circulation are reportedly increased as well. In addition, CD11b (MAC-1) and β2-integrins expression in both endothelial cells and leukocytes increases, suggesting that the interaction of endothelial cells with leukocytes is enhanced during a heatstroke attack[34].

Heat-induced inflammation enhances the neutrophil-platelet interaction even further. Through their azurophilic granules, neutrophils have released neutral serine proteases, such as elastase and cathepsin G, known to enhance these interactions[35]. Furthermore, Sylman et al. described an increased adhesion of platelets to endothelium in culture by using microfluidic channels; endothelial cells triggered by heat thereby activate further platelet adhesion, secretion of vWF and extracellular matrix components[36]. Such in vivo studies, conducted by Roberts et al., revealed enhanced tissue factor (TF) and vWF staining on the endothelial surface along with leukocyte-platelet aggregation within the setting of heatstroke in a primate model[37]. Their study revealed widespread apoptosis in a hematopoietic and parenchymal cells, significant thrombosis along with concomitant bleeding, transmigrated white blood cells, and disrupted endothelial integrity. Apart from direct cell-to-cell contacts, thermal stress also induces the shedding of microvesicles (MVs) from platelets as part of

cell-to-cell communication. Human volunteers subjected to heat stress caused by exercise show an increase in CD41 (GP IIb-IIIa)-+ platelet microvesicles[38]. Platelets along with other cells strengthen their intercellular contacts after thermal trauma through both direct and indirect mechanisms. Huisse et al. performed a study, analytically examining heatstroke patients during the heat wave during 20023 in Paris, comparing them to patients with healthy control and severe sepsis to investigate links between significant inflammation and coagulation during heatstroke[3]. A substantial decline in platelet count was found among patients diagnosed with heatstroke, along with alterations in the cellular origins of MVs distribution, these including significantly reduced amounts of platelet-derived MVs (AV/CD41) compared to normal controls, contributed by the procoagulant activity detected among those diagnosed with heatstroke. However, such a quantitative decrease of circulating platelet-derived MVs, probably because of their accumulation in organs, may associate with multi-organ failure like that observed in sepsis[39].

5. Laboratory Characteristics of Heat-Associated Illness

The postmortem pathological studies in the patients of heatstroke have identified the complex cytotoxic effects of heat. Several case reports have reported cases of exertional heatstroke[40-42]. The main cause of death was DIC, characterized by coagulation necrosis, microthrombosis, and rhabdomyolysis of various organs. Numerous patients developed complications similar to hemorrhagic syndrome resembling consumption coagulopathy scenario. It was also found that patients with heatstroke with bleeding had an increased mortality and shock incidence than those without[43]. Zhou et al. studied pathological changes in fatalities due to classic (non-exertional) heatstroke[44]. They mentioned that there were some pronounced systemic inflammatory responses, coagulation pathway activation, and fibrinolysis with massive hemorrhagic diathesis and microthrombosis. Another study about histopathological alterations within a baboon model of heatstroke was performed by Roberts et al., according to whom thrombosis, vascular congestion, hemorrhage, and an increase of inflammation cells existed throughout different organs[37]. For example, they documented the presence of intracapillary thrombi and triggered platelets interrelating with neutrophils and endothelial cells within the renal glomeruli.

As mentioned before, heatstroke is generally characterized by endothelial injury and microvascular thrombosis. In normal conditions, endothelial cells work to maintain smooth flow of blood by controlling platelet and leukocyte adhesion. Healthy endothelial cells constrain the activation of platelets by covering surface with a glycocalyx and releasing substances that will prevent blood cell adhesion; these include nitric oxide and prostaglandin I2. When, however, endothelial cells are damaged by heat, they facilitate cellular adhesion by releasing vWF and expressing components of the extracellular matrix[6]. The microscopic examinations of small blood vessels through light and electron microscopy reveal the existence of DIC by the form of microthrombosis and the existence of bleeding. Ultrastructural analyses are wanting to focus the seriousness of endothelial cell damage and the participation of platelets. These microthrombi are comprised significantly of platelets. Some structures resemble vesicles and granules which are commonly related to platelets. They stick to injured endothelial surfaces and are believed to initiate clot cascade. Though, such structural variations were extremely variable concerning their shape, size, and composition, related to the stage of the illness as well as the timing of autopsy[45].

