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Advancements in understanding inflammatory responses and the development of cardiovascular diseases under cold stimulation

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Abstract

Cold stimulation has been linked to acute myocardial infarction and other cardiovascular diseases. Residents in the frigid zones, such Heilongjiang Province, experience a higher incidence of adverse cardiovascular events during winter, posing a significant health threat and increasing the overall medical burden. Cold stimulation serves as an detrimental stressor, inducing inflammation in the body. Therefore, understanding the role of inflammatory responses induced by cold stimulation in the occurrence and development of cardiovascular diseases is of paramount importance. Given the impact of cold on inflammation in cardiovascular diseases and the expanding array of anti-inflammatory methods for the treatment of cardiovascular diseases, delving into the inflammatory responses mediated by can significantly complement cardiovascular disease management. This review explorest the synergistic relationship between cold stimulation and inflammation induction, elucidating how this interplay influences the occurrence and progression of cardiovascular diseases.

Keywords

cold stimulation; inflammatory response; cardiovascular diseases; cold exposure; inflammatory factors

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1 Introduction

Cold, as an intense stressor, exerts a profound impact on the body, particularly affecting residents in high altitude and latitude areas, often characterized as frigid zones. In these regions, individuals face a an extremely low-temperature climate, with temperatures plummeting to −10 °C and below during the cold season (October to April). The relationship between cold exposure and cardiovascular diseases is robust, and the complications arising from cold exposure contribute significantly to cardiovascular morbidity and mortality in winter[1]. The occurrence and progression of cardiovascular diseases in response to cold stimulation are intricately linked to inflammation. Upon exposure to cold, the body's temperature regulation system undergoes disturbances, leading to hormonal, metabolic, and neurological disorders, tissue damage, and the release of inflammatory factors. This cascade of events includes the infiltration of inflammatory cells, constituting a dynamic and complex process. In recent years, researchers have paid increasingly focused on the role of cold-induced inflammatory responses in the initiation and progression of cardiovascular diseases. Their attention is centered on unraveling the mechanism underlying cold-induced inflammatory responses and comprehending the adverse effects of such inflammation on the cardiovascular system.

2 Relationship between cold exposure and inflammation initiation

2.1 Cold exposure induces inflammatory responses by damaging tissues

In the face of cold exposure, the body employs a mechanism known as cold-induced thermogenesis or adaptive thermogenesis to maintain a stable core temperature by increasing metabolism and generating heat[2]. This intricate process involves thyroid hormones and catecholamines at the body fluid level, white/brown adipose tissues at the tissue level, and the liver and skeletal muscle at the organ level[3-6]. Peroxidation plays a crucial role in initiating the inflammatory response during this cold exposure. T3 thyroxine binds to the nuclear receptors THR1 and THR2 and subsequently promotes the transcription of the nuclear respiratory

factors NRF-1 and NRF-2. This enhances the uncoupling ability of the oxidative phosphorylation electron transport chain[7]. These factors, in turn, interact with peroxisome proliferator-activated receptor-γ coactivator (PGC-1), increasing mitochondrial numbers and promoting the expression of oxidative phosphorylation complexes. However, this process leads to an inevitable increase in the production of reactive oxygen species (ROS). The oxidative respiratory chain releases ROS as a fundamental process in the mitochondria, responding to heightened oxidative stress through a positive feedback loop. This feedback loop results in an increase in superoxide dismutase and initiates the autocatalytic cascade. In most cases, this cascade enables mitochondria to reduce oxidative damage through the oxidation-antioxidative system without causing cellular damage. However, excessive levels of superoxide anion and hydroxyl free radicals cannot be completely removed during cold exposure[8]. They cause direct damage to mitochondria through peroxidation, causing irreversibly damage to cells and ultimately leading to oxidative stress-induced tissue and organ damage[9]. This is not a tissue-specific phenomenon, and cold exposure-induced peroxidation damage has been observed in the liver, lung, pancreas, and adipose tissue[9-12]. Furthermore, the role of programmed cell death in the cold-induced inflammatory process cannot be overlooked. Liu e*t al.* observed the induction of hepatocyte pyroptosis through the NLRP3/Caspase-1/GSDMD classical pathway during cold exposure[13]. Pyroptosis, a unique form of regulated necrotic cell death characterized by cell membrane pore formation, can cause cell enlargement, lysis, and the release of inflammatory mediators, inducing a robust inflammatory response. The inflammatory response following tissue injury involves not only the accumulation of ROS but also the participation of c cold-inducible RNA binding protein (CIRP). Discovered as a damage-associated molecular pattern after exposure to moderate cold shock, CIRP can induce inflammatory responses[14]. Additionally, cold-induced apoptosis, autophagy, and other processes mediate tissue damage and remodeling like the myocardium and brain[15-17]. However, the precise initiation of an inflammatory response by these processes is not well established. Collectively, these studies suggest that cold causes tissue damage by inducing peroxidation and other processes, which further initiates an inflammatory response.

