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Pathogenesis and preventive measures of environment-related cardiovascular disease in northern China

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Abstract

Cardiovascular diseases (CVDs) have been the top-ranked cause of human death in the world for years, according to the World Health Organization. Accumulating evidence from epidemiological data supports the view that the risk of CVDs is higher in northern China than in southern area. There is no doubt that living environment has become a crucial factor contributing to the occurrence and progression of CVDs in northern region. However, there have not been any clinical guidelines for the prevention strategy of environment-related CVDs, especially for cold exposure. Thus, there is an urgent need for better understanding of the clinical characteristics and underlying mechanisms of cold-induced CVDs in order to formulate and implement proper and effective measures for minimizing the risk of CVDs for people residing in low-temperature area. Cold exposure, air pollution, lack of sunlight and irrational diet are believed to be crucial factors responsible for environment-related CVDs, and preventive measures might be carried out accordingly to decrease the high risk of CVDs in northern China.

Keywords

cold environment; cardiovascular disease; northern China

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A large number of epidemiological studies confirm that individuals living in frigid zone have a higher risk of multiple cardiovascular diseases (CVDs), such as ischemic heart disease (IHD), hypertension, cardiac arrhythmia and heart failure, which lead to increased death[1]. The differences of living environment have been considered one of the most important factors responsible for the increase in CVDs[2-3]. However, there have not been any authoritative guidelines for the prevention and treatment of CVDs for these patients in cold environment. Thus, geographically targeted interventions are urgently needed to mitigate the CVD-related health and social burden in frigid zone.

It has been recognized that there is a wide geographical distribution of CVDs risk factors and their clusters throughout China. In a nationwide population-based cohort study in China, 983 476 individuals from 31 provinces were included, and after standardizing age and gender, the overall high CVD risk was 10.3%, with a range of 3.1%-24.9% among all the provinces. Moreover, the results showed that northeast China (12.6%) and northern China (11.4%) had relatively higher prevalence of high risk of CVDs, whereas southern China (8.0%) was lower[4]. Various factors contribute to the high prevalence of CVDs in northern China, including cold exposure, air pollution, inadequate sunlight, and unhealthy diet.

1 Cold exposure and CVDs

Compared with other regions, northern China experiences a longer and colder winter, with far lower average annual temperature. People in northern China expose to cold for a long time. A study comparing the cold tolerance of people from north with those from south reached a surprising conclusion that the northern residents are more sensitive to cold[5]. Immense amount of evidence from epidemiological data supports that cold exposure is closely correlated to various CVDs, including hypertension, myocardial infarction (MI), atrial fibrillation (AF), and heart failure (HF), resulting in adverse prognosis and high mortality. A cross-sectional study including 506 673 adults (aged 30-79 years) recruited from 10 diverse urban or rural regions in China showed that blood pressure was strongly inversely associated with outdoor temperature, and the systolic blood pressure peaked in cold seasons[6]. Moreover, ambient temperature is closely related to hypertensive disorders in pregnancy[7], and maternal exposure to cold spells during pregnancy is associated with

hypertension in offspring later in life[8]. When temperature is lower than 15.6°C, the risk of myocardial infarction increases by 1.6% for every 1°C decrease[9]. Moreover, it has been demonstrated that HF admissions and mortality are closely associated with cold temperatures, especially in the older population[10]. A prospective study including 200 patients with dual chamber implantable cardioverter-defibrillators found that lower temperatures within the initial 48 hours were positively associated with the new onset episodes of AF and that the risk of AF increased by 3% for every 1°C decrease in ambient temperature[11]. More importantly, temperature is closely related to the prognosis of patients with AF, and the risk of cardiovascular events and all-cause mortality are higher during colder months and seasons[12].

The activation of sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), inflammatory response, gut microbiota dysbiosis and endothelial dysfunction are thought to be responsible for the high risk of CVDs in residents under cold exposure.

1.1 Cold activates SNS and RAAS

Continuous hypothermia stimulation can increase SNS activity. SNS is an important regulatory mechanism for maintaining body homeostasis. Excessive activation of SNS can increase arterial blood pressure, secondary inflammation, and plaque formation, which results in atherosclerosis. Healthy people with extreme cold exposure showed an increase in the muscle sympathetic activity, which is associated with increased blood pressure[13], and changes in the ratio of low-frequency to high-frequency of heart rate variability (HRV) can be observed while sleeping in low temperature surroundings[14]. Moreover, cold exposure increases the angiotensin II (AngII) level in patients with major cardiovascular events[15-16]. These results indicate that cold exposure causes the activation of SNS and RAAS[15,17-18]. Chen *et al*.[19] found that adult offspring of parent rats that had exposed to cold had increased activities of the peripheral and central sympathetic nervous systems. In addition, administration of clonidine, a centrally acting α2 adrenergic receptor agonist, lowered blood pressure to a greater degree in the prenatal cold-exposed offspring than control ones, indicating that the increase in peripheral sympathetic nerve activity can be ascribed to the activation of central nervous system.

