Increased incidence of heatstroke in India: Is there a genetic predisposition?

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Abstract

Epidemiological studies have shown that heat waves lead to increased mortality due to heatstroke. Many authorities including the Indian Meteorological Department have predicted that various parts of India will experience heat waves more frequently in the near future. Therefore, higher frequency of heat waves may cause more heatstroke mediated casualties in India. Although heatstroke deaths are preventable, the Government of India and its various nodal agencies seem to lack in proper planning on this front. Currently it is believed that heatstroke deaths are due to failure of cooling mechanisms and simultaneous accumulation of heat from either metabolic processes or passively from the hot environment. But, the contribution of any erroneously hyper-activated heat generating mechanism(s) to heatstroke has not been investigated so far. Futile calcium (Ca$^{2+}$) handling in skeletal muscle is known to be the cause of malignant hyperthermia that is an analogous disease condition where body temperature of the patient increases rapidly. Further, it has been shown recently that mutation in ryanodine receptor makes the channel unstable leading to release of Ca$^{2+}$ from the sarcoplasmic reticulum of skeletal muscle activating futile Ca$^{2+}$-handling. Therefore, the possibility of mutation in Ca$^{2+}$-handling proteins as a factor predisposing to heatstroke needs to be studied. This will help in identifying individuals who are genetically susceptible to heatstroke in India and open up scope to channelize prevention efforts accordingly. Such exploratory research on Indian population requires financial as well as administrative support from the key agencies of the Government of India.

Key words: Heatstroke, Ca$^{2+}$-handling proteins, thermoregulation, heat waves

Introduction

Global warming has received much scientific and political attention in last four decades. As fallout of global warming, in the last two decades many parts of the world have experienced long durations of hot environment (hotter than the average temperature by >5°C) so called as heat wave conditions (HWC) (1-5). The temperature in India is projected to rise progressively in the next decades (Fig. 1) by many studies around the globe (1,2,6,7). In the past decades, there have been reports of casualties of both human and animals from the areas affected by HWC (7-17). The HWC associated casualties has been reported with different terminologies such as, heatstroke, sunstroke, environmental hyperthermia-related death, loo-induced death due to hyperthermia, heat hyperpyrexia etc (18-20) primarily due to overlap between these conditions. Here we have chosen to use “Heatstroke” as a broad term and heat induced heatstroke (HIHS) to indicate cases induced by the HWC.

Many different parts of India experience moderate to severe HWC each year and many in regions where it is associated with significant humidity. It has been noted that HWC associated with high humidity result in more HIHS cases than in the dry ambience. The recent report from Indian
Meteorological Department (IMD), Ministry of Earth Sciences, Government of India, forecasts that average temperature of India will rise in next few years, which indicates an increased occurrence of severe HWC in the next decade. Therefore, it is timely to discuss the scientific basis for HIHS cases, preparedness of governments, and further research.

**Types of heatstroke and occurrence**

Heatstroke is a condition usually diagnosed by an elevated core body temperature (Tc>40°C) and symptoms might include dysfunction of central nervous system (CNS), delirium, convulsions or seizures, coma which can result in a life-threatening situation. Heatstroke can be categorized into two types depending on the possible cause; classic and exertional (18,21-25).

**Classic heatstroke** is caused by environmental exposure and results in core hyperthermia above 40°C. Classic heatstroke can develop slowly over several days and can present with minimally elevated core temperatures. It is often associated with CNS dysfunction, delirium, convulsions making it difficult to distinguish clinically from sepsis. This condition primarily occurs in the elderly and those with chronic illness.

**Exertional heatstroke** is a condition primarily affecting younger, active persons often reported after strenuous exercise. It is frequently associated with high core body temperatures and characterized by rapid rise in body temperature within hours. This can be lethal if not contained within first hours of onset. The progression of severity depends on many factors like environmental condition, age of the person, medications, association of other comorbidities etc.

