Twenty-Seven Ways a Heat Wave Can Kill You:
Deadly Heat in the Era of Climate Change

Camilo Mora, PhD; Chelsie W.W. Counsell, MSc; Coral R. Bielecki, BS; Leo V Louis, BS

Heat waves, sporadic events of extreme heat, pose a threat to human life. Deaths in excess of 70 000 people during the 2003 European heat wave, 10 000 people during the 2010 Russian heat wave, and high death tolls from numerous other heat waves[1] are staggering demonstrations that extreme climatic conditions are already exceeding human thermoregulatory capacity. The area of the planet experiencing heat wave conditions similar to those that have killed people is expanding and is currently inhabited by ≈30% of the world's human population.[1] Because the planet will warm another 1°C by 2100 if we curtail greenhouse gases or 3.7°C if we do not, our choices for deadly heat are now between more of it or a lot more of it.[1] Here we carried out a systematic synthesis of deadly heat physiological pathways to make the point that the human body is sensitive to heat and that heat waves can harm anyone (even the young and healthy[2,3]) in ways that extend beyond cardiovascular diseases. We suggest that only the rapid reduction of greenhouse gases paired with large economic investment in adaptation will help us escape the health risks of heat waves.

How Deadly Heat Kills

Ambient conditions that prevent body heat dissipation (eg, too hot, too humid, or both) trigger dangerous physiological responses or pathways that have been a topic of considerable medical interest for "military personnel, athletes, and occupations exposed to extreme heat, such as mining."[4] To systematically synthetize these deadly pathways, we searched online databases (ie, PubMed and Google Scholar) using the key words *pathophysiology* and *heat illness*, *heat stroke*, or *heat stress*. We categorized pathways in a table listing physiological mechanisms by columns and vital organs impacted by rows. We performed secondary searches combining as key words the mechanism (column name) and organ (row name) of empty cells in our table to ensure that empty cells represented a lack of evidence. In total, we identified 5 physiological mechanisms triggered by heat exposure (ie, ischemia, heat cytotoxicity, inflammatory response, disseminated intravascular coagulation, and rhabdomyolysis) and 7 vital organs that can be critically impacted (ie, brain, heart, intestines, kidneys, liver, lungs, and pancreas; Table). Of 35 possible combinations (5 physiological mechanisms times 7 vital organs), we found medical evidence for 27 different pathways by which physiological mechanisms triggered by heat can lead to organ failure and ultimately death (Table). No single publication reported all physiological pathways highlighting the comprehensive scope of our synthesis.

Dying from extreme heat can result by 1 or several pathways. When the human body is exposed to heat, the hypothalamus triggers a cardiovascular response that dilates blood vessels to redirect blood from the core to the periphery of the body, where heat is dissipated to the environment. This compensatory shunting of blood to the skin results in inadequate blood flow to other organs (ie, ischemia; 1 of the 5 identified mechanisms). Ischemia and subsequent hypoxia (ie, low oxygen) lead to the production of reactive oxygen and nitrogen species. Another heat damaging mechanism occurs when body temperature surpasses cell thermal tolerance (ie, heat cytotoxity). Both, ischemia and heat cytotoxity, cause cell death (ie, necrosis) and break down the integrity of cell membranes.

Cell damage from thermal and chemical injury (through heat cytotoxicity and ischemia, respectively) can affect the functioning of several organs. In the heart, compounding factors of heat cytotoxicity, ischemia, and hypokalemia (ie, a potassium deficiency because of sweating and urination) can lead to the fragmentation of the myocardium. This assault on the heart muscle increases the risk of cardiac arrest because of the loss of myofibrillar striations and decreases the effectiveness of the body to regulate heart rate and blood pressure. Stress on the heart can be further exacerbated by dehydration, which thickens the blood and causes vasoconstriction, increasing risks of coronary thrombosis and stroke. Cell damage from heat cytotoxicity and ischemia can lead to other serious conditions, such as acute tubular necrosis in the kidneys, permanent loss of brain function, liver endotoxins in the blood, inflammation of the pancreas, and not enough oxygen getting to the lungs and into the blood because of injury of the pulmonary endothelium.