2.2 The production of inflammatory factors is a key process in the inflammatory response to cold stimulation

As mentioned above, cold induce tissue damage; therefore, observing changes in serum inflammatory factors is essential to assess the state of cold-stimulated inflammatory response. Previous studies on cold exposure have reported elevated levels of various inflammatory factors. C-reactive protein (CRP), an acute inflammatory protein and common stress protein, plays a role in inflammation. CRP significantly influences the biological effects of acute inflammation, with serum CRP levels rapidly increasing during acute inflammation. Conversely, CRP levels decrease exponentially within 18 to 20 h after the end of cold stimulation[18-19]. Notably, a persistent accumulation of serum CRP during cold exposure, consistent with the duration of cold exposure, has been noted. In a 5-week cohort study, the hs-CRP level increased by 24.9% when the average temperature was lowered by 4°C[20]. This cumulative effect may indicate a chronic inflammatory response caused by continuous exposure to a low temperature. In addition, the levels of certain inflammatory factors, such as IL-6 and TNF-α, were found to surpass normal levels during cold, indicating the effect of cold on inflammation[21-22]. The molecules upstream of these inflammatory pathways were also upregulated during cold exposure. Teng e*t al.* analyzed the effect of chronic cold exposure on the lung inflammatory network and found an enhancement of the expression of Toll-like receptor 4 (TLR4), which recognizes pathogens and endogenous ligands, triggering an inflammatory response[23]. Furthermore, the TLR4/myeloid differentiation protein antigen 88/nuclear factor-κB (NF-κB) classical signaling pathway is implicated in inflammation. TLR4 is also a crucial component in the activation of NLRP3 in the pyroptosis pathway, further emphasizing the effect of cold exposure on the inflammatory network. Interestingly, the levels of inflammatory factors do not consistently align with the degrees of cold exposure. Elevated levels of inflammatory factors underscore the impact of cold exposure on inflammation and are closely associated with tissue damage. Sánchez-Gloria e*t al.* reported that cold exposure increased the levels of TNF-α, IL-6, and IL-1β in the lung tissue and plasma, thickened the medial wall of the pulmonary artery, and raised the pulmonary artery pressure[24]. Conducting correlation analyses between these inflammatory factors and cold exposure, along with constructing a comprehensive cytokine network, will aid in uncovering the inflammatory effects of cold stress on multiple systems and organs in the body. This approach can also identify additional pathways related to inflammatory factors during cold exposure.

2.3 The interaction between inflammatory cells and inflammatory factors is an important mechanism in cold stimulation-mediated tissue injury

Local inflammation initiated by cold exposure relies significantly on the interplay between local inflammatory cells and pro-inflammatory/anti-inflammatory factors. Macrophages, as traditional inflammatory cells, play a pivotal role in both initiating and progressing inflammation. Investigating the pathophysiological regulation of the life cycle checkpoints of cells and the mechanisms underlying the activation of signaling pathways is essential to understanding the exacerbation of the inflammatory response during cold exposure. The functional response of macrophages to microenvironmental stimuli and

signal activation plays an important role in the local environment during the inflammatory response induced by cold exposure. Cold stress leads to the generation of ROS, causing mitochondrial damage, influencing intracellular oxygen sensing, and promoting the metabolic reprogramming toward aerobic glycolysis in macrophages[25]. This metabolic state is indicative of macrophage polarization to the M1 phenotype[26]. These metabolic changes coincide with lactic acid accumulation and TCA cycle inhibition. Additionally, lactylation of lysine residues, an epigenetic modification, is associated with metabolic reprogramming promoting the transcription of anti-inflammatory genes following macrophage activation. Cold exposure has been shown to elevate the level of histone acetylation[27]. Lactate-induced histone lactylation and acetylation affect macrophage differentiation by modifying NF-κB (p65) and STAT6 promoters, closely tied to the macrophage-mediated inflammatory response[28-29]. These processes ultimately drive the inflammatory activation of macrophages, which, in turn, interact with inflammatory factors, triggering an inflammatory response.

