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Liver damage in cases of general thermal trauma. Part 1. Pathomorphophysiology (scientific review)

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Abstract. Due to global warming, hundreds of thousands of people suffer from heat-related injuries annually in Eurasian countries and the USA, with tens of thousands of fatalities. The liver, in addition to the central nervous system, is among the most sensitive organs to hyperthermia. The leading pathogenic factors in the development of this pathological condition include intestinal barrier dysfunction, systemic inflammatory response syndrome, coagulation disorders, circulatory ischemia, hypoxia with energy deficit, endotoxemia, free radical oxidation activation, excessive cytokine and acute-phase protein production, denaturation and overproduction of heat shock proteins associated with proteostasis, mitochondrial dysfunction, and multiple organ dysfunction syndrome. Irreversible morphological changes in the liver can occur immediately after exposure to the temperature factor, but sometimes hepatocellular damage may only be detected after 24–48 hours. Hepatocyte necrosis and intrahepatic cholestasis reach their maximum on the 2nd–3rd day after overheating and may serve as a cause of death in 5–10% of patients, although 40% of patients exhibit liver cytolysis without cholestasis. The recovery period begins on the 7th day. Fatal outcomes are often due to hemorrhagic centrilobular hepatocyte necrosis and acute liver failure. Biochemical markers of liver damage in heat stroke will be discussed in Part 2 of the report.

Key words: general overheating, heat stroke, hepatic injury, pathomorphology, pathophysiology.

After the post-industrial period, the average global temperature has increased by 1.2 °C, and the last seven years have been identified as the hottest in the history of global observations. Annually, hundreds of thousands of people in Eurasian countries and the USA suffer from heat-related injuries due to general overheating, with tens of thousands of fatalities [1, 2]. Therefore, unintentional general body overheating is a significant problem today. Heat stroke (HS) is a syndrome with complex pathological mechanisms, including microvascular damage, thrombosis, inflammation, and apoptosis, leading to multiple organ dysfunction syndrome. It is defined as an increase in body temperature above 40 °C with central nervous system dysfunction [3].

Although the incidence of HS increases every year, the number of severe cases with multiple organ dysfunction and fatalities remains relatively small. Currently, research on the pathophysiology of HS is limited by two aspects: the complexity of the mechanisms of development and course, and the lack of a sufficient cohort of clinical studies to provide reliable medical evidence regarding the pathogenesis and treatment of HS [4, 5].

Heat stroke can manifest in two variants: classical heat stroke (CHS) or exertional heat stroke (EHS) under conditions of high external temperature [3, 5]. Classical HS with liver involvement is more common in individuals with limited physical abilities, the elderly, and those with weakened immunity and thermoregulation dysfunction in a high-temperature environment [3, 4, 7]. Drug-induced hyperthermia in humans can occur due to hypothalamic thermoregulatory process disruption and increased peripheral vessel constriction, hindering effective heat dissipation. This has been widely documented as a severe complication of ecstasy (MDMA) use, leading to body temperatures exceeding 40 °C [5, 6, 8]. The risk of liver failure can be significantly increased in cases of leptospirosis, viral and toxic hepatitis history, prolonged (uncontrolled) use of nonsteroidal anti-inflammatory drugs (mostly paracetamol) [3, 9], consumption of cognitive enhancers, nootropics, energy drinks, prescribed or illicit drugs, and certain genetic diseases [5].

The liver is highly sensitive to hyperthermia [10, 11] and is considered one of the first organs to be affected in HS, often accompanied by severe consequences, including fatal outcomes [12, 13]. Some degree of liver damage is a common symptom of heat stroke, particularly EHS, when the core temperature exceeds 39 °C [14, 15]. This risk needs to be emphasized as it is often underestimated. The incidence is higher than typically believed, especially during physical exertion [16, 17]. Liver damage is observed in 34–64% of patients who have suffered HS [7, 19, 20]. The presence of liver damage in HS, especially in severe cases, has been associated with high hospital mortality [4, 9, 20], reaching 25–45% [21–23]. Acute liver failure (ALF) is rarely the leading symptom in patients with heat stroke during physical exertion, but in case of EHS the course of the pathological condition can be more severe [24, 25]. ALF arises due to excessive strain on military personnel and young individuals engaging in intensive physical work in high-temperature and high-humidity conditions, often during the early summer months [4, 24]. For example, they may engage in long-distance running [7, 26], train in impermeable attire, or wear radio- or chemical protective gear while participating in military operations and exercises [26].