In a murine model of heatstroke exposed to 39.5 °C, the researchers observed depressed platelet counts, with elevated volume of platelets, with endothelium damage and coagulation activation markers: high D-dimer, but also soluble thrombomodulin levels. Organ damage, as the study described, may have been enhanced by fibrinolytic suppression, especially since D-dimer levels were low in animals with severe organ injury[46]. In humans, hyperthermia affects the coagulation system, central nervous system, kidneys, and liver. In an observational study by a Japanese medical group with 1,799 patients diagnosed with heat-related illnesses, it was determined that there were positive correlations between severity of the illness and the levels of alanine aminotransferase (ALT), creatinine, and blood urea nitrogen (BUN), but negatively correlated by the severity with the platelets. It was noted in the study that severe cases of the heat-related illness were commonly associated with coagulation disorders[47]. Another

multicenter observational study from Japan reported that higher scores of Glasgow Coma Scale and lower counts of platelets were independent predictors of mortality. In this study, the AUC of DIC score, for JAAM criteria established for mortality prediction, was determined to be 0.776[48]. Recently, Hifumi et al. studied 705 heatstroke patients and found that the presence of DIC was independently associated with a higher mortality[49].

Recently, a multicenter retrospective study analyzing 163 cases of heatstroke reported significant correlations of platelet count, APTT, and PT-INR with patient outcomes. The median platelet count for survivors was noted as 145 (95% CI: 45–195) × 10^9/L in comparison to those who did not survive 38 (95% CI: 24–69) × 10^9/L[50]. Zhong et al. also studied the relationship of the platelet counts of patients suffering from heatstroke with the outcome, reviewing in total 186 patients with normal counts in 120 (64.5%) and low counts in 66 (35.5%)[51]. This study proved that the reduction of platelet counts correlated well with the level of severe organ dysfunction, particularly coagulation, liver, and kidney function. These findings suggest that both counts of platelets and activation of coagulation point out the indicator of thermal damage and its role in the hyperthermia pathophysiology. Min et al. evaluated heatstroke-induced changes in coagulopathy with the help of viscoelastic testing in 106 patients[52]. They further classified patients into hypercoagulable and hypocoagulable groups with the help of the activated clotting time. Results showed that 34 were hypercoagulable (32.1%), 44 were hypocoagulable (41.5%), and 28 did not have obvious coagulopathy at admission. Those with hypocoagulability had more multisystem organ failure and mortality. Jin et al. utilized intravital microscopy to examine the kinetics of blood flow in heat-stressed mice at 41°C[53]. The authors detected high pulmonary permeability and a slowing down in blood flow that did not correlate with the presence of thrombosis in the model. However, el-Sabban et al. observed thrombi formation in venules and arterioles in animal model stressed at 45°C[54].

6. Relationship with Other Coagulopathies

Coagulopathy typically arises as an aftermath of sepsis; rather, it is one of the most prevalent complications in patients with sepsis-induced coagulopathy. The pathophysiological characteristics of SIC include diffuse microvascular thrombosis followed by organ failure[55]. Organ failure and fibrinolysis in the presence of coagulopathy typically characterize DIC, which is a commonly associated complication with DIC. These are consequently dictated by the nature of the disease, the degree, and the stage of the disorder[6]. In the initial stages of trauma or hematologic malignancy, coagulopathy typically presents as severe hemorrhage from profound thrombocytopenia and depletion of other clotting factors, combined with increased fibrinolysis[56-57]. On the other hand, in SIC, because of overproduction of plasminogen activator inhibitor-1 (PAI-1) from endothelial cells and breakdown of plasminogen by DNA-bound elastase from NETs, fibrinolysis is significantly decreased[58]. This decrement in formation of plasmin eventually reduces fibrinolysis. This fibrinolytic defect is important in enabling microthrombosis that eventually leads to multiple organ failure and gives a thrombosis-dominant form of coagulopathy[59]. In heatstroke-induced coagulopathy, it is well established that, in addition to inhibited fibrinolysis caused by the increased production of PAI-1 from damaged endothelial cells, platelet function and coagulation are severely compromised, and a clinical presentation that often involves both thrombosis and bleeding occurs with heatstroke-induced coagulopathy[60].

