



Histopathological Changes in Organs Due to High Environmental Heat in Male Wistar Rats

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10.18805/IJAR.B-5571

ABSTRACT

Background: Environmental heat significantly affects the morphological and histological structures of mammals. This study aims to identify the histopathological changes induced by high environmental temperatures, specifically hyperthermia, in rats.

Methods: Twenty male wistar rats (n=20) were divided into two groups: (A) Experimental group (n=10), in which rats were exposed to hyperthermia in a biological oxygen demand (BOD) incubator until death and (B) Control group (n=10), kept at room temperature (24±1°C). Histopathological analysis was performed following standard procedures, including organ extraction, fixation, grossing, washing, dehydration, clearing, embedding, block preparation, section cutting, staining, mounting and microscopic examination.

Result: Histopathological examination revealed that hyperthermia caused mild satellitosis and neuronophagia in the brain. The heart exhibited severely congested blood vessels with hemorrhages and cardiomyocytes showed pyknotic changes. In the kidneys, morphological changes included cloudy swelling of tubular epithelial cells with pyknotic alterations in the epithelial cell lining. The liver showed severe congestion in the sinusoid, hepatic artery and portal vein, along with rounding of Kupffer cells. The lungs exhibited hyperplasia of peri-bronchial lymphoid follicles.

Key words: Biological oxygen demand (BOD) incubator, Histopathology, Hyperthermia, Morphology, Wistar rats.

INTRODUCTION

Hyperthermia is defined as an increase in body temperature above the upper physiological range, typically between 39°C and 45°C (Angilletta *et al.*, 2019). It most commonly results from fever due to illness, heavy exercise, or exposure to hot environments. In clinical settings, hyperthermia can be strategically induced, either alone or in combination with radiation or chemotherapy, to treat various malignant diseases, affecting local or systemic areas (Ganta *et al.*, 2004).

Animal studies have shown that vascular changes occur almost immediately following hyperthermia, although some organs exhibit greater resistance to heatstroke than others. These changes include capillary dilation, altered vascular pathways and interstitial extravasation, all of which are observed in most organs after just 30 minutes at 40.5°C (Walter *et al.*, 2016). The causes of sudden death in hyperthermic conditions vary, ranging from nonspecific to specific morphological changes in the organs, depending on whether the event is acute, subacute or chronic. The detrimental effects of hyperthermia are linked to a range of pathophysiological pathways, including indirect cellular damage, systemic effects like intestinal bacterial translocation and localized effects such as cytokine activation and inflammatory responses (Gali *et al.*, 2024).

There are two primary mechanisms through which hyperthermia may occur. Literature suggests that myocardial oxygen consumption significantly decreases with an increase in body temperature, leading to reduced cardiac output and blood pressure (Indhu *et al.*, 2019). This, in turn, causes various forms of damage to

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How to cite this article: Kumari, A. and Sinha, R.K. (2025). Histopathological Changes in Organs Due to High Environmental Heat in Male Wistar Rats. Indian Journal of Animal Research. 1-10. doi: 10.18805/IJAR.B-5571.

Submitted: 14-02-2025 **Accepted:** 03-05-2025 **Online:** 21-06-2025

cardiomyocytes, including subendocardial bleeding, myocardial necrosis and fibrin fiber rupture. Studies have also explored the impact of heat stress on the embryonic circulatory system in rats, with results indicating tachycardia, a 13% increase in mean blood flow and elevated vascular resistance when body temperature rises from 37°C to 42°C. Heatstroke is characterized by a hypermetabolic state induced by the release of large amounts of calcium from the sarcoplasmic reticulum in heart muscle cells (Mol *et al.*, 2024).

High body temperatures trigger various physiological and metabolic responses (Sarubbi *et al.*, 2024). Acute heating of cells and tissues leads to structural changes in the nucleus and cytoskeleton, disruption of vascular and basement membranes and enhanced programmed cell death (apoptosis) (Zhao *et al.*, 2022). Rats have served as experimental subjects in numerous studies investigating heatstroke (Li *et al.*, 2024a).