The use of analeptic drugs (modafinil) by athletes can induce discrete hyperthermic effects in dry heat, during physical activity, or at rest. This is related to a lower level of sweating, which can reduce heat tolerance [5].

Liver injury in heat stroke may be reversible and asymptomatic but less commonly accompanies severe hepatocellular damage or liver failure (ALI/ALF), both of which have a poor prognosis [24, 27]. Liver injury results from several factors, including hyperthermia, hypoxia, endotoxemia, coagulation disorders, or sepsis. Often, it is one of the first symptoms of severe multi-organ failure [17, 25, 28, 29].

Hepatocellular failure in heat stroke is closely associated with clinical manifestations of ischemia and hypercytokinemia in the gastrointestinal tract (GIT), leading to the reorga-

nization of the intestinal cytoskeleton with increased tight junction permeability, destruction of the epithelial cell structure, increased mucosal permeability, and impairment of reticuloendothelial system function [32, 33]. In normal conditions, blood from the GIT reaches the liver via the portal vein system before entering the general circulation, enabling the liver to actively participate in metabolism, immune response, and detoxification. Therefore, in heat stroke, the liver plays a role not only as a victim but also actively contributes to its pathogenesis [34, 35]. Heat stress reduces the production of bile acids in the intestine, leading to increased permeability of the intestinal mucosa and barrier dysfunction, allowing the translocation of bacteria and endotoxins into the systemic circulation [4, 36–38]. The redistribution of blood away from the splanchnic circulation promotes bacterial translocation (endotoxemia) and the development of an immune-inflammatory response [39], with major symptoms resembling those of sepsis [30, 35]. Increased endotoxin levels move into the mesenteric and portal-drained viscera, further increasing endotoxin delivery to the liver. Endotoxins include lipopolysaccharides, ammonia and its derivatives (resulting from increased proteolysis, impaired renal excretory function, and hepatic protein synthesis), lipid peroxidation products (e.g., diene conjugates, epoxides, lipid hydroperoxides, malondialdehyde, etc.), and excess molecules of intermediate mass (500–5000 Da), such as polyamines, oligosaccharides, oligopeptides, glycoproteins, etc. In heat stroke, the increased influx of endotoxin exceeds the functional capacity of Kupffer cells (resident macrophages of the liver) to neutralize them [30, 38]. Endotoxin translocation from the gut lumen to the bloodstream is a key factor triggering the systemic inflammatory response syndrome (SIRS) and multi-organ failure with circulatory impairment and liver damage [4, 27, 32, 40]. The increased endotoxin burden leads the liver to produce acute-phase proteins through induced plasma albumin synthesis, which has been observed in patients and laboratory animals who died from heat stroke due to endotoxemia and liver necrosis [32, 38, 40, 41]. The importance of intoxication in the pathogenesis of heat stroke is supported by the fact that most heat stroke victims die several hours after the cessation of excessive heat exposure, when body temperature is already approaching the normal range.

Protein denaturation increases at temperatures above 41 °C. While most prevalent proteins have a higher temperature resistance, other proteins undergo degradation and active aggregation, subsequently triggering apoptotic pathways. These processes quickly recover after the cessation of hyperthermia, although the DNA synthesis and related processes require more time [15, 42]. Results from experimental and clinical studies have shown significant alterations in the oxidative-reductive status of inflammation, mitochondrial dysfunction, and proteostasis-related pathways, which are essential for maintaining the necessary protein pool for normal cell function [19].