7. Management of Heatstroke Targeting Platelets

There are few studies on the use of antiplatelet therapy in cases of heatstroke. Chen et al. recently conducted an animal model study on the influence of aspirin on the synthesis of interleukin-1β, which can serve as a therapeutic agent in cases of heatstroke[61]. The study made use of rats to induce heatstroke by subjecting them to a high ambient temperature of 41°C along with 65% humidity and then treated rats with the aspirin. The findings suggested that aspirin pre-treatment might prevent heatstroke by improving heat and fatigue tolerance through systemic down-regulation of NO synthase and IL-1β activity. Since the study did not focus on the effects of aspirin as an antiplatelet, mechanisms would be relevant because platelets release a variety of cytokines, such as

IL-1β[62]. The dexmedetomidine, has properties related to sedation, analgesic-sparing, stabilization of cardiovascular system, and reducing delirium. In rat models of heatstroke, dexmedetomidine protected the endothelial glycocalyx and reduced mortality rates[63]. The direct effects of dexmedetomidine on platelets are not known, but it is believed to decrease the platelet adhesion to the endothelium. A study by Shi et al. focused on HSP27 inhibition of actin polymerization and its protective effects against ischemia/reperfusion-induced endothelial injury[64]. Although it was not a study related to heatstroke, HSP27 may protect against the endothelium-platelet and endothelial damage induced by heat. In summary, there is no conclusive confirmation for antiplatelet therapy in heat disorder management; the approach may hold promise for further investigation.

CONCLUSION

Platelets have a significant role in progression of heat-associated conditions. For instance, some of the differences in the heat tolerance between humans and camels may be due to their platelets' differing capacity to respond to heat stress. In heatstroke, microthrombosis accompanied by hemorrhage is a common pathological finding, and platelets are an integral constituent of the thrombus that ensues. It often presents because there is clotting as well as bleeding, due to impaired coagulation and reduced platelet activity. Platelets are involved, but thus far, the effectiveness of antiplatelet therapy for heat-related disorders has not been proven.

REFERENCES

1. Young SS, Young JS. Overall warming with reduced seasonality: temperature change in New England, USA, 1900–2020. Climate. 2021;9(12):176.
2. Hemmelgarn C, Gannon K. Heatstroke: thermoregulation, pathophysiology, and predisposing factors. Compend Contin Educ Vet. 2013;.E4.
3. Huisse MG, Pease S, Hurtado-Nedelec M. 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;36:2288–95.
4. 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;44:306–11.
5. Bouchama A, Abuyassin B, Lehe C, et al. Classic and exertional heatstroke. Nat Rev Dis Primers. 2022;8(1):8.
6. Iba T, Connors JM, Levi M, Levy JH. Heatstroke-induced coagulopathy: biomarkers, mechanistic insights, and patient management. EClinicalMedicine. 2022;44:101276.
7. Rao GH, Smith CM II, Escolar G, White JG. Effects of heat on platelet biochemistry, structure, and function. J Lab Clin Med. 1993;122(4):455–64.
8. Gader AM, Al-Mashhadani SA, Al-Harthy SS. Direct activation of platelets by heat is the possible trigger of the coagulopathy of heat stroke. Br J Haematol. 1990;74(1):86–92.
9. Al-Mashhadani SA, Gader AM, Al-Harthi S. The role of platelets in the coagulopathy of heatstroke: a study of platelet aggregation in heatstroke patients during the
10. Makkah pilgrimage (Haj) to Makkah. Platelets. 1997;8(1):37–42.
11. White JG. Effects of heat on platelet structure and function. Blood. 1968;32(2):324–35.
12. Gader AG, Ghumlas AK, Hussain MF, et al. The ultrastructure of camel blood platelets: a comparative study with human, bovine, and equine cells. Platelets. 2008;19(1):51–8.
13. Al Ghumlas AK, Abdel Gader AG, Hussein MF, et al. Impact of heat on the structure and functions of camel platelets: a comparison with human results. Platelets. 2008;19(3):163–71.
14. Wang Z, Shi Q, Li S, et al. Hyperthermia causes platelet apoptosis and shedding of glycoprotein ibalpha ectodomain. Platelets. 2010;21(3):229–37.
15. Polanowska-Grabowska R, Gear AR. Heat-shock proteins and platelet function. Platelets. 2000;11(1):6–22.
16. Kozawa O, Matsuno H, Niwa M, et al. HSP20, low-molecular-weight heat shock-related protein, acts extracellularly as a regulator of platelet functions: a novel defense mechanism. Life Sci. 2002;72(2):113–24.
17. Suzuki H, Kosuge Y, Kobayashi K, et al. Heat-shock protein 72 promotes platelet aggregation induced by various platelet