Given the broad consequences of hyperthermia, numerous models have been developed, with heatstroke

induced by high temperatures in dry air being the most common. Depending on the cause of sudden death—whether acute, subacute, or chronic—the morphological changes observed in organs can range from nonspecific to specific (Kanchan, 2016). Hyperthermia is known to cause multiorgan damage. For example, a study analyzing the effects of heat stress on the hearts of broilers found heart enlargement, right atrial blood accumulation, cardiac myofibrillar degeneration with hemorrhage and an increase in cardiac output in rats (Gonzalez *et al.*, 2020). Heat stress also leads to brain edema and gliosis, vascular degeneration, hydropic degeneration and kidney congestion (Dervisevic *et al.*, 2023). The stimulation of the renin-angiotensin system during heat stress is known to decrease blood flow. In the lungs, hyperthermia causes capillary stasis in the alveolar walls, alveolar hemorrhage and focal fibrosis. The liver experiences congestion, sinusoidal dilation, necrosis and other forms of damage during heat stress. Suryawanshi *et al.* observed that in cases of diaphragmatic hernia in cattle and buffaloes, there were significant clinico-haematobiochemical alterations, including elevated liver enzymes, indicating hepatic stress and damage (Suryawanshi *et al.*, 2023). One of the most affected organs is the kidney. Findings suggest that heat stress leads to significant changes in the renal corpuscles and the proximal and distal convoluted tubules of the renal cortex (Vlad *et al.*, 2013). Although these are some examples of organ damage caused by heat exposure, the full spectrum of its effects remains broad and warrants further study.

This study aims to investigate the physiological and pathological consequences of prolonged exposure to elevated environmental heat, specifically focusing on the point at which the body experiences breakdown within the nervous system. By identifying this critical threshold of hyperthermia, the research will comprehensively assess its impact on the histopathological structure of various organs. Additionally, the study will examine the biochemical and physical alterations induced by sustained high-temperature exposure, offering deeper insights into the systemic effects of extreme environmental stress on human health.

MATERIALS AND METHODS

Ethical approval statement

The experiment was conducted at the Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India, in full compliance with ethical principles for animal research. The study was approved by the Institutional Animal Ethics Committee (IAEC) under protocol #1972/PH/BIT/05/23/IAEC.

Subjects

The experiment was conducted at the Birla Institute of Technology Mesra, Ranchi, Jharkhand, India, during the year 2023-2024 in full compliance with ethical principles

for animal research. The experiment involved twenty male Wistar rats, each with a body weight ranging from 190 to 210 grams, which were obtained from the Animal House at the institute. The rats were housed in controlled laboratory conditions for 7 days prior to the experiment, maintained at $24\pm1^{\circ}\text{C}$ with a 12-hour light/dark cycle to facilitate acclimatization. Food and water were provided *ad libitum* under these standard conditions.

Heat stress model

Rats were exposed to heat stress in a biological oxygen demand (BOD) incubator (deluxe automatic) set at 42°C with a relative humidity of 45-50% on the experimental day. The animals were divided into two equal groups for the experiment:

- (i) Experimental Group (n=10): Acute heat exposure at 42°C until death.
- (ii) Control Group (n=10): Kept at room temperature ($24\pm1^{\circ}\text{C}$).

Both experimental and control rats were placed into the incubator at the preset environmental temperature, under anesthetized conditions (urethane, dosed according to body weight).

Experimental model of hyperthermia

Hyperthermia was induced in the experimental rats by placing them sequentially in the BOD incubator. Each rat was kept in the incubator for four continuous hours of heating. Survival times were recorded continuously, starting from the moment the animals were introduced into the incubator at 42°C until signs of nervous system breakdown occurred.

Histopathological procedure

Following four hours of heat exposure, the rats were sacrificed. Tissue samples were harvested and fixed in 10% formalin for 8 to 10 hours at room temperature to prevent autolysis. The tissues were then sectioned into pieces of 0.3 to 0.5 mm in size. The specimens were placed in a capsule and washed with slow-running tap water for at least 8 hours to remove excess formalin and allow water to penetrate the tissue.

Subsequently, dehydration was carried out using alcohol in increasing concentrations (50%, 70%, 90%, 100%, 100%), with each step lasting 1 hour to replace water with alcohol. Following dehydration, the tissues were cleared in xylene to remove alcohol, also in two stages, before being infiltrated with a mixture of xylene and melted paraffin wax at 50°C overnight.

