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The influence of climate change on human cardiovascular function

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ABSTRACT

Climate change is considered to have great impact on human health. The heat waves have been associated with excess morbidity and mortality of cardiovascular diseases (CVD) across various populations and geographic locations. Important role in the heat-induced cardiovascular damage has endothelial dysfunction. It has been noticed that hot weather can impair tone and structure of the blood vessels via interfering with variety of biological factors such as nitric oxide synthesize, cytokine production and systemic inflammation. Also, due to dehydration and increased blood viscosity, by promoting thrombogenesis, heat has important impact on patients with atherosclerosis. During chronic exposure to the cold or hot weather cardiovascular function can be decreased, leading to a higher risk of developing heart attack, malignant cardiac arrhythmias, thromboembolic diseases and heat-induced sepsis like shock. It has been shown that changes in the ambient temperature through increasing blood pressure, blood viscosity, and heart rate, contribute to the cardiovascular mortality. The majority of deaths due to heat waves especially affect individuals with preexisting chronic CVD. This population can experience a decline in the health status, since extreme ambient temperature affects pharmacokinetic parameters of many cardiovascular drugs. Increased mortality from ischemic or hemorrhagic stroke can also be related to extreme temperature variations. On a cellular level, higher ambient temperature can limit storage of ATP and O_2 increase amount of free radicals and toxic substances and induce neuronal apoptotic signal transduction, which all can lead to a stroke. Preserving cardiovascular function in context of extreme climate changing tends to be particularly challenging.

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Cardiovascular system; climate change; health; heat-related mortality

Introduction

Modern society is currently experiencing tremendous worsening of the global climate patterns. Although the importance of climate change has been known for many years, recent years brought new, fresh updates, claiming that no region in the world is spared from its negative impacts. Global climate is changing rapidly and with every new, not only decade but year, humanity is faced with horrifying and warning facts about major victims of its activity: oceans, precipitations, global sea and most importantly—human health.

Among many consequences climate has on the environment, from human health point of view, the most important factor is rising of a global temperature due to global warming. Knowing that the global mean temperature in 2017 was $0.46 \pm 0.1\,^{\circ}C$ above 1981–2010 average and $1.1 \pm 0.1\,^{\circ}C$ above preindustrial levels[1] many researchers suggest that rising of the environmental temperature has reached an upsetting level of urgency, mostly referring to its impact on human health. As such, ways of preventing health consequences represent one of the most important international questions that need to be answered to, and a major aim should be redirecting available resources to prevent its further adverse implications.

Global climate changes and human health

Climate change is affecting our health both directly and indirectly, and that influence is stronger than ever. Scientists' growing interest for the connection between climate and health is best understood if we know that the number of published articles, including original papers, only 2 years ago was 3-times greater than at the beginning of the decade. That scientists' attention for this link seems to be more and more abundant throughout the years and many new studies

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is confirming that dynamic. Being one of the most discussed health-related climate factor, ambient temperature is considered to have the most important influence on human health.[2] Strong, important correlation between ambient temperature and total morbidity and mortality has been known for years. However, connection between temperature and health is more complex, undetermined and indirect. Through qualitative changes in water, air, soil and ecologically-based dynamic, one should expect occurrences of different diseases, varying from benign allergies and injuries to wide-spectrum infectious diseases and neurodegenerative disorders.[3] Outcome of such multifactorial, nonlinear correlation is much harder to predict, requires a multidisciplinary approach with strategies for prevention made from different policymakers.

It is known that with every 1 °C of temperature rising, total morbidity and mortality is 3% greater in hotter regions, with average temperature around 26 °C.[4] Confirmation for this data comes from many epidemiological studies that were analyzing ambient temperature-related excess mortality across various regions of the world. These studies indicate a common pattern of attenuation in cold-related and rise in mortality associated with the heat. Important regional differences across the world are mainly attributed to the specific geographical position one region has, making proximity of the Equator and living in the tropical region countries independent risk factors for the increased temperature-related mortality.[4]