Both of above categories of heatstroke cases can be found in India and even in many cases it might be very difficult to strictly categorize into either of the two as symptoms of both the kinds may be observed. HIHS cases in India affect mostly people working under the sun in the middle of the day during HWC (9,12,15). The failure of thermoregulation lead to HIHS and so thermoregulation needs to be considered in brief. Mammals including humans have evolved an efficient mechanism of thermoregulation with a thermostat in the CNS/ hypothalamus to sense the ambient temperature by sensory neurons dispersed all over the skin. Heating and cooling mechanisms are recruited depending on the temperature difference between the ambient and set temperature in the thermostat. Thermoneutrality is the temperature at which human body neither gains from nor dissipates heat to the environment. For humans, the temperature of thermoneutrality can range from 25 to 31°C depending on the acclimatization status of the individual. As the ambient temperature rises above the thermoneutrality cooling mechanisms are recruited depending on need. Perspiration or sweating is the most efficient cooling mechanism for humans as sweat glands are distributed in skin all over the body (26,27). The rate of sweating is graded and increases as ambient temperature continues to rise. But when ambient temperature increases beyond 40-45°C the net gain...
of heat from the environment becomes higher than the cooling capacity of the body and heat starts to be accumulated. The rate of heat accumulation can even be more during exercise or physical activity under sun and add to HIHS. Another factor which also has a significant influence on heat dissipation vs. accumulation is relative humidity (27,28). If environment is humid cooling due to evaporation of sweat is less and leads to increase in heat accumulation raising the chances of HIHS, although probability of death from heatstroke is not solely dependent on body temperature as explained in details by Sucholeiki (26).

Reported HIHS Cases

**Worldwide:** Report of death due to hyperthermia was first reported in 1946, while first report of heatstroke from India came only in 1975 (29). The study by Hart et al in 1982 is probably the first study focused towards defining the clinical characteristics of heatstroke in human patients (30). However, all these studies are mostly non-HIHS cases. Cases of HIHS due to HWC were first reported in 1993 from Philadelphia County, USA where majority of the affected persons were elderly (12,31-33). It is in 1995, when many HIHS cases were reported around the world. The city of Chicago, USA was probably the worst hit reporting about 700 deaths within 7 days (13 to 20 July, 1995) (34,35). Second worst hit region was probably England and Wales, which recorded hottest August since 1659 and about 600 cases were reported in July/august 1995 (36,37). The most interesting causes reported in this study for HIHS deaths were; “heat island” effect caused by the heat retaining properties of the densely built urban buildings, level of air pollutants and relative socioeconomic deprivation (1,10,38-40). Chicago and Milwaukee area experienced another HWC in 1999; however the death toll could be contained better than 1995 showing better preparedness of the related personnel (41-43). Next worst hit year was 2003, when cases of HIHS were reported from worldwide including France (~15,000), Spain (~6,100), Portugal (~2,000), Italy (~3,000), and to lesser extent in western European counties (40,44-54). HIHS cases from Japan and Australia have been reported (22,55,56). In all the above incidences in the developed world most susceptible population were elderly, beyond 65 years of age (57,58). HIHS cases have also been reported among Haj pilgrims in Saudi Arabia (59-60).

**India:** Ironically, HIHS was reported for the first time form the Indian subcontinent by the British troops during Indian Mutiny (1857) although at that time it was called as ‘Classic Fatigue Syndrome’ (29). However, the designated Indian Government agency IMD started recording deaths due to HWC only since 1979. But, most of the HIHS data from various parts of India has not been analyzed critically and presented as scientific literature. IMD Annual Reports on ‘Disastrous Events’, reported 1662 deaths in 1998 and 1539 deaths in 2003 from all over India (3). However, Orissa government reported 2042 HIHS deaths in the year 1998 in the state of Orissa alone indicating absence of consistency in data from different agencies in India (61). However, many newspapers from different parts of India reported casualties due to HWC. In Andhra Pradesh alone when the temperature touched 49ºC in 2002 over 1000 people lost their lives (29). Based on media (news paper, television etc.) reports, the most affected states in India are; Orissa, West Bengal, Andhra Pradesh, Tamil Nadu, Bihar, Uttar Pradesh, Maharashtra and Delhi (Fig. 2).