After the impregnation process, the tissue blocks were placed in an L-shaped mold and cooled in a refrigerator for 10-15 minutes (embedding). The blocks were then sectioned to 4-5 μm thickness using a microtome. The sections were mounted with Dibutylphthalate Polystyrene Xylene (DPX) and stained with hematoxylin and eosin (H and E). Following de-waxing, histopathological changes were observed under a light microscope and significant findings were photographed and included in the results

section (Luna, 1968) (Fig 1). Tissue samples were collected from organs such as the brain, heart, kidney, liver and lungs.

Markers of hyperthermia

Body temperature

The changes in body temperature of the rats were recorded as a crucial indicator of their physiological response to the hot environment (Sinha, 2013). A telethermometer (Scan-96, Micron, India), connected to a thermistor probe, was used to monitor body temperature (Aggarwal *et al.*, 2013).

Level of corticosterone

Corticosterone levels were measured to assess the physiological stress response. Blood was collected from the trunk after decapitation under urethane anesthesia and plasma was separated by centrifugation. The plasma was then quickly assayed for corticosterone levels using the spectrofluorometric method, as previously described (Lim *et al.*, 2025). Changes in corticosterone levels were compared between experimental and control groups.

Statistical analysis

All statistical analyses were conducted using MS Excel. Data from the experimental group were compared with the control group using t-tests to assess significant differences in various parameters following heat exposure.

RESULTS AND DISCUSSION

Markers of hyperthermia

Body temperature

In the heat-exposed group, continuous heat exposure led to a significant rise in core body temperature compared to the control group. The hyperthermic rats exhibited a highly significant increase in body temperature ($P < 0.01$), indicating a profound impairment of thermoregulatory mechanisms under extreme heat conditions.

Corticosterone results

The physiological stress response in the hyperthermic rats was confirmed by a significant elevation in plasma corticosterone levels following continuous heat exposure. Statistical analysis revealed a highly significant increase in plasma corticosterone concentrations ($P < 0.01$) when compared to control rats, indicating acute activation of the hypothalamic-pituitary-adrenal (HPA) axis (Fig 2).

Histopathological analysis results

Brain

A comprehensive comparison between the control and heat-exposed groups revealed significant histopathological changes in the brain tissue of the stressed rats. While the control group exhibited typical brain tissue morphology (Fig 3A), the heat-stressed rats showed notable alterations. The most prominent changes included mild to moderate satellitosis, characterized by glial cells surrounding

degenerating neurons (Fig 3B) and pronounced neuronophagia, where degenerating neurons were engulfed by glial cells (Fig 3C). These findings provide new insights into the glial responses to heat-induced neuronal damage, which had not been previously described in hyperthermia-related brain injuries. The prevalence of neuronophagia and satellitosis highlights a unique and previously underexplored aspect of the neurophysiological impact of extreme heat stress, advancing our understanding of heat-induced neurological damage.

Heart

In contrast to the control group (Fig 4A), the heat-exposed rats exhibited significant morphological alterations in the heart, particularly in the cardiomyocytes. Notably, there was severe congestion of blood vessels accompanied by hemorrhage and pyknotic changes were observed in the nuclei of cardiomyocytes (Fig 4B, 4C). These findings align with early signs of cellular distress, indicating a profound impact of heat stress on cardiac tissue. Additionally, degenerative changes in the cardiomyocytes were evident,

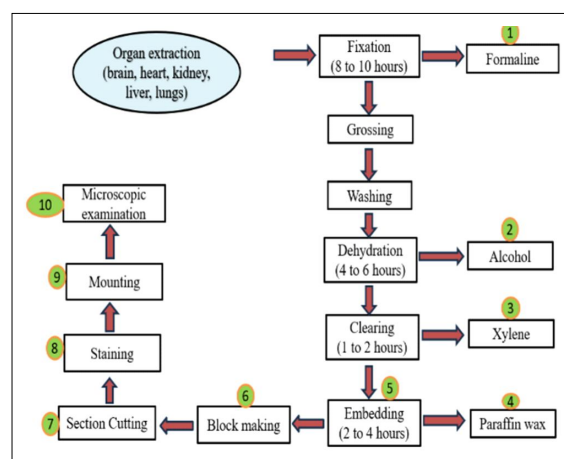


Fig 1: Flow chart of the overall procedure of histopathology.