Another important viewpoint of health consequences related to the heat is represented by different characteristics of individuals. Environmental factors (including climate change) have different modifying influence considering different characteristics of the exposed person. Every person has a unique lifestyle and potential physiological susceptibility for being at higher risk. Being in the heat-sensitive age group, occupational labors directly related to the sunlight exposure or having a household in urban areas, together with other factors given in Table 1 can enhance harmful effects of climate on health.[5] Those are all characteristics one must take into consideration in order to evaluate individual heat tolerability rate and estimate the risk for heat stroke. Very often, those factors do not act independently, exclusively, their contribution is rather simultaneous and interconnected, but many of them, like profession, can be modifiable, attenuating the risk for long-term health consequences. Also, disease pathophysiology itself and drugs used in the treatment of such diseases can put inevitable restraint of being outside during hot days.

Table 1. Common factors that contribute to the heat-related increasing in mortality and morbidity from CVD.

Confounding variables	Impact on CVD response in excessive heat environment
Sex	Men usually spend more time outdoor
Age	Physiological susceptibility among infants and elderly
Location	Increased CVD mortality in urban areas
Socioeconomic status	Limited access to health care and lower educational level in low-to-middle income countries
Occupational exposure	Occupations with direct exposure to sunlight
Regional air quality	Enhancing or modifying effect of the air pollution on temperature
Comorbid diseases	Hypertension, cardiac and kidney diseases, diabetes

Cardiovascular function and high ambient temperature

In the context of global warming, cardiovascular diseases (CVD) make biggest proportion of the heat-induced mortality. European cardiovascular disease statistics, according to European Heart Network claims that each year, CVD causes 3.9 million deaths, accounting for 45% of the all-cause mortality.[6] Over the past 25 years, the absolute number of CVD cases increased in Europe, with increases in the number of new CVD cases found in most countries. Among CVD, coronary heart disease is being the leading cause of death. Globally, CVD take more lives than all forms of cancer and chronic lower respiratory diseases combined and are expected to cause over 23.6 million deaths by 2030.[6]

Having in mind the multifactorial etiology of CVD, further action plan should specially cover those modifiable factors seen in the environment, as those are common exogenous factors attributing to CVD mortality.

Cardiovascular function—a molecular insight

What happens to subcellular structures after being exposed to a severe thermal stress? Probably the most important protective superfamily of proteins that play key role in the protein preservation and prevention of its degradation after acute or prolonged stress are called heat shock proteins (HSP).[7] HSP represent highly conserved and ubiquitously expressed family of proteins that have crucial role in cell protection after exposure to severe stress. Upregulation of HSP synthesis is considered a powerful, physiological mechanism for protecting major cell structures against disturbing factors.[7,8] As their concentration is increased many fold after acute or prolonged stress stimuli, they are also considered a part of the systemic stress response.

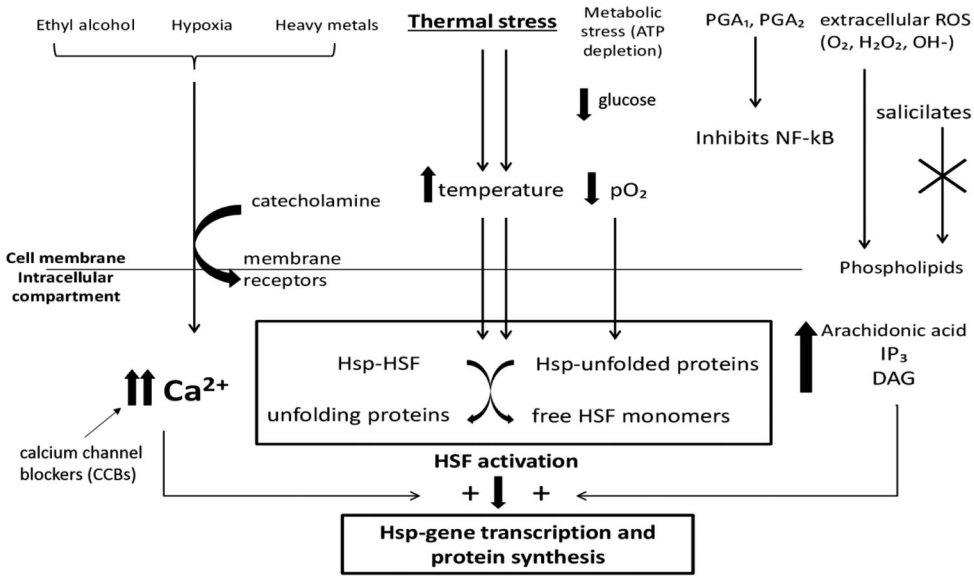

Figure 1. Different stimuli for the activation of HSP-gene transcription and potential sites for drug interaction.