1.2 Cold stress exacerbates systemic inflammation

One study aimed to investigate the effects of cold stress on the quail cecum revealed that cold stress caused inflammatory injury in cecal tissues[20]. Bao *et al*.[21] found that low temperature (18°C) upregulated the expressions of inflammatory cytokines including interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, IL-13 and granulocyte macrophage colony-stimulating factor (GM-CSF). Furthermore, tumor necrosis factor (TNF)-α in airway epithelial cells was isolated from asthma model mice, highlighting the important role of cold exposure in activation of inflammation. Zhang *et al*.[22] revealed that long-term (21 d) cold exposure enhanced inflammatory response in mice with elevated TNF-α and IL-6 concentrations in peripheral blood samples. In an experimental study, male Sprague-Dawley rats were exposed to cold environment (5°C) after knockdown of IL-6[23]. It was found that IL-6 small hairpin RNA (shRNA) prevented cold-induced inflammation by inhibiting leukocyte infiltration, intravascular superoxide synthesis and cardiac collagen deposition, as well as decreasing systolic blood pressure[23]. Yu *et al*.[24] discovered that in addition to stimulating cytokines, cold exposure (4±1)°C significantly raised blood pressure, NLRP3 inflammasome level and fibrosis in the aorta of Sprague-Dawley rats, which could be attenuated by tranilast, an inhibitor of NLRP3. In northern China, people who are exposed to low ambient temperature for a longer time have an enhanced defensive response to low temperature stimulation, thereby increasing circulating inflammation. Clearly, cold exposure contributes to CVDs partly via activating systemic inflammation.

1.3 Cold induces gut microbiota dysbiosis

The gut microbiota and its metabolites have been implicated in the pathogenesis of many diseases, such as CVDs and diabetes[25]. Cold exposure has been reported to reshape the composition-correlated metabolic pattern of the gut microbiota, ultimately resulting in cardiovascular alterations[26]. Compared with the mice raised at room temperature, the diversity of gut microbiota significantly decreased, and the abundance of Bacteroides increased in mice exposed to cold temperature. Zhang *et al*.[27] demonstrated that cold exposure decreased the expression of phosphorylated endothelial NO synthase (eNOS) protein and triggered the production of gut-derived inflammatory cytokines, TNF-α, and IL-6 in aorta, which caused vascular dysfunction. Moreover, cold exposure also increased gut permeability, inhibited tight junction protein expression in proximal colon, leading to gut barrier dysfunction, which allowed lipopolysaccharide, a harmful metabolite, to activate vascular inflammatory reaction.

1.4 Cold exposure leads to endothelial dysfunction

Cold exposure can cause endothelial dysfunction through endoplasmic reticulum stress, inhibition of adiponectin and up-regulation of uncoupling protein (UCP), thus promoting the growth of atherosclerotic plaque and increasing plaque

instability[28-30]. Persistent cold stress induces activation of SNS and RAAS, producing continuous stress of endoplasmic reticulum in endothelial cells[28-29]. Noticeably, in cold areas, people are more likely to have a high level of plasma homocysteine due to smoking, high-fat diet and folic acid deficiency, which promote endoplasmic reticulum stress and endothelial cell apoptosis[31]. Cold exposure decreases the expression of adiponectin in vascular system, which in turn inhibits eNOS and weakens its protective effect on endothelial cells. Moreover, cold exposure enhances the activity of endothelin-1 (ET-1), a key factor regulating blood pressure and endothelial function, upregulates ET_A-R and downregulates ET_B-R, which in turn lead to vasoconstriction and sodium retention, eventually causing hypertension[18,32].

As for other possible mechanisms, studies in blood flow rheology indicated an association between “cavitation”, a term in the field of ultrasonography and the progression of intracoronary atherosclerotic plaque and thrombosis[33]. However, it remains to be elucidated whether cold exposure could contribute to the pathogenesis of MI via hemodynamic changes as predicted by computer simulation[34]. Cold exposure might also cause dysfunction of energy metabolism by dampening mitochondrial function, giving rise to vascular calcification (VC), a possible end-stage pathological process of CVDs, and VSMC phenotype switch modulated by hypoxia-induced autophagy[35-36].