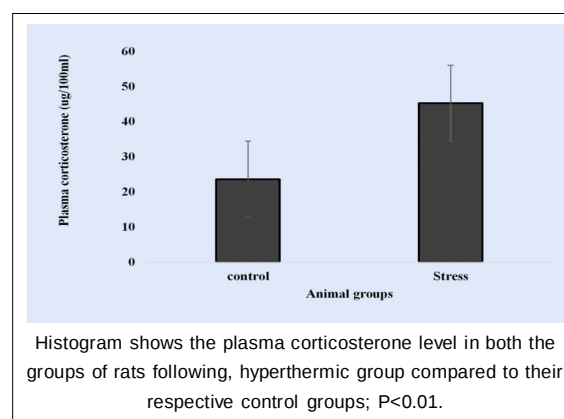


Fig 2: Data shown in mean $\pm$ S.E.

including a mild loss of cross-striation in cardiac muscle fibers (Fig 4D), which is a hallmark of structural damage. These changes reflect the onset of cardiac dysfunction, which may predispose the heart to further complications under prolonged heat stress. This study provides novel insights into the specific mechanisms of heat-induced myocardial damage, particularly through the identification of pyknotic changes and the loss of cross-striation in cardiomyocytes, which were not fully explored in previous research on hyperthermia-induced cardiac injury.

Kidney

Compared to the control group (Fig 5A), the heat-exposed rats exhibited marked histopathological changes in the kidneys. The most notable change was cloudy swelling of the tubular epithelial cells, accompanied by pyknotic changes in the lining epithelial cells (Fig 5B), indicating severe cellular stress. Vacuolar degeneration was detected in the epithelial cells interspersed between the tubules, suggesting an adaptive response to hyperthermia-induced

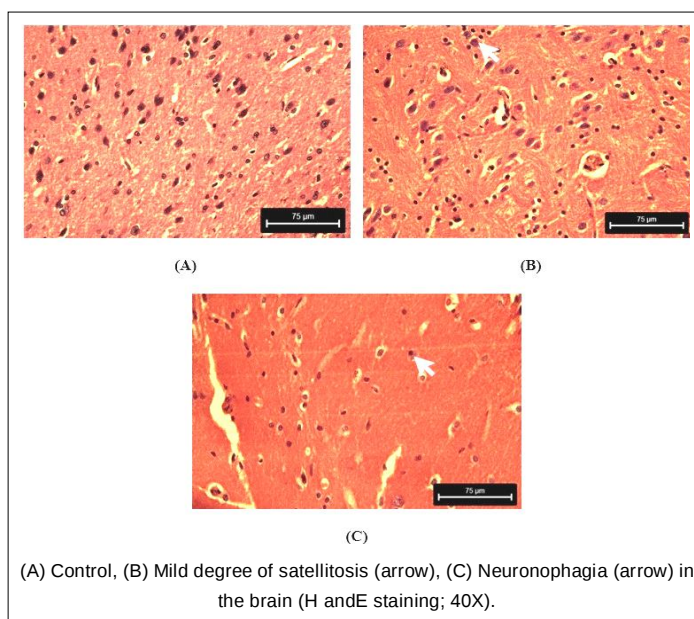


Fig 3: Histopathological changes in brain tissue.