Specific HSPs have a great role in thermo-tolerance and represent an important factor for survival in high temperatures.[7]

Variety of stressors, including metabolic and oxidative stress, cause significant alteration in the transcription of different HSP family members.[7] Other common triggers are represented in the Figure 1. Heat stress is a major cell stimulus for enhancing transcription rate of the new HSP but it is necessary to emphasize that the set point and the intensity of constitutively synthesized new HSPs depends on the environment temperature at which person lives. Also, acclimatization process, tropic climate inhabitation or slow, steady increase in temperature activate HSP-gene transcription and subsequent protein synthesis less then sudden hyperthermia.[8]

Signal pathway that leads to the alteration in transcription of HSP is well known and the process includes a variety of steps. Control of their transcription is upregulated by the heat shock factors 1 and 2 (HSF1, 2) which are inactive under non-stressed conditions. Temperature-dependent increase in protein degradation and unfolding is an important stimulus for releasing free HSF monomers, which can be activated subsequently. There are many other, indirect HSF activation pathways that include protein and tyrosine kinases, hormone receptors and phospholipids of the cell membrane.[9]

In the cardiac tissue, acute thermal stress increases diastolic intracellular calcium concentration, wall stretching and alpha-adrenoceptor stimulation, which all together can enhance HSP-gene transcription. That initial rise of calcium ions concentration is from the intracellular storages, presumably from endoplasmic reticulum. Subsequent increasing in calcium ions is due to its influx from extracellular space. HSF1 is constitutively synthesized and localized in cytosol. In the resting state represent HSP-binding monomer that is extremely sensitive to temperature changes. Upon activation, HSF1 migrates from the cytosol to nucleus and after meeting with heat shock elements (HREs) and binding to DNA HSP-transcription process begins.[10]

Another physiological function of HSP is chaperoning activity. Chaperones are proteins that mediate post-translation modification of protein folding and assembling, but do not take part in its final structure. So, after releasing from ribosomes, primary function of chaperones is maintaining proteins in unfolded state in order to cross plasma cell membranes properly. Heat shock negatively affects several functional structures inside the cell. Those intracellular changes include fragmentation of the Golgi apparatus, mitochondria swelling, aggregation of intermediate filaments and condensation of nucleoli and reduced solubility of cytosolic proteins.[11] As mentioned previously, upon heat stress, HSP migrate from the cytosol to nucleus only 1h after heat stimuli.[11,12] During and after recovery phase those proteins migrate back to perinuclear region. Considering that protein chaperoning is also occurring within the cell organelles, due to cell damage as a consequence of heat stress that process can be severely disrupted. However, at this point we would like to highlight that proteins lose their native, three-dimensional structure due to increased temperature, and that stimuli is major factor for HSPs synthesis through the activation of the HSF.[11] Since

cardiomyocytes express many isoforms of those proteins, another important issue considering HSP is cardioprotection. To date, mortality after acute or chronic ischemic heart disease is still a concerning global health problem. Since both vascular and cardiac compartment contain different subtypes of HSPs,[11] one of the possible pharmacological measures for the prevention of cardiovascular disease includes enhancing activity of those proteins. However, developing heart has limited capacity for the producing cardiac HSPs so this can be important reason for higher susceptibility among newborns of developing heat stroke. Although fetal heart contains very low level of HSPs, upon development its concentration is increasing, reaching peak only 2 weeks after birth. For cardioprotection, normal cardiac morphogenesis and development most important subtypes of HSPs are Hsp70, Hsp27 and αB-crystalline.[11] Vascular tissue, endothelial and smooth muscle cells also produce protective HSPs induced by heat or ROS. Interestingly, elevated transcription of such HSPs in great blood vessels is coupled with NO synthase.[12] After significant increasing in endothelial intracellular cGMP levels concomitant vasodilatation is occurring—another defense mechanism in heat response.