The adipose tissue, highly active during cold exposure, undergoes changes in inflammatory cells, offering compelling evidence of the cold-inflammation association. Regulatory T cells (Tregs), identified as key players in adipose tissue homeostasis during cold exposure, in maintaining the homeostasis of adipose tissues during cold exposure. Regulatory T cells (Tregs), identified as key players in adipose tissue homeostasis during cold exposure, exhibit significant induction observed by Becker *et al.* in response to short-term cold exposure. Activation of β3-adrenergic signaling by the sympathetic nervous system, particularly the transformation of Tregs from naive CD4-T cells and the expression of the FOX3 transcription factor, reflects manifestations of fat-resident Tregs controlling local inflammation. This highlights the crucial role of anti-inflammatory cells in tissue inflammation during cold exposure[30]. However, diseases, such as obesity and diabetes, can attenuate this effect[31]. In addition, inflammatory cells, including neutrophils, a strongly link to cardiovascular lesions[32-33]. Despite limited reports on changes in inflammatory cells during cold exposure, exploring their role may provide additional evidence for the association between cold and cardiovascular damage.

3 Cold-induced inflammation is associated with cardiovascular diseases

3.1 The role of cold-induced inflammation in atherosclerosis

Cold-induced inflammation is associated with cardiovascular diseases, notably in the context of atherosclerosis (AS), a leading cause of global mortality. AS, a chronic inflammatory disease affecting blood vessels, involves intricate processes such as inflammatory infiltration, intimal thickening, formation of macrophage and smooth muscle foam cells, and the development of a necrotic core. Chronic inflammation is a constant presence throughout the AS process[34]. It is noteworthy that AS, development is not solely mediated by vascular endothelial damage and lipid deposition. In the early AS stage, marked by vascular endothelial damage and lipid deposition, the inflammatory response is triggered following vascular endothelial injury. Cold exposure may contribute to endothelial injury by inducing hemodynamic disorders in the vascular lumen[35]. This results in the expression of various surface adhesion factors, such as ICAM, on the cell surface in the injured area[36]. The adhesion factors interact with surface receptors on monocytes, promoting their adhesion. Subsequently, monocytes migrate to the subintima, where scavenger receptors like CD36 facilitate the uptake of oxidized low-density lipoprotein, transformation them into foam cells[37]. As AS progresses to the middle and late stages of AS, smooth muscle cells in the middle of the artery migrate to the subintima and undergo transformation into fibrochondrocyte-like and macrophage-like cells[38]. These intricate processes underscore the association between cold-induced inflammation and the progression of cardiovascular diseases, particularly AS.

Fibrochondrocyte-like cells contribute to AS development by producing collagen fibers in the plaque. In contrast, macrophage-like cells, akin to macrophages, rupture post-lipid uptake, releasing high levels of pro-inflammatory molecules that intensify the local inflammatory response[39]. The degradation of collagen fibers by matrix metalloproteinases (MMPs), released during macrophage necrosis, leads to plaque rupture[40], and thrombogenesis mediated by platelets after plaque rupture further links inflammation to AS development[41]. Cold exposure exacerbates this process by promoting the secretion of various inflammatory factors by pro-inflammatory cells. Cold-induced increases in serum IL-2, IL-6, and TNF-α levels enhance the inflammatory response within the plaque. Cold also activates the pro-inflammatory phenotype of macrophages, leading to increased macrophage accumulation in the plaque, heightening plaque vulnerability and pressure[42-43]. Consequently, this escalation contributes to increased plaque rupture and adverse cardiovascular events, including death, in patients exposed to cold. Moreover, adipose tissues, especially those surrounding the heart and blood vessels, are highly active during cold exposure. Analyzing changes in these tissues is particularly important for understanding the relationship between cold and vascular damage[44]. Cold exposure elevates the expression of uncoupling protein 1 in the large and middle arteries like thoracic aorta and coronary artery in the perivascular adipose tissue, similar to brown adipose tissue[45]. In addition to promoting

uncoupling heat production, uncoupling protein 1 inhibits the activation of the NLRP3/Caspase-1/IL-1β inflammatory pathway.