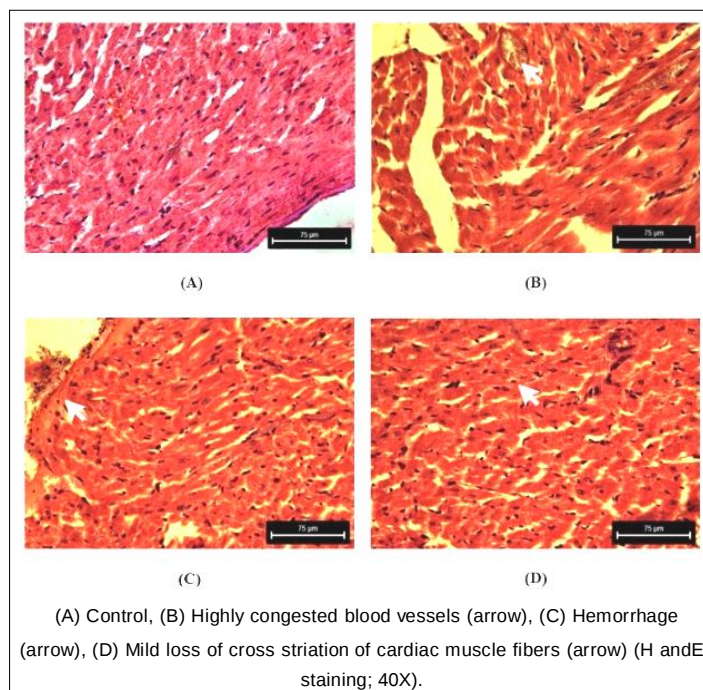


Fig 4: Histopathological changes in heart tissue.

oxidative stress. Additionally, blood vessels in the kidneys were significantly congested and dilated (Fig 5C), indicating potential vascular dysfunction. Interestingly, vacuolar degeneration was absent in the cortical and medullary epithelial cells of one rat, while the remaining rats consistently exhibited these changes, reinforcing the pathological impact of heat exposure. These findings offer

new insights into renal damage progression under extreme thermal stress, underscoring a potential link between hyperthermia-induced stress and early nephropathy.

Liver

The liver tissue of the heat-exposed rats exhibited notable pathological alterations compared to the control group

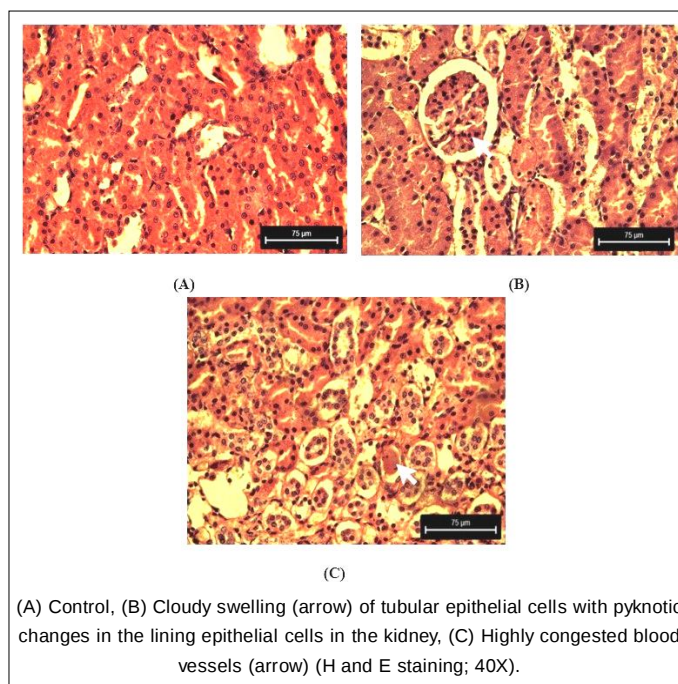


Fig 5: Histopathological changes in kidney tissue.

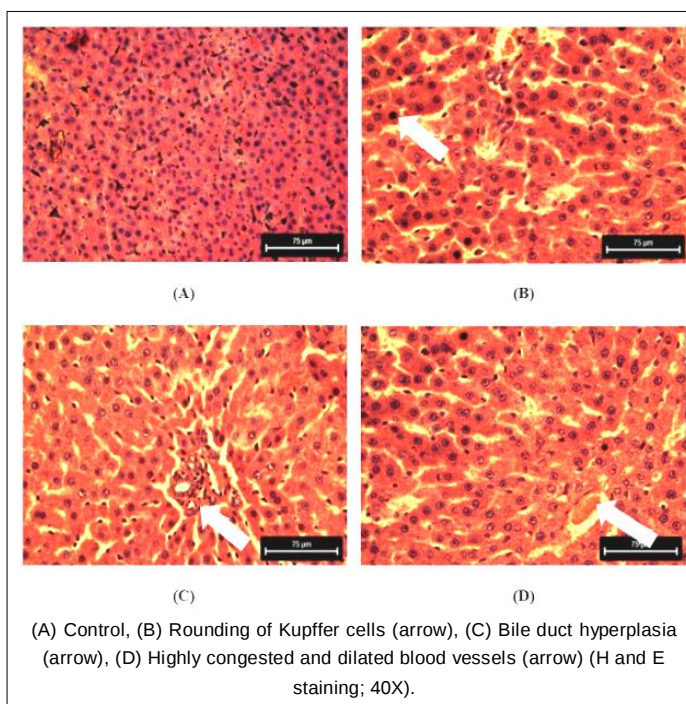


Fig 6: Histopathological changes in liver tissue.