Under normal circumstances, an increase in organ temperature induces the expression and/or activation of heat shock proteins (HSPs), which protect cells from heat-induced apoptosis [12]. Heat stroke induces HSP expression to protect the structural integrity of cellular proteins through chaperone activity, regulated cell cycle expression, DNA replication, and repair genes, as well as optimizing the folding of new proteins and refolding denatured or misfolded proteins [15, 19]. This action is crucial because it supports protein transport within the cell, reduces protein aggregation, and ultimately limits cellular apoptosis by directing proteins toward lysosomal degradation [15, 42, 43]. HSP70 expression can effectively prevent organ damage, and pharmacological blockade of poly[ADP-ribose] polymerase-1 (PARP-1) can significantly suppress the excessive inflammatory response with improved prognosis [44]. Inhibition of PARP-1 can also reduce various forms of liver injury, markedly increase HSP70 and HSP27 expression at the mRNA and protein levels. PARP-1 disrupts the binding of heat shock factor-1 and HSP gene promoters [4]. Increased expression of HSP72 is accompanied by a noticeable improvement in mitochondrial function and glucose tolerance, and its activation reduces triglyceride accumulation in hepatocytes; conversely, the loss of HSP72 increases lipid accumulation and reduces fatty acid oxidation [15, 45]. Although HSPs are generally considered protective proteins, recent research has shown that overproduction of HSPs induces an immunostimulatory effect, leading to cytokine production [15]. Heat shock proteins can also contribute to circulatory impairment during excessive heat stress [46].

Not only HSP but also hyperthermia in general can lead to an elevated cytokine and inflammation mediator response [42]. Due to the high number of cytokine receptors, hepatocytes are very sensitive to cytokine action and respond by synthesizing acute-phase proteins (C-reactive protein). Hepatocyte receptors for growth factors have the ability to influence hepatocyte proliferation and protection in response to HS [15].

Results of differential gene and protein expression analysis indicate that the effect of thermal injury through the indirect erythroid 2 (Nrf-2) pathway in response to oxidative stress leads to an oxidant burst in parenchymal tissue [19]. Oxidative stress acts as a pathogenic mediator to stimulate inflammation. The SIRS leads to acute hepatocellular liver injury [19]. SIRS plays a crucial role in cell damage following heat exposure by activating pathways that lead to severe hepatocellular necrosis and apoptosis [5, 7, 24]. SIRS is induced by factors including elevated levels of cytokines and chemokines, disturbances in coagulation/fibrinolytic response regulation, and the release of damage-associated molecular patterns (DAMPs), apoptosis, and hepatocyte necrosis, leading to distributive shock [26, 46]. Cytokines are considered key mediators of SIRS in heat-induced systemic multiple organ failure and are associated with the severity and outcome of heat stroke. Many proinflammatory cytokines, such as interleukins (IL)-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and others, have been significantly increased in patients with heat stroke [4] and are capable of enhancing the expression of macrophage-related markers (CD11b and CD68). Furthermore, phosphorylation of IκBα (a major inhibitor protein) of NF-κB (nuclear transcription factor responsible for cellular adaptive responses) is a critical regulator of immune and inflammatory responses. Two distinct NF-κB signaling pathways have been described: 1) the canonical pathway, primarily activated by pathogens and inflammatory mediators, and 2) the non-canonical pathway, mostly activated by developmental cues. The most prevalent form of NF-κB activated by pathological stimuli through the canonical pathway is the p65:p50 heterodimer. Excessive activation of p65 and subsequent transactivation of effector molecules are an integral part of the pathogenesis of many inflammatory processes. NF-κB p65 was significantly increased by heat stress, and microRNA-155 (miR-155) expression was also increased. High miR-155 expression in heat-stressed microglial cells was inversely correlated with the expression of liver X receptor alpha (LXRα), encoded by the NR1H3 gene in humans. Targeting LXRα functionally, miR-155 enhances NF-κB signaling activa-

tion and promotes immune inflammation in hepatocytes exposed to excessive heat [47]. A 2-hour heat stress was identified as a threshold condition, defined by the time after which there is an enhanced change in hepatocyte regeneration characteristics. After 2 hours of heat exposure, the expression of IL-6, TNF-α, and IL-1β gradually increased, reaching its peak at 6 hours of the recovery period and persisting until 24 hours after heat stress [47].