In models of obesity and diabetes, the effect of cold exposure diminishing the expression of uncoupling protein 1 was notably reduced, leading to a significant increase in plaque size in the arteries[46]. These findings strongly support the association between cold exposure and the inflammatory response in the process of AS. Consequently, there is a strong rationale for conducting studies that specifically analyze the correlation between cold exposure and arterial plaque inflammation.

3.2 Myocardial inflammation under cold stress

Moving on to myocardial inflammation under cold stress, numerous studies have consistently reported that cold stimulation causes myocardial injury. A prevalent observation in these studies is a significant increase in oxidative stress in the myocardium, accompanied by an imbalance between antioxidant enzymes and oxidants[47-49]. The overproduction of ROS during cold exposure directly triggers oxidative stress, initiating various processes such as autophagy, apoptosis, and the production of multiple molecules. These processes collectively induce myocardial injury, fibrosis, remodeling, and ultimately lead to myocardial inflammation[50-52].

Lv, e*t al.* examined myocardial inflammation following chronic cold stress-induced myocardial injury[53] and revealed significant upregulation of myocardial high mobility group box-1 protein, IL-6, and TNF-α. Interestingly, inducible nitric oxide synthase and cyclooxygenase-2 were not significantly upregulated during chronic cold exposure. Moreover, classical inflammatory pathways, namely NF-κB and mitogen-activated protein kinase (MAPK), were found to be activated. These pathways play a key role in inducing, promoting, and regulating the myocardial inflammatory immune response, closely tied to myocardial injury, stress-induced hypertrophy, and heart failure[54]. Furthermore, the activation of the NF-κB pathway is associated with the activation of the myocardial pyroptosis signaling pathway[55], known to contribute to cold stress-induced liver injury. Pyroptosis, a pro-inflammatory programmed cell death mechanism mediated by perforin (DSDMD), induces swelling and rapid lysis of cells, releasing high levels of necrotic substances, are released, leading to local inflammation and the secretion of inflammatory factors. The inflammatory pathway can be initiated as early as the activation of the upstream pyroptosis executive protein GSDMD. The NLRP3 inflammasome, a key effector molecule of pyroptosis signaling pathway, is strongly linked to the inflammatory pathway. Nicorandil has been reported to effectively inhibit the TLR4/MyD88/NF-κB/NLRP3 signaling pathway, reducing pyroptosis in rats with myocardial infarction[56]. Qian e*t al.* confirmed this effect, demonstrating induction of myocardial pyroptosis *via* the NF-κB-GSDMD axis after myocardial infarction[57].

Exploring the mechanism underlying inflammation-induced myocardial injury during cold exposure and identifying the regulatory targets for improving and controlling myocardial inflammation offer valuable insights for developing potentially effective treatments for myocardial injury in residents of cold regions (Fig. 1).

4 Research progress and limitations of inflammation during cold exposure

Studies published thus far on the effect of inflammation on the cardiovascular system under cold conditions are limited. This limitation may stem from e inflammation being influenced not only by the body's immunity but also by factors like stress, infection, trauma, and heredity. Consequently, most researchers have focused on understanding the effects of cold exposure on cardiovascular damage. Nevertheless, cold stands as a confirmed factor affecting the occurrence and development of cardiovascular diseases, as demonstrated by numerous epidemiological and clinical studies that deviate from traditional research approaches. Analyzing changes in the inflammatory response to cold stimulation may provide a new perspective for understanding how cold mediates inflammatory damage to the cardiovascular system. This perspective is crucial for preventing and reversing cardiovascular diseases and averting cardiovascular events. Therefore, researchers have gradually developed an interest in studying the effect of cold on the inflammatory process in cardiovascular diseases. Recent years have seen relevant studies aiming to formulate strategies to reduce the inflammatory response caused by cold in the cardiovascular system.

Crosswhite, e*t al.* reported that AAV vector-delivered short hairpin RNA (shRNA) for TNF-α effectively suppressed cold-induced expression of TNF-α, IL-6, and phosphodiesterase-1c, leading to the inhibition of macrophage infiltration[58]. This intervention resulted in a reduction in pulmonary hypertension, arterial remodeling, and right ventricular hypertrophy. Similarly, Wang e*t al.*[59] demonstrated the amelioration of cold-mediated aortic and coronary remodeling through the silencing of NADPH oxidase subunit gp91 (phox) using AAV vector-based RNA interference. Additionally, AAV delivery of ET1-shRNA for endothelin-1 (ET1) prevented cold-induced ROS production, cardiac hypertrophy, and controlled the increase in blood pressure[60]. These studies underscore the significant role of selectively inhibiting inflammation-related targets in the preventing further injury during cold exposure, highlighting targeted therapy for cold-induced inflammation as a novel strategy for drug discovery and development.