(Fig 6A), suggesting hepatic dysfunction. Kupffer cells were rounded and hypertrophic (Fig 6B), indicating an activated immune response likely driven by oxidative stress and inflammatory signaling caused by heat stress. Bile duct hyperplasia was observed (Fig 6C), which may represent a compensatory response to thermal stress-induced hepatocellular injury. Hepatocytes showed signs of cloudy swelling and mild vacuolar degeneration, along with narrowing of the sinusoidal space, indicating early-stage metabolic disturbances. Additionally, severe congestion was observed in the sinusoids, hepatic artery and portal vein (Fig 6D), pointing to vascular dysfunction and impaired hepatic microcirculation.

Lungs

The lung tissue of heat-exposed rats exhibited significant histopathological changes indicative of severe pulmonary distress. Pronounced hyperplasia of peri-bronchial lymphoid follicles was observed, suggesting an immune-mediated response to hyperthermia-induced lung injury. The alveoli showed emphysematous changes (Fig 7A), potentially linked to oxidative stress and alveolar wall destruction.

Key findings also included highly congested and dilated blood vessels, with severe capillary congestion (Fig 7B), indicative of compromised pulmonary microcirculation and potential endothelial dysfunction. Interstitial pneumonia was evident, with a significant infiltration of mononuclear cells and neutrophils, reflecting an inflammatory response to thermal insult. Mild interstitial

pneumonia was also present, characterized by thickening of inter-alveolar septae due to lymphocytic and epithelioid cell infiltration, suggesting the onset of pulmonary fibrosis. Mild bronchopneumonia was also detected, with mononuclear cell infiltration in the bronchiolar lumen (Fig 7C), indicating early-stage airway inflammation and potential respiratory dysfunction. The co-occurrence of emphysema, pneumonia and vascular congestion provides new insights into the cumulative impact of hyperthermia on lung.

Whole-body hyperthermia induced in rats at a high temperature of 42°C led to a significant elevation in body temperature, followed by the development of severe lesions in multiple visceral organs. These changes were accentuated through electron microscopic analysis, underscoring the destructive consequences of heat exposure (Iba *et al.*, 2025). Heat stroke, a life-threatening condition, leads to Multiple Organ Dysfunction Syndrome (MODS), with extreme heat stress disrupting the homeostatic balance of the organism. The body's adaptive responses to such stress demonstrate a clear effort to maintain internal stability, but the prolonged exposure to high temperatures ultimately overwhelms these mechanisms. (Bhateshwar *et al.*, 2023) highlighted that in small ruminants, heat stress leads to alterations in physiological and biochemical profiles, affecting body weight, rectal temperature and respiratory rate, which are indicative of the challenges faced by homeothermic animals in arid and semi-arid regions.

As the rats were subjected to acute heat stress, their central body temperature soared to dangerous levels,