Angiotensin peptides are important components of the renin-angiotensin system (RAS). Previous studies confirmed the significance of angiotensins Ang II and Ang-(1-7) as potential biomarkers in inflammatory diseases. The level of angiotensin peptides changes during thermal injury and is likely associated with excessive production of reactive oxygen species (ROS). In thermal injury-induced liver damage, the expression of Ang II was increased, while levels of Ang-(1-7) decreased, corresponding to their receptors and converting enzymes [48, 49]. AVE 0991, an analog of Ang-(1-7) that exerts Ang-(1-7)-like effects on the endothelium, and unopposed Ang-(1-7) can significantly inhibit ROS generation and reduce levels of NADPH oxidase 4 (NOX4), NLR family pyrin domain-containing 3 (NLRP3) inflammasome, caspase-1, and IL-1 in thermal injury-induced liver damage. This mechanism is closely associated with excessive ROS production and subsequent induction of cell pyroptosis [4, 50].

Heat stress can induce oxidative and nitrosative stress or other negative cellular reactions, ultimately leading to damage to intestinal epithelial cells and apoptosis [4]. Heat-induced oxidative stress increases the production of reactive oxygen species and reactive intermediates (free radicals and peroxides) that have a harmful effect on cellular lipids, proteins, and nucleic acids. They appear both within the first 2–3 minutes of heat exposure and during the development of thermal injury when their concentration increases by 8–10 times compared to normal levels. Concomitantly, signs of inhibition of tissue antioxidant enzymes (superoxide dismutase, reduced glutathione) are registered, leading to excessive formation of «water pores» with disturbances in the functional properties of cell membranes [4, 19].

Intense heat stress can cause damage to endothelial cells and apoptosis. In addition to the release of cytokines, which further enhances the inflammatory response, damaged endothelial cells contribute to the exposure of collagen fibers under the endothelium, stimulate coagulation factor XII, and subsequently activate fibrinogen to form a fibrin clot, leading to endogenous coagulation dysfunction. At the same time, endothelial cells can release tissue factors and activate coagulation factor VII, leading to exogenous coagulation dysfunction. Moreover, studies have shown that suppression of endothelial cell apoptosis was closely associated with reduced coagulation disturbances in thermal injury, which can effectively reduce heat-induced liver damage [4, 51]. In the process of coagulation, platelets and coagulation proteins are consumed at a faster rate than they are produced [40, 51]. Serotonin from platelets is released and participates in pathophysiological processes, such as the liver's response to injury, regulation of liver function, and liver regeneration [52].

Hepatorenal syndrome (HRS) exacerbates the propensity of heat stroke to cause disseminated vascular coagulation syndrome (DVCS), which is a common consequence. Consumption coagulopathy in HS differs from hypoprothrombinemia seen in HRS due to factor VIII [22]. HS-induced coagulation is indicated by prolonged prothrombin time, activated partial thromboplastin time, elevated D-dimer levels, and thrombocytopenia. In HS, levels of tissue thromboplastin, thrombin-antithrombin complex (TAT), and soluble thrombin complex (TM) sharply increase, while levels of key physiological anticoagulants are significantly reduced, including antithrombin and proteins C and S. TM can bind thrombin to convert protein C into activated protein C (APC) [4]. In combination with vascular stasis, this leads to microthrombosis of the vascular network and cellular ischemia [8, 15]. Of all causes of hypoxic hepatitis, hyperthermia accounts for 0.5% [23]. The liver's physiological response to hyperthermia remains fairly constant across different mammalian species, with significant changes in systemic and peripheral vascular networks. During heat stress, vasodilation and subsequent selective hyperperfusion redirect splanchnic blood flow to the periphery for maximum heat dissipation [14, 15, 17, 24], resulting in microcirculatory blood flow in the liver possibly decreasing to the level of vascular stasis, leading to inadequate oxygen supply to visceral tissues, causing hypoxia-induced cellular damage [15, 23].