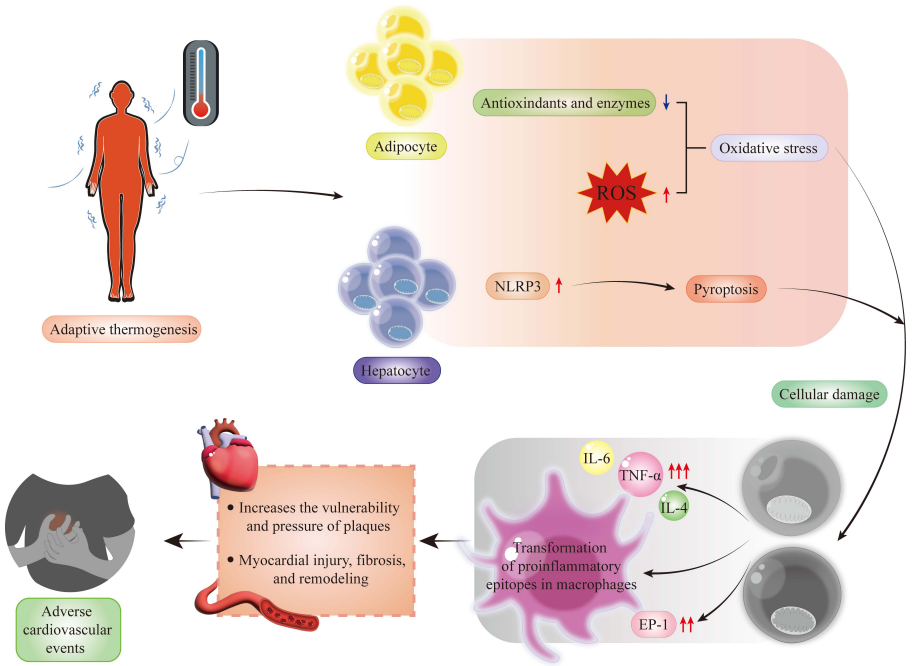

Fig. 1 Schematic presentation of potential mechanisms underlying inflammation and cardiovascular conditions induced by low ambient temperature

Predicting the extent of cardiovascular injury using the levels of inflammatory factors poses an urgent challenge. Stress and infection increase the levels of inflammatory factors in the body. Due to the poor specificity of conventional inflammatory factors, determining the levels of inflammatory factors induced by cold using conventional methods proves inadequate. Therefore, there is a pressing need for specific molecular biomarkers to monitor this process. CIRP, discovered during cold exposure, has been established to be strongly correlated with the inflammatory response process[61]. However, subsequent in-depth studies revealed that CIRP is not stimulus-specific, as its expression changes during sepsis, cancer, and other diseases. Consequently, further studies analyzing new biomarkers from currently known or unknown inflammatory pathways are warranted.

In summary, immediately after cold exposure, tissues undergo an increase in oxidative phosphorylation, leading to an imbalance of oxidant and antioxidant systems mediated by adaptive thermogenesis. The resulting ROS not only inflict oxidative damage to tissues but also activate classical inflammatory pathways, including NF-κB and MAPK, thereby inducing inflammatory damage to cardiovascular tissues during cold exposure. Additionally, cold exposure-mediated programmed cell death mechanisms, such as pyroptosis and autophagy, are involved in the inflammatory response. The identification of specific biomarkers for cold-induced inflammation and therapeutic targets holds the potential to effectively reduce the incidence of cold-induced cardiovascular death in residents in cold areas. Looking ahead, further exploration into the initiation and progression of cold-induced inflammation, as well as the specific mechanisms of its impact on the development of cardiovascular diseases, is essential.

Author contributions

Ma G P and Cai H X: Conceptualization, Writing-Original draft preparation, Writing- Reviewing and Editin. Li Z Y and Lu R Z: Conceptualization, Supervision. Fang S H and Yu B: Supervision, Project administration.

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Conflict of interest

Yu B is an Editorial Board Member of Frigid Zone Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of this Member and his research groups.

Data availability statement

Not applicable.

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