2 Air pollution and CVDs

Air pollution is a crucial environmental risk factor contributing to global cardiovascular (CV) mortality and disability, especially the fine particulate matter ≤2.5 μm (PM 2.5). It has been established that PM 2.5 and inhalable particulate matter ≤10 μm (PM 10) are significantly higher in northern China than in other regions. The ESCAPE study confirmed that nonfatal acute coronary events increased by 13% with a 5 mg/m^3 elevation following long-term exposure to PM 2.5[37]. Another study reported that short-term PM 2.5 exposure increased the relative risk of acute CV events by 1% to 3% and the relative risk for acute MI by 2.5% per 10 mg/m^3[38]. More importantly, short-term exposure to PM 2.5 accounts for up to 5% of MI incidence worldwide[39]. Recently, one study conducted in China confirmed that the risks for CV morbidity and mortality are markedly increased with increasing exposure to polluted air, with the relative risk for CV mortality being increased by 9% per 10 mg/m^3 elevation[40]. Furthermore, a meta-analysis showed that a short-term increase in gaseous components and PM (both PM 10 and PM 2.5) increased the risk for heart failure hospitalization or death[41]. Substantial evidence supports a link between air pollution and the development of cardiometabolic risk factors, such as hypertension, insulin resistance and cardiac arrhythmias[42-44]. However, the mechanism underlying PM-induced CVD remains largely unknown. PM may cause vascular dysfunction such as increased blood pressure and exacerbation of atherosclerosis, increased susceptibility of the heart to ischemic damage, and increased risk of thrombosis through direct and indirect effects[42, 45-47].

PM may increase the risk of cardiovascular events by the following indirect actions. The pulmonary and systematic oxidative stress as an early response to PM inhalation initiates many secondary processes[48-49]. First, the inflammatory mediators induced by PM entering the alveoli penetrate into the circulation[50]. Second, the activation of alveolar sensory receptors affects cardiac autonomic nerve function and humoral endocrine function through afferent nerves[51]. Finally, other unidentified blood-borne mediators may exert cardiovascular effects[52]. Oxidative stress and inflammation are more critical pathogenic mechanisms than the direct action of PM[45,53-54]. Long-term exposure to environment rich in PM activates the NLRP3 (Nacht, LRR and PYD domain signaling protein 3) inflammasome pathway and systemic inflammation in mice[55]. Reactive oxygen species (ROS) can directly or indirectly activate membrane receptors, such as Toll-like receptors2/4 (TLR2/TLR4) and the nucleotide-binding domain leucine-rich repeats of Nod-like receptors, *etc*., causing and exacerbating downstream inflammatory cascades[56-58]. A study about HECT E3 ubiquitin ligases provides a novel insight that living environment may be responsible for the occurrence of oxidative stress by affecting the expression of HECT E3 ubiquitin ligases, eventually causing alterations in vascular function and fundamental pathways such as the NF-κB and NLRP3 signaling pathway[59].

3 Sunlight and CVDs

Epidemiological data from clinical research showed that people in northern region were more likely to suffer from vitamin D deficiency compared with those in southern region, because the ultraviolet light decreased with increasing latitude[60]. Vitamin D deficiency has been identified as an important risk factor of CVDs. Mounting studies have shown that vitamin D deficiency significantly increases CVDs events. Studies uncovered that the majority of patients with acute MI present vitamin D deficiency or insufficiency and low serum vitamin D concentration is associated with the high risk of major adverse CVDs events (MACE) and increasing incidence of HF[61-64]. As the latitude increases, the gradual decline of UVB in the environment causes progressive increase in blood pressure proportional to latitude, which can be alleviated by exposing to sunlight and taking high-dose vitamin D_2 supplementation[65-67].