The primary causes of heat shock are heat-induced dehydration and cardiomyopathy. Besides dehydration, there is a significant reduction in blood volume due to increased vascular permeability from endothelial damage [23]. The liver independently responds to systemic factors that dictate hepatic blood flow during general overheating of the body (41.8–42.2 °C) in humans. When cardiac output doubles, hepatic blood flow significantly decreases, indicating peripheral vasodilation, often observed in response to radiant heat [14, 15, 17]. Liver injury can also result from secondary hypoperfusion of the sympathetic nervous system with blood flow decentralization to optimize heat dissipation from skin capillaries [54].

Elevated temperature and subsequent increased hepatic metabolism are characterized by increased oxygen consumption by mitochondria with concomitant hyperproduction of CO2, indicating impaired oxidative phosphorylation [15]. In humans with HS, the rate of metabolism increases, reaching a plateau, and then rapidly decreases as the temperature rises. The reverse is observed when cooling critically ill overheated patients, where a significant decrease in metabolic rate, as assessed by oxygen consumption (VO2) and carbon dioxide production (VCO2), is noted upon cooling the body from 39 °C to 37 °C. There is a significant increase in glucose release from hepatocytes, primarily due to increased glycogenolysis in the liver associated with an enhanced metabolic state, similar to what is observed during physical exercise [15]. The increase in hepatic metabolic activity significantly contributes to heat production, thus completing a vicious cycle [54].

It is believed that hepatocyte hypoxia is the primary cause of liver dysfunction in critically ill patients, characterized by increased consumption due to hypermetabolism induced by hyperthermia («metabolic hypoxia»). Regardless of the underlying pathogenesis, the final common pathway is hepatocellular dysfunction due to insufficient oxygen supply to meet the actual metabolic needs of mitochondria [55]. Reduced liver blood flow is also of great significance [14, 17]. Liver injury includes a decrease in splanchnic blood flow and an increase in metabolic demand, creating a state of relative circulatory hypoxia [22]. Sudden drop in arterial pressure with regional circulation impairment leads to dystrophic changes in the liver [56]. It is believed that the cause of these changes is liver ischemia due to microthrombosis and vascular endothelial damage [5, 18, 26].

At a core temperature above 42 °C, oxidative phosphorylation becomes uncoupled, and metabolic demand can no longer be met [12]. Mitochondria are the primary consumers

of oxygen in cells and contain various oxidative-reductive carriers for electron transfer. Electron transport chain leads to ATP production in five protein-lipid enzymatic complexes (Complex IV) located in the intermembrane space of mitochondria. Mitochondria play a crucial role in the activation and regulation of hepatic apoptosis under various pathological conditions [19].

As a typical molecule associated with damage-associated molecular patterns (DAMPs), the nuclear non-histone high mobility group box 1 protein (HMGB1, amphoterin) can mediate HS-induced Nlrp3 inflammasome activation through Toll-like receptor 4 (TLR4, CD284) and receptor for advanced glycation end products (RAGE) signaling, thereby inducing IL-1β activation and hepatocyte pyroptosis, ultimately leading to severe liver injury. Inhibition of HMGB1, suppression of Nlrp3, or blockade of caspase-1 can significantly prevent Nlrp3 inflammasome activation, thus reducing liver damage during HS. Macrophages and monocytes activated by proinflammatory factors are important sources of HMGB1, while HMGB1 can also be released from necrotic or damaged cells. Heat stress significantly increases HMGB1 expression in liver macrophages and plasma. Thrombomodulin (TM) intervention can reduce HMGB1 levels in plasma even with delayed treatment. These findings suggest that TM may not only mitigate HS-induced liver damage by optimizing the state of systemic coagulation but also effectively limit excessive inflammatory responses [4].