**Epidemiological comparison:** If one compares statistics of HIHS cases between India and developed countries few distinct differences that emerge clearly are: 1) age-wise distribution is more homogeneous in India compared to the developed countries where old-age population is primarily affected. 2) Most susceptible groups in India seem to be daily-waged workers and labourers.

Majority of the HIHS affected individuals in India are in their physically active adult life (aged between 20-55 years) and earning members of family. Therefore, the socio-economic cost of this public health issue (HIHS) is much higher for India than appreciated. Another interesting angle to look at is urban workers are more susceptible to HIHS than rural at same temperature, which probably can be explained with “heat island” effect. This situation can be expected to worsen in the near future with increasing unplanned development like; construction of multistory cement buildings, laying down of asphalt roads, aggressive mining, unplanned growth of over-polluting industries etc. leading to massive denudation of the forest cover. Fortunately, death due to HIHS can be minimized as HIHS is preventable. This needs better preparedness and planning on the part of government, non-governmental organizations as well as informed people. Further, the molecular basis of HIHS is currently unknown there is a bottleneck to design prevention strategy or treat such patients (discussed in more details below).

**Preparedness to meet this challenge in near future**

As IMD has already forecasted a progressive increase in temperature in India in next decade, central government and specially the affected state governments should have better plans to tackle with this problem. However, the central government of India seems to be reluctant to this upcoming problem in the near future, as HIHS has not been designated as a calamity under National Disaster Management Authority (NDMA) (62-64). Neither special funds have been mobilized...
Fig. 2: Recent occurrence of deaths due to HIHS in different parts of India. Compiled from various sources including newspapers. There is very few published literature on the statistics of HIHS case in various states of India. The map of India used here was downloaded from www.mapsofindia.com.

to augment research both clinical and basic designed towards understanding the molecular mechanism of HIHS under the umbrella of Indian Council of Medical Research (ICMR), Ministry of Science and Technology (MST), Council of Scientific and Industrial Research (CSIR), or Department of Biotechnology (DBT). It can be pointed out that while research efforts have been augmented by many of these scientific bodies for many recently observed diseases like SARS (Severe Acute Respiratory Syndrome), chikanguniya etc. HIHS is neglected.

However it is noteworthy that some government of affected states like Orissa has recognized HIHS as a disaster, after death of 2045 people due to the HWC in 1998. The government of Orissa set up an organization named “Orissa State Disaster Management Authority (OSDMA)” in December 1999 after two massive disasters in two consecutive years; HIHS deaths in 1998 and super-cyclone in 1999 (61). OSDMA has mandate to manage disasters by increasing preparedness and also to take up the mitigation activities. OSDMA took up massive awareness campaigns against HIHS resulting in reduced deaths in the following years due to HWC. Similar measures are required in other affected states. At the same time debate needs to be started among scientific research communities as well as clinical personnel with practical experience in HIHS death cases to understand molecular mechanisms leading to HIHS.

Current strategies of treatment for heat stroke

Although no effective drug is known, the most successful among the treatment measures is cooling of the body. Rapid cooling of patients by conduction by placing them on large ice blocks and aeration by blowers has been used in Middle Eastern countries. Cold water immersion, body cooling blankets and “spray and fan techniques” have been utilized in different parts of the world. Sophisticated body cooling units (BCUs) have been reported from western developed countries, while its locally adaptable methods have been used in third world countries (29). An ingenious method of ‘cold intravenous infusion’ has been tried successfully in
the Haj pilgrims in Saudi Arabia (29). On the other hand, research at biochemical/molecular level in recent decades has shown the hope of finding therapeutic intervention in near future. Interleukin-1 receptor antagonists and glucocorticoids have been shown to be protective (65-67). Heat Shock Proteins (HSPs) and agents increasing HSPs production have also been proposed (25, 68).