Heat shock has no influence on mitochondria energy metabolism, since tissue levels of ATP, ADP, and AMP stay intact after whole body heating.[12] During recovery phase, those levels are significantly rising. Another possible protection mechanism includes preservation of mitochondria cell membrane. Similar to energy metabolism, intracellular calcium levels are slightly changed, so after the recovery phase contractile function of a heart is recovered. Interestingly enough, after exposure to the heat stress, cardiac electrical stability is settled, lowering the risk of postishaemic arrhythmia occurrences. Cardioprotective role of HSP is also achieved by attenuating membrane phospholipids degradation and reduction in arachidonic acid accumulation.[13] Interestingly, inflammation itself and products of inflammation response lead to a higher production of the Hsp70 mRNA molecules. Combination of the local inflammatory process and rise in the body temperature induce HSP-gene transcription. That represents another possible mechanism of cardioprotection. Enhanced tissue levels of HSPs protect cells from undergoing apoptotic signal pathway.[13] Production of HSPs and proapoptotic signal transduction share some common steps and the proposed mechanism for this negative feedback is probably competition between major components of those pathways. Overexpression of the HSPs protects against apoptosis via inhibiting production of proapoptotic enzymes called caspases. Inversely, expression of apoptotic Fas ligands attenuates HSF1-DNA binding via inhibiting HSF1 phosphorylation. This means that HSPs production and induction of apoptosis are mutually exclusive events within the same cell. This conclusion is supported by the fact that antioxidative drugs inhibit HSP-gene transcription and that leads to higher thermal sensitivity and caspase activity.[14]

Physiology of heat-induced cardiovascular response

Severe consequences high temperatures have on human health are represented through direct effects of thermal stress. When the heat exceeds the ability of human protective mechanisms to cool the organism down, a cascade of pathological events will finally lead to the cardiovascular impairment. Mechanism of heat-induced cardiovascular dysfunction is further explained. After activating sweat glands, dilating blood vessels and increasing skin blood flow, consequent water loss leads to a dehydration followed by hemoconcentration and increased risk of an ischemic stroke and thromboembolism.[15] Redirecting blood flow from the gut increases gut epithelial membrane permeability and allow more bacteria to get into systemic circulation. Once they get into the blood stream and after releasing different endotoxins and lipopolysaccharides (LPS), activated immune response starts to break down, developing syndrome of systemic inflammatory response (SIRS) and multiple organ dysfunction syndrome (MODS). On the other hand, thermal stress can directly damage vascular endothelium which can be an additional factor in the genesis of cardiovascular dysfunction.[15,16] Common climate-associated diseases include hypertension, heart rate disturbances, acute/chronic kidney disease, ischemic heart disease, tromboembolic disease, obesity and metabolic syndrome.[16] Various climate patterns across the world cause seasonal differences in frequency and severity of those diseases, but many of them have a higher incidence during summer, in tropic areas and during hot waves.

Daily water intake has a great role in maintaining homeostatic mechanisms of regulation water balance. Obligated physiological daily water loses through lungs, skin and urine often do not go beyond 1 l. However, in hot environments water loss only via sweat glands can exceed 3–4 l/h, especially in subjects working outdoors.[17] After dehydration occurs mental and psychical health can worsen, total sweat volume decreases while hyperosmolarity will finally lead to a kidney stone forming and glomerular injury. Mechanisms by which inadequate water intake in