activators in rats. Biomed Res. 2017;38(3):175–82.
18. Rigg RA, Healy LD, Nowak MS, et al. Heat shock protein 70 modulates platelet integrin activation, granule secretion and aggregation. Am J Physiol Cell Physiol. 2016;310(7):C568-C575.
19. Jackson JW, Rivera-Marquez GM, Beebe K, et al. Pharmacologic dissection of the overlapping impact of heat shock protein family members on platelet function. J Thromb Haemost. 2020;18(5):1197–209.
20. Hoter A, Rizk S, Naim HY. Cellular and molecular adaptation of Arabian camel to heat stress. Front Genet. 2019;10:588.
21. Li F, Xiao H, Zhou F, et al. Study of HSPB6: insights into the properties of the multifunctional protective agent. Cell Physiol Biochem. 2017;44(1):314–32.
22. Niwa M, Kozawa O, Matsuno H, et al. Small molecular weight heat shock-related protein, HSP20, exhibits an anti-platelet activity by inhibiting receptor-mediated calcium influx. Life Sci. 2000;66(1):PL7-12.
23. McLemore EC, Tessier DJ, Flynn CR, et al. Transducible recombinant small heat shock-related protein, HSP20, inhibits vasospasm and platelet aggregation. Surgery. 2004;136(3):573–8.
24. Lang D, Dohle F, Terstesse M, et al. Down-regulation of monocyte apoptosis by phagocytosis of platelets: involvement of a caspase-9, caspase-3, and heat shock protein 70-dependent pathway. J Immunol. 2002;168(12):6152–8.
25. Espersen GT, Elbaek A, Ernst E, et al. Exercise-induced changes in cytokines and subpopulations of lymphocytes in human peripheral blood. APMIS. 1990;98:395–400.
26. Robins HI, Kutz M, Wiedemann GJ, et al. Induction of cytokines in humans by 41.8 degrees C whole body hyperthermia. Cancer Lett. 1995;97:195–201.
27. Camus G, Nys M, Poortmans JR, et al. Endotoxaemia, production of tumour necrosis factor alpha and polymorphonuclear neutrophil activation following strenuous exercise in humans. Eur J Appl Physiol Occup Physiol. 1998;79:62–8.
28. Geng Y, Ma Q, Liu YN, et al. Heatstroke induces liver injury via IL-1β and HMGB1-induced pyroptosis. J Hepatol. 2015;63(3):622–33.
29. Dehbi M, Uzzaman T, Baturcam E, et al. Toll-like receptor 4 and high-mobility group box 1 are critical mediators of tissue injury and survival in a mouse model for heatstroke. PLoS One. 2012;7(9)
30. Oishi S, Tsukiji N, Otake S, et al. Heme activates platelets and exacerbates rhabdomyolysis-induced acute kidney injury via CLEC-2 and GPVI/FcRγ. Blood Adv. 2021;5(7):2017–26.
31. Shields AM, Panayi GS, Corrigall VM. A new-age for biologic therapies: long-term drug-free therapy with BiP? Front Immunol. 2012;3:17.
Eisinger F, Patzelt J, Langer HF. The platelet response to tissue injury. Front Med. 2018;5:317.
32. Tong H, Wan P, Zhang X, et al. Vascular endothelial cell injury partly induced by mesenteric lymph in heat stroke. Inflammation. 2014;37(1):27–34.
33. Bouchama A, Hammami MM, Haq A, et al. Evidence for endothelial cell activation/injury in heatstroke. Crit Care Med. 1996;24(7):1173–8.
34. 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;89:261–5.
35. Selak MA. Neutrophil-platelet interactions in inflammation. Receptor. 1994;4(1):3–7.
36. Sylman JL, Artzer DT, Rana K, Neeves KB. A vascular injury model using focal heat-induced activation of endothelial cells. Integr Biol. 2015;7(7):801–14.
37. 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(6):1130–6.
38. Wilhelm EN, González-Alonso J, Chiesa ST, et al. Whole-body heat stress and exercise stimulate the appearance of platelet microvesicles in plasma with limited influence of vascular shear stress. Physiol Rep. 2017;5(21).
39. Joop K, Berckmans RJ, Nieuwland R, et al. Microparticles from patients with multiple organ dysfunction syndrome and sepsis support coagulation through multiple mechanisms. Thromb Haemost. 2001;85(5):810–20.
40. Chao TC, Sinniah R, Pakiam JE. Acute heat stroke deaths. Pathology. 1981;13(1):145–56.