Heat cytotoxicity and ischemia can also break down cell membranes increasing the permeability of organs to pathogens and toxins. In the pancreas, erosion of the endothelial wall enables leukocyte infiltration exacerbating the inflammation

From the Department of Geography, University of Hawai'i at Mānoa, Honolulu, HI (C.M.); Hawai'i Institute of Marine Biology, University of Hawai'i at Mānoa, Kāne'ohe, HI (C.W.W.C.); School of Forestry and Environmental Studies, Yale University, New Haven, CT (C.R.B.); and Department of Natural Resources, Cornell University, Fernow Hall, Ithaca, NY (L.V.L.).

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.117.004233/-/DC1.

Correspondence to Camilo Mora, PhD, Department of Geography, University of Hawai'i at Mānoa, Honolulu, HI 96822. E-mail cmora@hawaii.edu

(*Circ Cardiovasc Qual Outcomes.* 2017;10:e004233. DOI: 10.1161/CIRCOUTCOMES.117.004233.)

Table. Organs Damaged by Physiological Mechanisms Triggered by Heat Exposure

Organs	Mechanisms				
	Ischemia	Heat Cytotoxicity	Inflammatory Response	Disseminated Intravascular Coagulation	Rhabdomyolysis
Brain	①	⑦	⑬	⑳	
Heart	②	⑧	⑭		
Intestines	③	⑨	⑮	㉑	
Kidneys	④	⑩	⑯	㉒	㉕
Liver	⑤	⑪	⑰	㉓	㉖
Lungs		⑫	⑱	㉔	㉗
Pancreas	⑥		⑲		

These interactions should be taken as feasible pathways through which heat can damage vital organs and result in death. The frequency in which these pathways were cited in the literature cannot be used as indication of the risk of occurrence of specific pathways because publications are more likely related to the extent to which novel insights are obtained for the different pathways as opposed to how frequent they occur. Supporting references are provided in Table I in the Data Supplement.

of the pancreas. In the brain, permeability of the blood–brain barrier allows infiltration of damaging toxins and pathogens increasing the risk of neurological damage. In the intestines, the erosion of the mucosal lining allows for the leakage of bacteria and endotoxins into the blood, critically leading to sepsis and the activation of a systemic inflammatory response (ie, the third identified mechanism). Although an inflammatory response can be a positive mechanism for healing epithelial wounds and controlling infection by facilitating access of white blood cells (ie, leukocytes), it can become detrimental if hyperthermia persists. In such a case, inflammatory mediators (eg, cytokines) disrupt cell homeostasis and organ function by exacerbating leakage from the impacted organs (ie, the inflammation that enables leukocyte infiltration can also facilitate leakage) and adding to epithelial injury (ie, activated leukocytes release nitric oxidase and enzymes, which can be erosive).

Systemic inflammation and injury of the vascular endothelium because of ischemia and heat cytotoxicity can trigger another damaging mechanism called disseminated intravascular coagulation. Here, proteins that control blood clotting (ie, thrombins) become overactive, potentially resulting in clots that cut off blood supply to vital organs. Subsequently, depletion of clotting proteins can lead to potentially fatal hemorrhaging even without injury. The fifth identified mechanism, rhabdomyolysis, occurs when heat cytotoxicity, ischemia, or hypokalemia break down skeletal muscle cells, thereby releasing myoglobin, which is toxic to nephrons and can cause acute renal failure by clogging kidney tubules. All of the above physiological responses are interrelated such that dysfunction in 1 organ has negative effects on others, triggering a vicious cycle of multiorgan deterioration,[5] which often leads to death, permanent disabilities, or lengthy recovery.[6]

Climate Change, Deadly Heat, and Global Health Disparities

Our synthesis reveals the multitude of ways to die during a heat wave and provides a worrisome glimpse into what a warming planet may have in store for us. The described deadly heat pathways can be triggered anytime that climatic conditions result in hyperthermia, highlighting that everyone can be at risk. More importantly, they also suggest even greater vulnerability for individuals with compromised thermoregulatory capacity (eg, the old, the young, and the sick), those with limited socioeconomic capacity (eg, the poor and the isolated), and those engaged in strenuous outdoors activities. Although some physical resilience to heat may be gained through acclimation, numerous constraints prevent humans from rapidly evolving higher heat tolerance.[4,7] Instead, the health impacts of heat waves could be reduced through social adaptations that limit heat exposure (eg, alert systems, air conditioning, and greening cities).[8,9] Although such protective measures have been effectively used in the past,[8,9] they may not be affordable for all of humanity,[4,7] and even among those who can afford them, a warming world will recurrently "imprison people" indoors[4,7] and may turn infrastructure failures (eg, power outages) into catastrophic events.