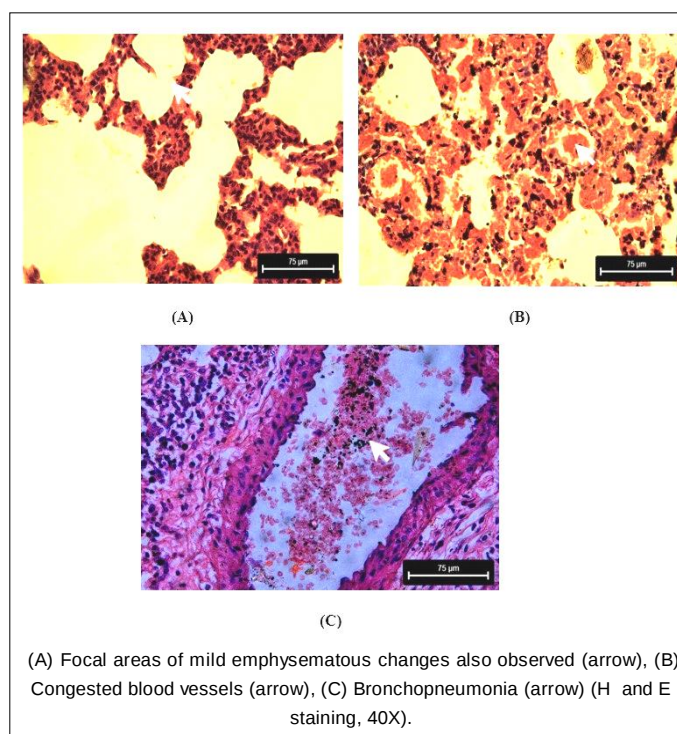


Fig 7: Histopathological changes in lung tissue.

ultimately causing nervous system breakdown. The elevated body temperature was followed by widespread damage to visceral organs, including the heart, liver, lungs and kidneys. These pathological changes were most pronounced in the lungs, liver and kidneys, with significant congestion and vascular damage. The increase in heart rate and blood flow to the muscles, brain and heart further compounded the stress, leading to systemic organ failure, which was further corroborated by electron microscopic observations. (Aswathi *et al.*, 2019) reported that in broiler breeder hens, acute heat stress resulted in significant physiological disturbances, including increased surface temperatures and altered serum biochemical parameters, reflecting the systemic impact of elevated temperatures.

Rats subjected to acute heat stress exhibited a significant increase in body temperature, in line with the findings of (Zhang *et al.*, 2023). Stress is defined by a sharp rise in body temperature, caused by sustained exposure to high environmental heat. Literature indicates that heat dissipation mechanisms are activated under such conditions, yet the body struggles to cope with the sudden temperature surge. This acute thermal stress is particularly potent because it disrupts the body's usual ability to regulate temperature, as mammals typically maintain a stable internal temperature with minimal circadian variation (± 1.00 to 1.50°C). Thermosensitive neurons in the hypothalamus play a critical role in detecting changes in temperature, integrating central and peripheral thermal data to elicit an optimal response for the given environmental conditions (Song *et al.*, 2016).

In line with previous studies, rats exposed to acute heat stress displayed elevated plasma corticosterone levels, indicating the activation of the stress response. Prolonged exposure to high temperatures rapidly mobilizes lipids and amino acids, triggering gluconeogenesis and resulting in heightened corticosterone secretion (Indu *et al.*, 2016). This adaptive response is essential for providing the energy necessary to cope with the physiological demands of heat stress. However, prolonged exposure may eventually lead to maladaptation, with corticosteroid levels returning to baseline as part of a feedback mechanism similarly observed by (Memon *et al.*, 2017).

The brain tissue of heat-stressed rats displayed distinct histopathological alterations, with mild satellitosis and neuronophagia observed, similar to findings by Ahmed *et al.* (2020) (Ahmed *et al.*, 2020). Gliosis, marked by an increase in glial cells, was evident. These cells responded to neuronal damage by surrounding degenerating neurons (satellitosis) and engulfing dead neurons (neuronophagia). The reactive alterations in astrocytes, including swelling, eosinophilic cytoplasm and nuclear vesiculation, are indicative of a response to tissue injury (Pekny *et al.*, 2016). The prominence of astrocytosis and its progression into a glial scar underscores the lasting impact of heat-induced neuronal damage.

The heart tissue showed significant changes, with severe congestion of blood vessels and hemorrhage, resulting from obstructed blood flow and increased afflux. Cardiomyocytes displayed pyknotic changes, reflecting the detrimental effects of heat-induced endothelial cell damage and elevated blood pressure, which likely triggered autonomic responses and vascular rupture (Mirza *et al.*, 2022). High temperatures can cause the degeneration of cardiomyocytes by denaturing proteins and inducing hypoxic conditions. Heat-induced vasodilation reduces blood flow to the heart, exacerbating hypoxia and leading to cellular death. The disruption of protein structures-critical for the formation of cardiac muscle fibers-further contributes to the loss of cross-striation and degeneration (Das, 2011; Labib *et al.*, 2022). The vacuolization of cardiomyocytes and loss of muscle contractility are clear markers of heat-induced myocardial damage.