Mitophagy plays a crucial role in regulating liver homeostasis [57]. As the most important mechanism for self-regulating mitochondrial quality and selective removal of damaged mitochondria, dysfunction of mitophagy leads to the accumulation of dysfunctional mitochondria, excessive activation of apoptosis-inducing factors, and increased release of reactive oxygen species (ROS), resulting in abnormal cell apoptosis [58]. In HS-induced liver damage, the important role of mitophagy has been confirmed. The transcription factor p53 has been described as a «guardian angel» gene that maintains genome stability. Translocation of p53 from the nucleus to the cytoplasm significantly increases in case of HS [59, 60].

Heat stress induces modulation of molecular pathways responsible for liver damage [19]. Nuclear factor erythroid 2-related factor 2 (Nrf2), a ubiquitous master transcription factor, enhances the expression of antioxidant enzymes and cytoprotective proteins, mediated by elements of the antioxidant response [61]. The response to oxidative stress is also associated with nuclear factor erythroid 2 (Nrf2), and the regulated inflammatory pathways of macrophage migration inhibitory factor (MIF) are enhanced in the liver affected by severe heat stress. In this context, the expression levels of the following molecules in the mentioned pathways were investigated: heat shock protein 90AB-1, peroxiredoxin-5, mitogen-activated protein kinases 1/2, heme oxygenase-1, apolipoprotein-1, and Il-10. The results suggested that the activation of these genes modulates the regulated pathways of Nrf2 and MIF in the liver during HS. Heat stress-induced changes in key liver functions are regulated by Nrf2 and MIF pathways. Irregularities in molecular signaling networks lead to mitochondrial dysfunction, as indicated by increased regulation of ATP synthase β and peroxiredoxin-1, along with reduced levels of glucose-6-phosphate dehydrogenase and increased cytochrome C activity in liver mitochondria [19, 62]. Dysregulation of the oxidative-redox state of the liver during HS leads to inflammation through regulated MIF pathways. Suppression of the antioxidant defense by Nrf2 plays a crucial role in the development of HS-induced oxidative stress [19]. As one of the most widespread and evolutionarily conserved transcription and growth factors in eukaryotes (nuclear cells), the group of recombinant high mobility group box 1 proteins (HMGB1, amphoterin) holds an important place in the diagnosis and treatment of HS. Macrophages and monocytes activated by proinflammatory factors are significant sources of HMGB1. HMGB1 levels positively correlate with the severity of disease progression and mortality during heat injury [43].

Programmed cell death mediated by Z-DNA-binding protein-1 (ZBP1), also known as DNA-dependent activator of interferon-regulatory factors, may activate the interaction with receptor-interacting protein kinase 3 (RIPK3) — mixed lineage kinase domain-like (MLKL) pathway of programmed cell necrosis [63]. The Z-nucleic acid transmitter ZBP1 plays a significant role in regulating the pathological characteristics of heatstroke through ZBP1-dependent signal transmission. Thus, a lethal mechanism of heatstroke has been identified in addition to the second function of ZBP1, distinct from its nucleic acid sensor function. ZBP1 drives heatstroke pathology through RIPK3 (receptor-interacting serine/threonine kinase 3) induced necroptosis activation. Heat stress increased the expression of ZBP1 through HSF1 and promoted the aggregation of ZBP1 fused proteins, followed by the recruitment of RIPK3, MLKL phosphorylation, and caspase-8 cleavage [4, 47, 64]. In response to heat stress, resident macrophages/Kupffer cells (KCs) play a crucial role in clearing intestinal endotoxin through phagocytosis, and their dysfunction explains the increased endotoxin concentration. 80–90% of resident KCs are the main source of macrophage inflammatory protein-1α (MIP-1α) [4], which is associated with excessive inflammation leading to multiple organ dysfunction syndrome in ischemia-reperfusion injury since MIP-1α can stimulate peritoneal macrophages to secrete tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6 in TI-induced liver injury [43]. c-Jun N-terminal protein kinases (JNK) are activated in response to heat and oxidative stress, binding and phosphorylating the regulatory protein c-Jun residues serine in the transcriptionally active domain. JNK plays a crucial role in the inflammatory response, cell apoptosis, and heat stress, especially in KCs. Inhibition of JNK phosphorylation in KCs significantly reduces inflammatory cytokines and MIP-1, while enhancing phagocytosis [4, 65].