With such widespread consequences for human health from a warming planet (not to mention linked impacts from droughts, wild fires, storms, floods, sea-level rise, etc), one would expect large public concern about climate change. Yet, according to Pew polls, only 36% of people in the United States, 54% across countries, are personally concerned about climate change. Among several explanations for this climate denial and reduced sense of concern is our optimism bias; basically, climate change may be bad but will not affect me. Remarkably, scientists may be unintentionally fostering this bias. For instance, the latest Intergovernmental Panel on Climate Change Report and the United States Climate Assessment both noted that heat waves pose a threat to human health through heat stroke, mainly in elderly, poor, or isolated people. This narrative can feed our optimism bias because heat stroke alone oversimplifies the many physiological ways by which heat waves kill and thus falls short of depicting our high sensitivity to heat; likewise, the suggestion that only some sectors are at risk could generate a false sense of security for those who are not in any of those vulnerable groups. Such an optimism,

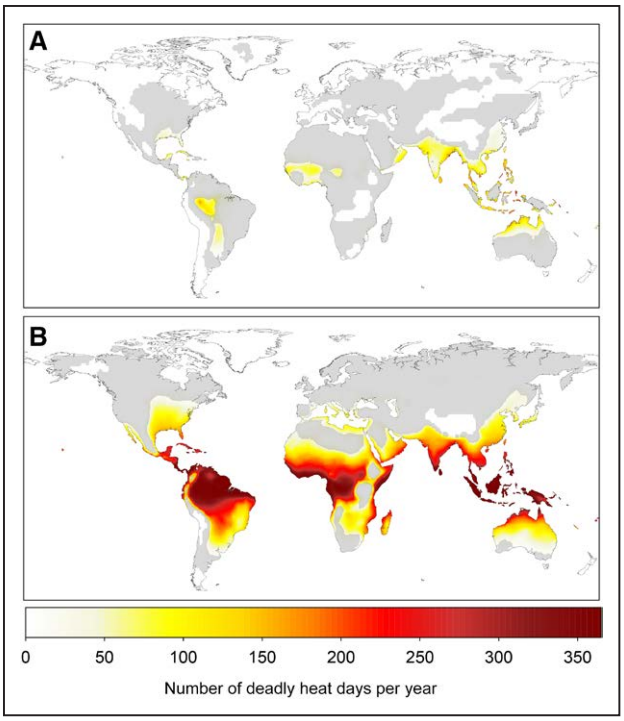

Figure. Global distribution of deadly heat. These maps illustrate the number of days per year in which climatic conditions exceed the threshold of temperature and humidity beyond which human death has occurred during prior heat waves. **A**, Yearly averages from 1995 to 2005 and (**B**) from 2090 to 2100 under business as usual emission of greenhouses (technically referred as Representative Concentration Pathway 8.5). Data taken from Mora et al.[1]

however, is unwarranted because as noted in this article, there is a multitude of ways things can go wrong during a heat wave (Table), and they can happen to anyone, with of course much greater risk to individuals with compromised thermoregulatory capacity and those frequently exposed to heat.

In a recent analysis,[1] we found that by 2100, under current emission of greenhouse gasses, 3 of 4 people in the world will be exposed to deadly heat conditions every year, with a higher occurrence of these conditions in intertropical areas (Figure). The impacts will manifest differently with perhaps larger economic burdens of adaptation for the wealthy and higher death tolls for the poor. Given large socioeconomic differences within and among countries, heat waves could exacerbate global disparities in health, especially given the diminished resources for several of these regions to respond to acceleration in warming. In the last decade, there has been >2300% increase in the loss of human life from heat waves as a result of less than ≈1°C warming.[10] With 27 ways to die during a heat wave, the death toll that occurred with <1°C of warming emphasizes the heightened risk to human life even under the optimistic target of allowing the planet to warm up by another 1°C. Clearly, reducing the dangers of a warming world will require us to outperform even our most optimistic projections of climate change mitigation yet.

Acknowledgments

We thank Drs Bénédicte Dousset and Lisa R. Leon, MD, for their comments and advice on the article and Dr Adam Smith for his contribution in the early collection of data. This article was developed as part of the graduate course on "Methods for Large-Scale Analyses" in the Department of Geography, University of Hawai'i at Mānoa.

Disclosures

None.