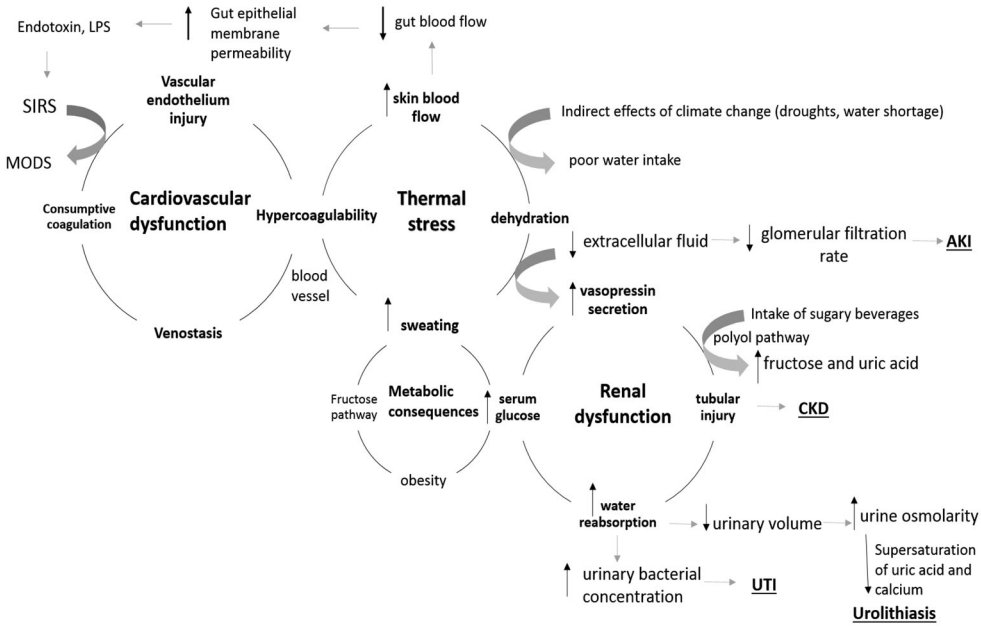

Figure 2. Complex interaction between thermal stress and cardiovascular, renal and metabolic function. (AKI—acute kidney injury, CKD—chronic kidney disease, UTI—urinary tract infection, SIRS—systemic inflammatory response syndrome, MODS—multiple organ dysfunction syndrome).

extreme hot conditions cause significant reduction in the kidney function involve vasopressin secretion and altered metabolism in sugar metabolism. Stimulation of vasopressin secretion and increases in intrarenal fructose generation cause cascade of events that will finally lead to renal insufficiency, making elderly with decreased glomerular filtration rate especially vulnerable. Metabolic consequences represent inevitable contribution to blood vessel injury and cardiovascular dysfunction (Figure 2).

Person's ability for coping with heat stress is predominantly influenced by good cardiovascular response. Although preserved cardiac function is a crucial and successful defense mechanism, in conditions of extreme climate it seems that high temperatures very often overpower even the healthiest heart, or at least, make changes to its functioning. Considering alteration in the cardiac parameters, stronger inotropy is probably due to amplified systolic function. On the other hand, compliance, which is a parameter for estimation of diastolic function, can be slightly changed. However, from a patient-doctor perspective, increased heart rate can be the most disturbing factor, having in mind potential discomfort one can experience. Preload, as a blood vessel dependent-characteristic is many times decreased, due to excessive systemic vasodilation[18] (Table 2). However, human vessels often show unpredictable and unstable dynamic due to complexity of central and peripheral regulation of their activity. Additionally, every vessel has its own intrinsic property (rhythmical contractile activity, RCA) which plays a great role in vascular resistance and consequently thermoregulation. Biophysical understanding of the blood vessels suggests that even at higher temperatures the system tends to preserve its chaotic, deterministic nature, being more complex and less predictable at physiological range temperatures. Although vasomotor nonlinearity of arteries and veins at different temperature and pressure perturbations shows certain differences, both activities can affect vascular tone regulation and diminish vasodilatation response at high temperatures.[19]

Major pathological pathways with its metabolic and dehydration-associated consequences have detrimental impact on people with hypertension, arrhythmias and thromboembolic disease.

Due to increased peripheral vascular resistance and accompanying peripheral circulatory changes (hypertrophy of vascular smooth muscle, fewer blood vessels and reduced sensitivity to baroreflex) an individual with systemic arterial hypertension is less able to adapt to extreme environmental conditions, being at higher risk of heat complications. Some previous studies have shown that cholinergic pathways are also involved in the central control of thermoregulation. Recent researches[20] pointed out that hypertension may be associated with increased peripheral sympathetic stimulation dependent on central cholinergic activity. Through modifying effect of cholinergic pathway, hypertensive people can lose heat more easily through suppression of adrenergic stimulation of the peripheral

Table 2. Alteration in cardiovascular parameters caused by heat stress and potential health risk.