Histological liver damage associated with heatstroke (edema, lightening, vacuolization, steatosis, and massive centrilobular necrosis) is likely a consequence of direct heat and hypoxia (liver hypoperfusion), endotoxemia, and high concentrations of cytokines and acute-phase proteins [17, 21, 24, 66].

The histopathological characteristics of liver damage in HS patients include degeneration and necrosis of liver lobules, often accompanied by significant damage, but early-stage HS is usually not associated with significant abnormalities on abdominal ultrasound and liver CT scans [9]. If the etiology remains unclear after extensive investigations, a liver biopsy should be considered [5]. Hepatocyte damage is caused by destabilization of the cell membrane and dysfunction of mitochondrial transport and proteins, which can reduce cell viability by 35% in isolated hepatocytes after exposure to heat up to 40.5 °C [15, 31, 67]. Cell death occurs at temperatures exceeding 41 °C, with potential lethality when the body's core temperature exceeds 42 °C [8, 15]. The most widespread hepatocyte damage in HS-induced liver injury is massive hepatocyte degeneration, including abnormal cell death. Pyroptosis is caspase-1-dependent programmed cell death characterized by cell swelling, rapid rupture of the plasma membrane, and release of proinflammatory intracellular agents. The NOD-like receptor pyrin domain 3 (NLRP3) family is an intracellular pattern recognition receptor that plays

a role in cellular pyroptosis by assembling into a multiprotein complex (inflammasome), allowing cells to rapidly respond to damaging factors. In case of HS, NLRP3-dependent pyroptosis is the main cause of abnormal hepatocyte death. Inflammasome stimulation induces activation of IL-1 β and pyroptosis of hepatocytes. Excess ROS is generated during heat stress, which is a key stimulator of NLRP3 inflammation and a potential target for negative regulation of cellular pyroptosis [4].

Extracellular vesicles (EVs) serve as mediators of intercellular communication. Proteins, lipids, and nucleic acids are delivered to recipient cells through EVS, modulating their biological processes and function [4, 43]. HS-induced liver injury can lead to a significant increase in EVS released from hepatocytes, contributing to liver damage, and the EV synthesis inhibitor GW4968 attenuates it [68]. Caspase-independent necroptosis is controlled by receptor-interacting protein 1 (RIP1), RIP3, and MLKL and is associated with increased plasma membrane permeability, leading to the release of danger-associated molecular patterns (DAMPs), such as HMGB1 and mitochondrial DNA, which trigger potent immune inflammatory responses [69]. EVS from hepatocytes during HS may promote necroptosis and apoptosis. Hepatocytes are not only victims of harmful stimuli but also actively participate in liver damage by emitting unique «danger signals» [4, 43].

Liver damage in some cases can be extremely severe, leading to hepatocyte degeneration and cholangiolary reaction, pyknosis, and nuclear fragmentation in Kupffer cells, indicating a mixed hepatocellular and cholestatic type [15, 17, 24, 67]. Depletion of glycogen stores with hepatocellular dysfunction is associated with hypercatabolism and persistent hypoglycemia [5, 70].