3.1 The activation of RAAS

Vitamin D inhibits the synthesis of renin and the activation of RAAS by acting on vitamin D receptors (VDR). It has been reported that the levels of renin, angiotensin II and aldosterone were significantly higher in mice with vitamin D deficiency than that in wild type mice, with obvious myocardial hypertrophy and collagen aggregation, which could be reversed by vitamin D supplementation[68]. Given that decreased sunlight in northern China hinders the generation of vitamin D, RAAS is likely to be hyperactivated, thereby inducing CVDs. Intriguingly, aldosteronism owing to RAAS activation during HF and vitamin D deficiency due to sunscreen effect of melanin could contribute synergically to hyperthyroidism in African-Americans[69]. Except for their separate roles in developing hyperthyroidism, there might be crosstalk between RAAS and vitamin D deficiency, indicating that the activation of RAAS due partly to vitamin D deficiency triggers the elevation of circulating parathyroid hormone, ultimately causing oxidative stress and proinflammatory condition which in turn exacerbate HF[69].

3.2 Inflammatory response

Vitamin D deficiency upregulates karyopherin α4 (KPNA4) followed by subsequent activation of NF-κB, a transcription factor promoting the release of inflammatory cytokines (IL-6, IL-8, TNF-α, *etc.*) and motivating ox-LDL phagocytization of macrophages to form early atherosclerotic lipid streak[70-72]. Such inflammatory response can be reduced by adequate intracellular 1, 25-$(OH)_2$-D_3 and inhibition of NF-κB activation can alleviate cardiac dysfunction and ventricular remodeling in mice, further suggesting that vitamin D protects cardiovascular system via repressing the expression of the proinflammatory molecule NF-κB[70,73].

3.3 Cardiac hypertrophy

Vitamin D plays a critical role in maintaining the systolic and diastolic functions of cardiomyocytes by regulating calcium uptake. Vitamin D deficiency can trigger cardiac dysfunction and myocardial energy metabolic disorders, leading to myocardial hypertrophy. Moreover, cardiomyocyte-specific deletion of the VDR gene results in cardiac hypertrophy by activating the pro-hypertrophic calcineurin/NFAT/MCIP1 pathway[74]. Recently, vitamin D deficiency was confirmed to cause cardiac dysfunction by inducing myocardial insulin resistance[75]. In addition, Kong *et al*.[76] revealed that the beneficial effect of vitamin D was mediated by the cyclin-dependent kinase inhibitor p21.

3.4 Endothelial dysfunction

Multiple enzymes are involved in vitamin D metabolism and VDRs are expressed in endothelial cells in the blood vessel wall. The concentration of 25(OH)D in the serum is negatively correlated with endothelial dysfunction[77]. Lacking of endothelial VDR, the vasodilator effect in endothelial cells is significantly weakened under the stimulation of acetylcholine perfusion[78]. The above studies demonstrated the crucial role of vitamin D and its receptor VDRs in modulating NO synthesis and endothelial function[79]. It is demonstrated that vitamin D stimulates the synthesis of NO in endothelial cells but inhibits the production of vasoconstrictors such as cyclooxygenase-1[80-81]. UVA can induce the conversion of cutaneous unstable NO derivatives to NO, which diffuses into deep tissues to increase the level of local S-nitrosoglutathione that then redistributes in the blood circulation and eventually decreases blood pressure[82]. The following studies have confirmed the relationships among UVA, NO and blood pressure: short-term whole-body UVA irradiation can cause rapid and long-lasting blood pressure decrease in humans[83], NO scavengers block the inhibitory effects of UV irradiation on weight and metabolic syndrome[84], and UVA irradiation combined with oral nitrite supplementation improves the training performance of athletes[85]. Moreover, vitamin D inhibits endothelial cell apoptosis by inhibiting oxidative stress, the release of cytochrome C from mitochondria, the activity of cysteine proteases, and the expression of apoptosis/autophagy genes, thereby improving endothelial cell function[86].

4 Irrational diet and CVDs in northern China

A large amount of data showed that unhealthy diet is an important risk factor for CVD. Residents in northern China usually consume high-salt, high-fat, high alcohol, and less vegetables, which contributes to the north-south difference in CVD mortality rate[87]. In 2013, 12 million Chinese died of high-salt diets, among which 31.5% was caused by cardiovascular and cerebrovascular diseases[88]. More importantly, the burden of diseases due to a high-salt diet in northern China is significantly higher than that in other provinces in China and limiting daily salt intake can reduce the occurrence of CVD[89-90]. As we know, high-fat diet puts human at a high risk of obesity, an independent risk factor for CVDs. Epidemiological data showed that the prevalence of overweight and obesity, particularly central obesity, was higher among residents in northern China than their counterparts in southern China[91-92]. The CHARLS study revealed that higher prevalence of metabolic syndrome was observed in middle-aged and elderly women residing in northern China[93]. One study including 820 older adults in northern China showed that excessive sodium intake and

alcohol drinking were both independently related to higher risk of hypertension[94]. Another study analyzed 16 100 CVD deaths among adults aged 25 to 69 in Shandong province and found that high sodium intake accounted for 19.9% of total CVD deaths. A considerable drop in CVD death can well be achieved with reduced sodium intake[95].