A Impact of heat stress on cardiac parameters	Heat stress	Higher risk for
Cardiac output	↑ ↑	
Heart rate	↑ ↑	cardiac arrhytmias
Stroke volume	↔	
Preload	↓ ↓	
Afterload	↓	
Diastolic function/Compliance	↔	people with underlying endocrine disorders **(hyperthyroidism)**
Systolic function/Inotropy	↑	
B Impact of heat stress on vascular parameters		hospital admissions (non-fatal CVD)
	Heat stress	
Blood vessels	↑ ↑	myocardial infarction
Blood viscosity	↑ ↑	thromboembolic disease
Blood pressure	↓ ↓	syncope due to hypotension
Cutaneous vascular volume	↑ ↑	cardiac arrest
Splanchnic and renal volume	↓	acute kidney disease

vessels and subsequent greater heat conduction to the periphery. These findings indicate that individuals with essential hypertension have greater whole body sweat rate and increased sweat evaporation, thus experiencing greater body cooling than normotensive individuals, especially after moderate physical activity in hot climate areas.[21]

Circadian rhythms at that time of year may lead to low potassium levels, which can lead to the heartbeat irregularities through stimulation of cardiac autonomic function. It is known that for every degree body's temperature rises, heart beats 10 beats per minute(bpm) faster.[22] Together with increase in serum blood clothing factors and platelets, it can be a trigger for atrial fibrillation, stroke and heart failure.[23] Proposed events leading to cardiovascular health damage are overlapping and complex, with its systemic implications on the whole body (Table 3).

Interaction between climate changes and drug effects

Combining different drugs in the treatment of chronic diseases is common in clinical practice, especially among elderly. Many prescribed medications can increase the risk of heat-related disorders.

Pharmacodynamics' interactions

Function of all three major organ components in adaptation to hot environment: hypothalamus, blood vessels and sweat glands-can be disrupted by the drug activity. Because central thermoregulatory organ-hypothalamus can be affected by various centrally acting drugs, psychiatric patients are most susceptible to overheat in the conditions of extreme climate. Patients taking antipsychotics should be under strict supervision by their doctors, especially during summer when the temperature is exceeding average annually temperatures. Dose adjustment of such drugs is necessary in order to prevent shutting down of hypothalamic activation of cooling mechanisms. Extreme cases have described heat-induced stroke and death after skipping the dose reduction step in those patients. Vasodilatation of the blood vessels is another important regulation factor. Drugs that cause cutaneous vasoconstriction, like ephedrine and epinephrine will diminish normal vasodilatation process, so those drugs should be carefully prescribed. Cholinergic activation of sweat glands is necessary in order to increase sweat production rate. However, many drugs with anticholinergic activity are commonly prescribed for transient flu syndromes, allergies and psychiatric

Table 3. Various interference between certain drugs and the normal thermoregulation.

Effects of medications in heat environment	Drug classes
Interference with sweating	Anticholinergics, Beta-blockers, Antihistamines, Phenothiazines, Vasoconstrictors
Interference with thermoregulation	Antipsychotics, serotoninergic agonists
Decreased thirst	ACE inhibitors, butyrophenone
Dehydration/electrolyte imbalance	Diuretics, alcohol, antibiotics
Reduced renal function	NSAIDs, sulfonamides, cyclosporine
Aggravation of heat illness	Vasodilators, calcium channel blockers, antihypertensive
Levels of drug affected by dehydration	Digoxin, Lithium, Warfarin, Antiepileptics
Interfere with subcelular level and HSP activity	Calcium channel blockers, α-adrenoceptor agonists

diseases. Tricyclic antidepressants, antihistamines and other medications can block sweat glands activity leading to overheat, and can increase the risk for a stroke.[24] Drugs can also interfere with subcellular structures and alter HSP-activity, important step in cardiovascular protection. Studies revealed that many calcium channel blockers (CCBs), via blocking calcium influx, have negative influence on the HSP-gene transcription. This point has important clinical relevance. Since many CCBs present add-on drugs in common antihypertensive therapy, those patients should be carefully monitored in extreme hot environment. Another important point in the terms of protection against heat stress is clinical use of α_1-adrenoceptor blockers. Because α-adrenoceptor stimulation through the activation of protein kinases regulate HSP production, drugs like prazosine can interrupt that process, thus people on these medications should be properly advised.[25]

However, among people with highest risk are patients who take medications that both cause vasodilatation (and consecutive hypotension), decrease in the cardiac output or psychiatric drugs. Since parasympathetic branch of the autonomic system can be protective in conditions of hot climate, anticholinergic and sympaticomimetic drugs should be avoided.