References

1. Mora C, Dousset B, Caldwell IR, Powell1 FE, Geronimo RC, Bielecki CR, Counsell CWW, Dietrich BS, Johnston ET, Louis LV, Lucas MP, McKenzie MM, Shea AG, Tseng H, Giambelluca TW, Leon LR, Hawkins E, Trauernicht C. Global risk of deadly heat. *Nat Clim Change*. 2017;7:501–506.
2. Padilla V. Avid Hiker Dies After Suffering from Heat-Related Issues. http://www.abc15.com/news/region-northeast-valley/anthem/hiker-stops-breathing-after-suffering-from-heat-related-issues. Accessed October 10, 2017.
3. Maeda T, Kaneko SY, Ohta M, Tanaka K, Sasaki A, Fukushima T. Risk factors for heatstroke among Japanese forestry workers. *J Occup Health*. 2006;48:223–229.
4. Hanna EG, Tait PW. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. *Int J Environ Res Public Health*. 2015;12:8034–8074. doi: 10.3390/ijerph120708034.
5. Varghese GM, John G, Thomas K, Abraham OC, Mathai D. Predictors of multi-organ dysfunction in heatstroke. *Emerg Med J*. 2005;22:185–187. doi: 10.1136/emj.2003.009365.
6. Yeo TP. Heat stroke: a comprehensive review. *AACN Clin Issues*. 2004;15:280–293.
7. Sherwood SC, Huber M. An adaptability limit to climate change due to heat stress. *Proc Natl Acad Sci USA*. 2010;107:9552–9555. doi: 10.1073/pnas.0913352107.
8. Lowe D, Ebi KL, Forsberg B. Heatwave early warning systems and adaptation advice to reduce human health consequences of heatwaves. *Int J Environ Res Public Health*. 2011;8:4623–4648. doi: 10.3390/ijerph8124623.
9. Bassil KL, Cole DC. Effectiveness of public health interventions in reducing morbidity and mortality during heat episodes: a structured review. *Int J Environ Res Public Health*. 2010;7:991–1001. doi: 10.3390/ijerph7030991.
10. World Meteorological Organization. *The Global Climate 2001–2010, a Decade of Climate Extremes*. Geneva, Switzerland: World Meteorological Organization; 2013.

KEY WORDS: climate change ■ disseminated intravascular coagulation ■ ischemia ■ mortality ■ rhabdomyolysis

Twenty-Seven Ways a Heat Wave Can Kill You:: Deadly Heat in the Era of Climate Change

Camilo Mora, Chelsie W.W. Counsell, Coral R. Bielecki and Leo V Louis

Circ Cardiovasc Qual Outcomes. 2017;10:
doi: 10.1161/CIRCOUTCOMES.117.004233
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713

SUPPLEMENTAL MATERIAL

Table S1. Organs damaged by physiological mechanisms triggered by heat exposure. Numbers in the table indicate the reference that document the given mechanism influencing the specified organ.

Mechanism→ Organ ↓	Ischemia	Heat cytotoxicity	Inflammatory response	Disseminated intravascular coagulation	Rhabdomyolysis
Brain	(*1-6*)	(*4, 5, 7*)	(*3, 7-10*)	(*11, 12*)	
Heart	(*3, 6, 8, 13*)	(*8, 14*)	(*8, 11*)		
Intestines	(*5, 8, 11, 14, 15*)	(*16-19*)	(*2, 5, 8, 11*)	(*2, 5*)	
Kidneys	(*4, 20*)	(*2, 5, 21, 22*)	(*2*)	(*2-4, 11, 12, 21*)	(*2-5, 11, 21*)
Liver	(*23, 24*)	(*5, 24*)	(*2, 5*)	(*11, 12*)	(*25*)
Lungs		(*3, 15*)	(*26-28*)	(*29*)	(*3, 4, 11, 29*)
Pancreas	(*20, 30-32*)		(*32*)		