HIHS lead towards other organ failure and/or comorbidity and has to be effectively managed while focusing on cooling the body (66). First condition that is frequently observed is hypotension and can be improved by blood volume expansion. Vasopressors, furosemide, mannitol, and/or sodium bicarbonate are helpful in protecting renal function in the presence of rhabdomyolysis. Recombinant activated protein C has been considered for use in Disseminated intravascular coagulation (DIC), a condition associated with HIHS (69). While seizures associated with HIHS can be managed with benzodiazepines (26). Dantrolene, an antipyretic medication that is successful in managing malignant hyperthermia, has been shown to have marginal effect on HIHS patients (18,26). But there are still large gaps in the current understanding of details of the molecular mechanisms leading to HIHS condition; however a better knowledge can open scope of finding new targets for pharmacological intervention and needs to be debated upon.

**Potential mechanisms contributing to heat stroke**

Human body is equipped with thermoregulatory processes that maintain its temperature nearly constant at 37°C. Heat is generated within the body by active thermogenic processes and also metabolic processes. Excessive heat is dissipated by evaporative cooling using sweating, which is controlled by central nervous system through hypothalamic thermoregulatory center (70,71). If the balance between heat production and heat dissipation is affected it results in either hypothermia or hyperthermia. Currently, it is believed that heatstroke is caused by a dysregulation in hypothalamic thermoregulatory center to efficiently cool the body in hot humid climate (Figure 3). However, failure of cooling alone without any heat production mechanism cannot explain the rapid rise in body temperature at a rate of 2-4°C/hour (observed in some HIHS patients). In the case of exertional HIHS, high intensity physical activity precedes the HIHS episode. During the main phase of body temperature increase active muscle contraction has already reached a basal level and its contribution to heat production must be minimal. Hence, the heat production inside the body must be coming from Non-Shivering Thermogenic (NST) mechanisms such as Brown adipose tissue (BAT) and muscle. However, BAT has been shown to be activated only by cold not heat and BAT is also

![Fig. 3: Molecular mechanism of HIHS](www.gerfbb.com)

HIHS is currently believed to be caused due to failure of cooling associated with accumulation of heat from metabolic processes. But the site of heat production during HIHS is not known. We propose that the mechanism of heat production in HIHS is similar to MH. Skeletal muscle Ca^{2+}-handling is activated via some unknown mechanism leading to heat production as shown in figure 4.
During each contraction, Ca$^{2+}$ is released into the cytoplasm from an internal store namely sarcoplasmic reticulum via the Ca$^{2+}$ release channel (RYR1). This leads to an increase in cytosolic calcium thereby activating myosin to interact with actin filaments. In this sequence Myosin ATPase hydrolyzes ATP to power muscle contraction. The cytosolic calcium is then taken up by Sarcoplasmic/endoplasmic reticulum Calcium ATPase (SERCA) into the SR lumen thereby causing muscle relaxation (84-86). These two ATPases, Myosin ATPase and SERCA use significant amount of ATP and generate heat from ATP hydrolysis. During exercise or shivering ATP utilization and heat production by myosin is well known. But in HIHS where temperature rises acutely, the individual is often immobile and therefore muscle contraction does not play an important role in heat production. This observation suggests that there must be other mechanisms for continuous increase in heat production. One possibility is some of these patients may very scant in humans in their adult life (72,73). Therefore, involvement of BAT mediated heat production in the case of HIHS can be ruled out. Studies from various laboratories including ours have shown that Ca$^{2+}$-handling in the skeletal muscle is involved in NST (73-77). Further, abnormal Ca$^{2+}$-handling is the basis for malignant hyperthermia (MH) (78-83), a lethal condition if untreated where body temperature increases above 40c as found in HIHS patients. This condition is often associated with mutations in ryanodine receptor 1 (RYR1) resulting in abnormal Ca$^{2+}$ release and such patients become susceptible to MH when exposed to anesthesia or heat. We suggest that a similar molecular mechanism may operate in the case of heatstroke and MH.

Proteins regulating Ca$^{2+}$- Cycling in muscle: Ca$^{2+}$ cycling is central to muscle contraction and this is achieved by a specialized set of proteins located in muscle membranes.