Liver injury is evident immediately after exposure to thermal factors [53], but in some cases of EHS, hepatocellular injury may only be detected 24–48 hours later [24, 40, 70, 71]. Hepatocyte necrosis and intrahepatic cholestasis reach their peak on the 2nd–3rd day after HS and can be a cause of death in 5–10% of patients [5, 10, 11], but 40% of patients have been found to have liver cytolysis without cholestasis [72]. On the 3rd day after HS, signs of hemato-lymphatic barrier disruption are observed, including the death of some endothelial cells, dilation and occlusion of Disse spaces, and disturbances in blood and lymph circulation, manifesting as increased volumetric density and volume of sinusoids; expansion of Mall spaces (small gaps between liver parenchyma and surrounding connective tissue that encloses the branches of the portal vein). During this period, hepatocytes exhibit subcellular signs of damage to the protein-synthesizing apparatus, mitochondrial damage in the matrix, and ribosome loss. On the 7th day after overheating, a decrease in the volumetric density of the T-dependent zone of liver lymph nodes is observed (recovery period), which is a stereotypical reaction of regional lymph nodes to the destabilizing effect of hyperthermia.

Autopsy of the livers of those who died due to HS and acute liver failure revealed massive hemorrhagic centrilobular hepatocyte necrosis with intact portal tract bile ducts, while individual undamaged hepatocytes were found in the periportal zone but with signs of structural degeneration [4, 24]. The liver of transplanted patients was not atrophic. The cut surface was generally yellowish and soft, indicative of steatosis without portal fibrosis. Portal tracts contained a moderate inflammatory infiltrate without significant periportal activity. Non-destructive lymphocytic or neutrophilic cholangitis and constant intrahepatic cholangiolary reaction with multiple acute neutrophilic cholangiolitis were observed. Massive coagulation lobular necrosis mostly affected 60% to 90% of the liver parenchyma and was accompanied by a moderate macrophage clearance reaction. Both macro- and microvesicular steatosis were mostly present, affecting 5% to 90% of hepatocytes and manifesting as liver fat dystrophy [40].

The mitotic ability of the remaining hepatocytes remained high (from 17 to 82 mitoses for 10 HPF). Other hepatocytes were mostly pale and swollen, with a periportal ductular reaction observed at the boundary with damaged liver parenchyma. Natural killer cells showed reduced cytotoxic activity in case of HS due to impaired target cell binding, which could be directly related to increased membrane fluidity and instability [15, 67].

Biochemical markers of liver damage in heatstroke will be discussed in part 2.

Conflict of interest

The authors declare no conflicts of interest and no financial interests in the preparation of this article.

Authors' contributions

O.V. Kravets — conceptualization; V.V. Yekhalov, V.A. Sedinkin — original text writing; D.A. Krishtafor — editing; O.V. Kovryha — translation.

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Ураження печінки при загальній тепловій травмі. Частина 1. Патоморфофізіологія (науковий огляд)

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Анотація. Внаслідок глобального потепління щорічно від загального перегрівання в євразійських країнах та США потерпають сотні тисяч осіб, а летальність внаслідок теплової травми налічує десятки тисяч загиблих. Печінка, окрім центральної нервової системи, належить до найчутливіших до гіпертермії органів. Провідними в патогенезі патологічного стану є порушення бар'єрної функції кишечнику, синдром системної запальної відповіді, розлади згортання крові, дисциркуляторна ішемія, гіпоксія з енергодефіцитом, ендотоксемія, активація вільнорадикального окиснення, надмірне утворення цитокінів та білків гострої фази, денатурація та надпродукція білків теплового шоку, пов'язана з протеостазом мітохондріальна дисфункція, синдром поліорганної недостатності. У печінці відзначають незворотні морфологічні зміни одразу після дії температурного фактора, але іноді гепатоцелюлярне ураження може визначитися лише через 24–48 год. Некроз гепатоцитів та внутрішньопечінковий холестаз досягають свого максимуму на 2–3-й день після перегрівання і у 5–10% пацієнтів можуть стати причиною смерті, але у 40% хворих було виявлено цитоліз печінки без холестазу. На 7-му добу розпочинається відновний період. Летальний кінець фіксували внаслідок геморагічного центролобулярного некрозу гепатоцитів та гострої печінкової недостатності. Біохімічні маркери ураження печінки при тепловому ударі будуть розглянуті у 2-й частині повідомлення.

Ключові слова: загальне перегрівання, тепловий удар, ураження печінки, патоморфологія, патофізіологія.

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