1. Chen S-H, Lin M-T, Chang C-P. Ischemic and oxidative damage to the hypothalamus may be responsible for heat stroke. *Curr Neuropharmacol* 2013; 11:129-140
2. Leon LR, Kenefick R. "Pathophysiology of heat-related illnesses" (DTIC Document, 2012).
3. Yarbrough BE, Hubbard RW, in *Management of Wilderness and Environmental Emergencies*. (Army Research Institution of Environmental Medicine, 1988).
4. Ceausu M, Hostiuc S, Dermengiu D, Curcă GC. Morphological diagnosis of hyperthermia-related deaths. *Rom J Leg Med* 2010; 18:239-246
5. Leon LR, Helwig BG. Heat stroke: role of the systemic inflammatory response. *J. Appl. Physiol.* 2010; 109:1980-1988
6. Hanna EG, Tait PW. Limitations to thermoregulation and acclimatization challenge human adaptation to global warming. *Int J Environ Res Publ Health* 2015; 12:8034-8074
7. Malamud N, Haymaker W, Custer R. Heat stroke. A clinico-pathologic study of 125 fatal cases. *Mil. Med.* 1946; 99:397-449
8. Bouchama A, Knochel JP. Heat stroke. *New Engl. J. Med.* 2002; 346:1978-1988
9. Kew M *et al.* The effects of heatstroke on the function and structure of the kidney. *QJM* 1967; 36:277-300
10. Shapiro SM. Bilirubin toxicity in the developing nervous system. *Paediatr Neurol* 2003; 29:410-421
11. Yeo TP. Heat stroke: a comprehensive review. *AACN Adv Crit Care* 2004; 15:280-293
12. Levi M, Ten Cate H. Disseminated intravascular coagulation. *New Engl. J. Med.* 1999; 341:586-592
13. O'Donnell TF, Clowes GH. The circulatory abnormalities of heat stroke. *New Engl. J. Med.* 1972; 287:734-737
14. Miyake Y. Pathophysiology of heat illness: Thermoregulation risk factors and indicators of aggravation. *Japan Med. Assoc. J.* 2013; 56:167-173
15. Hemmelgarn C, Gannon K. Heatstroke: thermoregulation, pathophysiology, and predisposing factors. *Compend Contin Educ Vet* 2013; 35:E4-E4
16. Leon LR, Blaha MD, DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. *J. Appl. Physiol.* 2006; 100:1400-1409

17. Lambert G *et al.* Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress. *J. Appl. Physiol.* 2002; 92:1750-1761
18. Oliver SR *et al.* Hyperthermia induces injury to the intestinal mucosa in the mouse: evidence for an oxidative stress mechanism. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2012; 302:R845-R853
19. Hall DM *et al.* Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *Am. J. Physiol. Heart Circ. Physiol.* 2001; 280:H509-H521
20. Warshaw AL, O'hara PJ. Susceptibility of the pancreas to ischemic injury in shock. *Ann Surg* 1978; 188:197
21. Varghese G, John G, Thomas K, Abraham O, Mathai D. Predictors of multi-organ dysfunction in heatstroke. *Emerg Med J* 2005; 22:185-187
22. Raju S, Robinson G, Bower J. The pathogenesis of acute renal failure in heat stroke. *South Med J* 1973; 66:330-333
23. Gaffin S, Hubbard R, in *Medical aspects of harsh environments*. (Office of the Surgeon General, U.S. Army, 2002), vol. 1, pp. 161-208.
24. Grogan H, Hopkins P. Heat stroke: implications for critical care and anaesthesia. *Br J Anaesth* 2002; 88:700-707
25. Knochel JP, Schlein EM. On the mechanism of rhabdomyolysis in potassium depletion. *J. Clin. Invest.* 1972; 51:1750
26. Yang H-H, Chang C-P, Cheng J-T, Lin M-T. Attenuation of acute lung inflammation and injury by whole body cooling in a rat heatstroke model. *BioMed Res Int* 2009; 2009:
27. Wu W-s *et al.* Melatonin reduces acute lung inflammation, edema, and hemorrhage in heatstroke rats. *Acta Pharmacol Sin* 2012; 33:775-782
28. Zhou R, Liu JW, Zhang D, Zhang Q. Heatstroke model for desert dry-heat environment and observed organ damage. *Am J Emerg Med* 2014; 32:573-579
29. El-Kassimi FA, Al-Mashhadani S, Abdullah AK, Akhtar J. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. *CHEST J* 1986; 90:571-574
30. Sakorafas GH, Tsiotos GG, Sarr MG. Ischemia/reperfusion-induced pancreatitis. *Dig Surg* 2000; 17:3-14
31. Hanumantharaya D, Dave U, Aprim Y, Al-Sarireh B, Middleton L. Ischemic pancreatitis in a patient with cardiogenic shock. *J Gastroenterol.* 2009; 9:
32. Mast JJ, Morak M, Brett BT, van Eijck C. Ischemic acute necrotizing pancreatitis in a marathon runner. *JOP* 2009; 10:53-54