Heat stress led to profound changes in the kidneys, particularly in the renal corpuscles and the proximal and distal convoluted tubules. The kidneys exhibited cloudy swelling of tubular epithelial cells, accompanied by pyknotic changes in the lining cells, suggesting a breakdown in cellular homeostasis. This phenomenon is likely due to the reduction in renal blood flow caused by vasodilation and increased blood flow to the skin for heat dissipation, ultimately resulting in decreased oxygen delivery to the kidneys and a lack of ATP energy (Vogt, 2020). Additionally, the pronounced vacuolar degeneration seen in the tubular epithelial cells supports the hypothesis that cellular swelling is due to the influx of ions and water, further exacerbating tissue damage (Savioli *et al.*, 2022).

Liver tissue in heat-exposed rats showed significant congestion in the sinusoids, hepatic artery and portal vein, consistent with findings from Wang *et al.* (2013) (Wang *et al.*, 2013). The activation of Kupffer cells-macrophages in the liver-was evident, as these cells changed shape in response to heat-induced inflammation (Hamada *et al.*, 1999). The congestion and narrowed sinusoidal spaces further reflected disrupted blood flow, while bile duct proliferation indicated a compensatory response to liver cell damage. This process, driven by oxidative stress and cellular injury, underscores the liver's attempt to repair itself in the face of heat-induced damage. Hepatic stellate cell activation and fibrosis were also observed, suggesting a long-term risk of hepatic insufficiency in animals subjected to prolonged thermal stress (Qian *et al.*, 2025).

Heat stress also caused significant changes in lung tissue, with hyperplasia of peri-bronchial lymphoid follicles and severe congestion in the pulmonary vasculature. The lungs displayed signs of inflammation, including interstitial pneumonia, with the infiltration of mononuclear cells and neutrophils. Additionally, thickening of the inter-alveolar septae due to the infiltration of lymphocytes and epithelioid cells suggested early-stage pulmonary fibrosis (Luca *et al.*, 2024). These observations are in line with findings from Yokohira *et al.* (2014), who demonstrated that prolonged

heat exposure leads to compromised pulmonary function, including disrupted surfactant production and impaired alveolar function. The structural damage, including localized emphysematous changes and bronchopneumonia, provides critical insights into the potential long-term effects of heat exposure on respiratory health (Yokohira *et al.*, 2014).

CONCLUSION

This study underscores heat stress as one of the most devastating forms of heat-related illness, surpassing conditions such as heat cramps and heat exhaustion in terms of its severe physiological consequences. The findings provide essential insights into the profound histopathological changes occurring in multiple organs subjected to extreme environmental heat, offering a deeper understanding of the systemic effects of prolonged heat exposure. Specifically, our results demonstrate that exposure to elevated temperatures leads to significant alterations in the histological integrity of various organs, with pathological changes ranging from congestion and inflammation to tissue necrosis. These findings are consistent with previous research, further affirming that hyperthermia can precipitate multi-organ dysfunction, with the potential for fatal outcomes. This study not only reinforces the catastrophic impact of heat stress on organ health but also establishes a critical foundation for future investigations, providing a vital framework for understanding how global warming and rising temperatures are increasingly threatening mammalian health on a physiological level.

ACKNOWLEDGEMENT

The authors sincerely thank Mr. Ahmad Hussain, research scholar at Birla Institute of Technology, Mesra, Ranchi, Jharkhand (India), for his valuable support during the histopathological experiments.

Funding

None.

Consent to participate

Permission to work with rats was obtained from the Institutional Animal Ethics Committee. The experiment was carried out following ethical guidelines for animal research at Birla Institute of Technology, Mesra, Ranchi, Jharkhand, India (protocol #1972/PH/BIT/05/23/IAEC).

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were carried out by Anjali Kumari and Rakesh Kumar Sinha. The first draft of the manuscript was written by Anjali Kumari and all authors provided comments on previous versions. All authors reviewed and approved the final manuscript.

Consent for publication

Not applicable.

Data availability

The data presented in this study were collected by the authors themselves, with no data sourced from other external sources. Therefore, no permissions were required for data access from other sources.

Conflict of interest

The authors declare no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the study's design, data collection, analysis, decision to publish or manuscript preparation.

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