**Fig. 4: Proposed mechanism of heat production during HIHS.** Association of Ca$^{2+}$-handling proteins in the skeletal muscle in HIHS has not been studied so far. Our studies showing involvement of SLN in heat production during cold challenge indicate that futile Ca$^{2+}$-transport in skeletal muscle is inducible and might be a key component of heat production during HIHS. This cartoon was prepared following the illustrations by Dr. Bers (96).
develop a condition leading to abnormal Ca\textsuperscript{2+} cycling that may activate SERCA mediated heat production. However the role of abnormal Ca\textsuperscript{2+} cycling in HIHS remains to be investigated.

**Genetic predisposition to heat stroke**

It is also a common observation that some individuals are more susceptible to heatstroke. However, to date there is no known mutation that predispose to HIHS. The mutations in any proteins that can activate the futile Ca\textsuperscript{2+}-cycling in skeletal muscles predisposing the bearer of the mutation to HIHS and are discussed below;

1. **Ryanodine receptor 1(RyR1):** Mutations in RyR1 has been well-characterized for causing MH in humans. The leak in RyR1 can be triggered by anesthetics or heat and leads to a continuous cycling of Ca\textsuperscript{2+} thereby causing increased ATP hydrolysis and excessive heat production leading to hyperthermia. The symptoms of MH and HIHS are similar and it might be possible that RyR1 mutations predispose people to HIHS. This is has not been investigated in various population in India. In a recent study it has been shown that RyR1 become inherently leaky in aging skeletal muscle (87). It is interesting to be pointed out that in the developed countries the older population is susceptible to HIHS. Older people might have leaky RyR1 that increase futile Ca\textsuperscript{2+}-handling in skeletal muscle predisposing them to HIHS. However, such a possibility has not been investigated.

2. **Calsequestrin 1 (CASQ1):** It is the major Ca\textsuperscript{2+}-binding protein present in the SR lumen and is a constituent protein of the RYR1 complex. CASQ1 regulates the RYR1 gate and its absence leads to a leaky RYR1 thereby resulting in increased Ca\textsuperscript{2+}-cycling (88-90). Recently, CASQ1 null mice were shown to be susceptible to MH when exposed to halothane and temperature above 40°C (91). This finding suggest that when the RYR1 complex is unstable its chance of opening the gate (so Ca\textsuperscript{2+}-release) at higher temperature becomes greater, indicating possible role of CASQ1 in activating the futile Ca\textsuperscript{2+}-cycle.

3. **SERCA-SLN:** Although, RyR1/CASQ1 can act as trigger for the futile Ca\textsuperscript{2+}-cycle cannot produce heat themselves. SERCA has long been proposed to be a thermogenic protein (73,75,92-94), although its regulation to cause heat production has been speculative. We have recently shown that SLN, an inhibitor of the SERCA, is important in body temperature maintenance (95). SLN is a small 31 amino acids single transmembrane peptide found in the skeletal muscle SR. In larger mammals including humans its expression is very high in all the skeletal muscles. Further, *in-vitro* studies have shown that SLN can increase heat production by uncoupling SERCA-mediated ATP hydrolysis from Ca\textsuperscript{2+}-transport (Fig. 4). Hence, mutation in either SERCA or SLN may affect heat production by their interaction.

**Conclusion**

Although, currently unknown it seems from the above discussion that mutation in any of the proteins that can initiate the dysregulated Ca\textsuperscript{2+}-transport in skeletal muscles might be a contributing factor in HIHS. Mutations in RyR1 are already known to predispose to MH which makes a convincing case for exploratory investigation to identify mutations in the above proteins in the people susceptible to HIHS. This knowledge can be translated to reduce casualties among the predisposed populations through public health approaches like awareness campaigns, clinical surveillance, provisioning of safer work, medical monitoring of working conditions etc. In order to make progress in this direction Indian government and central government agencies (ICMR, DST, DBT and Prime Minister’s Office) have to make initiative. Specifically, ICMR should plan out research strategy in this direction in the near future. One first step might be to set up a task force team to assess the extent of HIHS mediated casualties in different parts of India as such statistical data on HIHS is lacking.

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