41. Charan NB, Robinson WA, Mathew M. Heat stroke, disseminated intravascular coagulation and death in a long-distance runner. J Assoc Physicians India. 1975;23(12):917–9.
42. Larcan A, Lambert H, Laprevote-Heully MC, et al. Heat stroke and disseminated intravascular coagulation. Apropos of 2 cases. Sem Hop. 1978;54(17–20):603–19.
43. Mustafa KY, Omer O, Khogali M, et al. Blood coagulation and fibrinolysis in heat stroke. Br J Haematol. 1985;61(3):517–23.
44. Zhou Y, Li L, Liu L, et al. Heat stroke deaths caused by electric blankets: case report and review of the literature. Am J Forensic Med Pathol. 2006;27(4):324–7.
45. Sohal RS, Sun SC, Colcolough HL, Burch GE. Heat stroke: an electron microscopic study of endothelial cell damage and disseminated intravascular coagulation. Arch Intern Med. 1968;122(1):43–7.
46. 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(8):1900–10.
47. Yamamoto T, Fujita M, Oda MY, et al. Evaluation of a novel classification of heat-related illnesses: a multicentre observational study (Heat Stroke STUDY 2012). Int J Environ Res Public Health. 2018;15(9):1962.
48. 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(1).
49. 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;44:306–11.
50. Xing L, Liu SY, Mao HD, et al. Prognostic value of routine coagulation tests in patients with heat stroke. Am J Emerg Med. 2021;44:366–72.
51. Zhong L, Wu M, Ji J, et al. Relationship between admission platelet count and 90-day mortality in exertional heatstroke: a 10-year cohort study. Front Med 2021;8:716058.
52. Min J, Wan P, Liu G, et al. Sonoclot signature analysis: a new point-of-care testing method for defining heat stroke-induced coagulopathy. Int J Gen Med 2021;14:6925–33.
53. Jin H, Li Z, Guo X, et al. Microcirculatory disorders and protective role of antioxidant in severe heat stroke: a rat study. Shock. 2016;46(6):688–95.
54. El-Sabban F, Fahim MA. Treatments with lead expedite hyperthermia-induced thromboembolism in mouse pial microvessels. Int J Hyperth. 1998;14(3):319–29.
55. Iba T, Umemura Y, Wada H, Levy JH. Roles of coagulation abnormalities and microthrombosis in sepsis: pathophysiology, diagnosis, and treatment. Arch Med Res. 2021;52(8):788–97.
56. Asakura H. Classifying types of disseminated intravascular coagulation: clinical and animal models. J Intensive Care. 2014;2(1):20.
57. 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(3):740–7.
58. Barbosa da Cruz D, Helms J, Aquino LR, et al. DNA-bound elastase of neutrophil extracellular traps degrades plasminogen, reduces plasmin formation, and decreases fibrinolysis: proof of concept in septic shock plasma. FASEB J. 2019;33(12):14270–80.
59. 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;112(6):701–12.
60. 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.
61. Chen AH, Song XD, Luo BD, Zou F. Protective and anti-fatigue effects of aspirin against heatstroke in rats. Sheng Li Xue Bao. 2005;57(4):446–52.
62. Pennings GJ, Reddel CJ, Traini M, et al. Rapid release of interleukin-1β from human platelets is independent of NLRP3 and caspase. Thromb Haemost. 2021 Jun 25.
63. Kobayashi K, Mimuro S, Sato T, et al. Dexmedetomidine preserves the endothelial glycocalyx and improves survival in a rat heatstroke model. J Anesth. 2018;32(6):880–5.

64. Shi Y, Jiang X, Zhang L, et al. Endothelium-targeted overexpression of heat shock protein 27 ameliorates blood-brain barrier disruption after ischemic brain injury. Proc Natl Acad Sci U S A. 2017;114(7)–52.