Pharmacokinetic interactions

Not only drug effects, but all pharmacokinetic processes, including route of administration can be affected by high environmental temperature. Studies dealing with the effects of external heating on the absorption and elimination of some orally administered drugs have shown minor changes in plasma drug concentrations, in contrast to systemic absorption of drugs which were taken transdermal or subcutaneously. Drug distribution can be slightly influenced by changes in blood volume due to excessive dehydration, which in turn reduces Vd of non-highly lipid-soluble drugs. It is known that enzymes lose their morphological stability and activity at higher temperatures. Hepatic enzyme activity contributes to the hepatic metabolism of high-extraction drugs, and an increase in the ambient temperature may be reflected as enhanced enzyme-catalysed reactions, reducing hepatic clearance of such drugs At high temperatures, renal blood flow is decreased which together with dehydration and hormonal changes reduce urine output and limit drug elimination. Taking antihypertensive medications augment water lose and dehydration and lead to renal damage, possibly culminating to the end stage kidney disease, which can increase Emergency Department(ED) visits and hospital admissions.[26] Additionally, patients who chronically use combination of thiazide and ACE-inhibitors/(angiotensin receptor blockers)ARBs may lead to increase the in serum creatinine, predisposing to acute kidney failure via volume depletion, decreased renal perfusion and lightning the response of the renin-angiotensin system in elderly patients, especially if earlier kidney damage is present.[27]

All those changes in pharmacokinetic processes must be taken into account when discussing medication-induced disorders in hot environment.

Conclusion remarks

Major future projections of the effects climate will have on human well-being, good health and food production are not consistent. Under different scientific scenarios climate will differently impact human health, but without a doubt, countries around every continent will face changed climate factors as a major threat. All over the world, global warming represents a major trigger and contributing factor for many diseases.

Many areas are faced with severe droughts, which is a climate consequence with the most obvious economic and health impacts. Droughts interfere with land capacity and fertility, limit clean water sources and use, reducing working places for agricultural workers, causing significant delay in population progression. Inevitable health perturbation caused by heat waves is mostly due to excess dehydration, especially in the environment of restricted food supplies caused by extremely high temperatures.[28]

Changed climate conditions impose higher adaptation demands and disrupt not only defense mechanisms, but normal psychological processes. Often, severity of heat stress overcomes all disposable efforts and cascade of subsequent pathophysiological events results in the disease outbreak. Another important segment is time spent outdoor during hot days. Physical activity is necessary; either if a person is a healthy individual who wants to maintain its good health, or if they are obese/hypertensive and that represent first-line, non-pharmacological treatment of those disorders. As non-exertional, passive heat stress can also cause a significant reduction in the body's ability to cool down, time spent in outdoor activities should be strictly limited.

Drugs used as chronic therapy can significantly change cardiovascular parameters, which in hot environment conditions can be very harmful. Not only drug effects, but also pharmacokinetic parameters of most commonly prescribed drugs must be taken into consideration.

Having in mind that annual and seasonal temperature variations in some parts of the world are particularly prominent, physicians should adjust dosage of many drugs, particularly those who can change cardiac heart rate and cardiac output.[29] Compared to winter, summertime is more important for safety issues, having in mind all possible changes, from drugs absorption to drug effects. From molecular to clinical point of view, water loss can disrupt all disposable intracellular physiological pathways, leading to an increased disease burden, mostly due to the cardiovascular disease. Thus, it is necessary to individualize every chronic therapy, educate family members to recognize early signs of a heat stroke and adjust physicians' advices to patients according to the regional climate.

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