It is currently believed that a high-salt diet can affect the cardiovascular system through multiple mechanisms[96-99]. First, high-salt diet can cause sodium and water retention and increase circulating blood volume. Second, high-salt diet increases plasma sodium chloride concentration followed by the activation of sodium/osmotic pressure receptors to excite the sympathetic nerves. Third, high-salt diet damages the vascular endothelium and mitigate the release and utilization of NO, resulting in peripheral vasodilation dysfunction. In addition, high-salt diet can also increase arterial stiffness, with the pro-fibrotic effect of transforming growth factor-β (TGF-β) being one of the key factors. On the other hand, high-fat diet increases the prevalence of obesity and metabolic syndrome, contributing to CVDs.

5 Preventive measures of cold-related CVDs

At present, there is a lack of authoritative guideline for formulating practical prevention and control measures for CVDs in northern China. Such measures could greatly reduce the morbidity and mortality of CVDs, thereby improving citizens physical condition in northern China[100].

First, the direct exposure to cold environment can be avoided by keeping warm. A simple and effective method is to add clothes such as hats, gloves, thermal insulation jackets, *etc.*[101]. Long-term measures such as wall and pipe insulation of houses and improvement of the heating facilities should be implemented[102-103]. During the follow-up of 1 840 families with thermal insulation reconstruction, it was found that increasing indoor temperature could significantly reduce the incidence of hypertension[104]. Secondly, the government should urge communities to include the elderly, people with chronic diseases, alcohol and drug users, as well as specific occupations (custodians of freezer lockers, meat packers, ice cream manufacturers, *etc.*) into high-risk groups of cold-related CVDs, by providing health education for them and implementing programs against cold environments[18,105-108]. Moreover, increasing outdoor activities moderately, supplementing vitamin D and reducing salt intake can effectively prevent the occurrence of CVDs[102,109]. Interestingly, researchers have proposed that TRPV1 might be used as a potential therapeutic target for cold stress-related comorbidities[110-111]. Lu *et al*. demonstrated that a TRPV1 antagonist ameliorated cold stress-induced myocardial hypertrophy under pressure overload, while Zhang *et al*. suggested that cold exposure-induced cardiac contractile and geometric dysfunction could be reversed by a TRPV1 agonist[110-111]. Therefore, further studies are needed to elucidate the specific role of TRPV1 in the regulation of cold exposure-induced CVDs.

Considering the large reaction surface area and the recognized toxicity of PM, as well as mixed pollutants composed of nitrogen dioxide and PM, reducing automobile exhaust emissions is an effective measure to reduce the incidence of CVDs. In addition, the use of masks and indoor air purifiers can protect the cardiovascular system to a certain extent[112].

Taking balanced diet is the probably most cost-effective and simple way to avoid the detrimental effects of a high-salt diet on the cardiovascular system. Moderate servings of egg (up to <1 egg/d), dairy products and whole grain may help reduce the risk of CVDs by attenuating oxidative stress, enhancing endothelial function, and alleviating systemic inflammation[113-116]. Moreover, daily consumption of fruits containing dietary fiber, potassium, vitamins and antioxidants is also a plausible way of decreasing the incident of CVDs[117]. In recent years, several dietary patterns, such as Mediterranean diet and Jiangnan diet, have proven benefits to the primary prevention of CVDs and diabetes and the management of metabolic syndrome as well[118-119]. In addition, ketogenic diet and intermittent fasting are beneficial to obese and diabetic populations, while it remains largely unknown whether they can effectively decrease cardiovascular risk or improve outcomes[120].

6 Conclusions

The high prevalence of CVDs in northern China has provoked the exploration of the underlying mechanisms of environment-related CVDs. Cold exposure, air pollution, inadequate sunlight and irrational diet might be the key factors contributing to the pathogenesis and progression of CVDs in frigid zones. Various measures can be taken to reduce CVDs, such as individual and domestic protection against cold weather and air pollution, vitamin D supplementation, a balanced diet and so on. With the precise mechanisms to be elucidated in the future, more targeted measures would be implemented to alleviate the burden of environment-related CVDs in northern China.

Conflicts of interests

Yue Li is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and his research groups.

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