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Effect of aging on cardiovascular responses to cold stress in humans

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Abstract

Cold exposure increases the risk of adverse events related to cardiovascular causes, especially in the elderly. In this review, we focus on recent findings concerning the impact of aging on the regulatory mechanisms of cold-induced cardiovascular responses. In response to cold exposure, the initial physiological thermoregulation in healthy young persons, such as cutaneous vasoconstriction to reduce heat loss, is attenuated in older individuals, resulting in a reduced ability of the older persons to maintain body temperature in cold environment. Impaired sympathetic skin response, reduced noradrenergic neurotransmitter synthesis, insufficient noradrenergic transmitters, and altered downstream signaling pathways inside the vascular smooth muscle may be among the underlying mechanisms for the maladaptive vasoconstrictive response to cold stress in the elderly. The increase in blood pressure during cold exposure in young persons may be further augmented in aging adults, due to greater central arterial stiffness or diminished baroreflex sensitivity with aging. Cold stress raises myocardial oxygen demand caused by increased afterload in both young and old adults. The elderly cannot adjust to meet the increased oxygen demand due to reduced left ventricular compliance and coronary blood flow with advancing age, rendering the elderly more susceptible to hypothermia-induced cardiovascular complications from cold-related diseases. These age-associated thermoregulatory impairments may further worsen patients' health risk with existing cardiovascular diseases such as hypertension, coronary artery disease, and heart failure. We searched PubMed for papers related to cold stress and its relationship with aging, and selected the most relevant publications for discussion.

Keywords

aging; cardiovascular; cold stress; hypertension; coronary artery disease; heart failure

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1 Introduction

There is substantial epidemiological evidence that cold weather is associated with increased cardiovascular morbidity and mortality[1-2], such as myocardial infarctions[3], aortic dissection[4] and heart failure[5]. In most studies, a day with a cold temperature is defined as a daily mean temperature below the 5th percentile of the individual frequency distribution[6]. Cold exposure places elderly populations at risk by increasing the risk of adverse events of cardiovascular causes. Around 14% of the Chinese people will be over the age of 65 by the end of 2050. Therefore, an aging population will considerably increase the burden of cold-related mortality with cold temperature[7]. It is widely accepted that older adults have an impaired cardiovascular response to cold exposure, which may further increase the risk of mortality during cold seasons. This review will provide an insight of the cardiovascular response to cold exposure in older adults with or without cardiovascular diseases and highlight recent research that determines age-related differences in thermoregulation and cardiovascular responses to a cold environment.

2 The cardiovascular response to cold stress in healthy young persons

This section briefly describes the cardiovascular responses to cold exposure in young adults providing as a baseline for contrasting the different responses of older adults. Cold exposure refers to a state when the body is exposed to cold temperature, which leads to lower body temperature. Different types of cold exposure have been used to simulate cold conditions in previous studies, including cold air, cold water

immersion, or contacting with cold objects. Different cooling methods may be used to investigate the thermoregulatory response to cold exposure, including whole-body cooling with water-perfusion suits, local cooling to the front head with an external application, hands with a cold pressor test, or the respiratory tract with cold air inhalation. During cold exposure, if the compensatory thermoregulation to reduce heat loss is unable to maintain the normal body temperature, it is called cold stress[8].

2.1 Cutaneous vasoconstriction

During passive cold exposure, lowering of skin and core temperatures stimulates activation of sympathetically mediated vasoconstriction[9-11]. Through the vasomotor alterations mediated by increased sympathetic nerve activity[12], the peripheral and visceral arteries vasoconstrict to reduce heat exchange between the body and the environment[13]. Vasodilation in cutaneous beds is insufficient to compensate for cutaneous vasoconstriction, resulting in a net increase in peripheral vascular resistance. Consequently, systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase by 5-30 mmHg and 5-15 mmHg, respectively. This occurs with skin cooling involving the whole body[14-17], face[18-20], local skin areas[16], whole-body cooling excluding the head[21-22], and cold air inhalation[23]. These alterations take place with skin cooling of the face[18-20], whole-body[14-17], and cold air inhalation[24].

2.2 Heart rate

The increase in heart rate (HR) is mainly caused by activation of the sympathetic nervous system with the cold air inhalation[24] or cold pressor test[16,24-26] rather than a direct effect of temperature on the heart. However, many experimental studies applying facial cooling alone report reduced HR[14,16,18-20,27-28] because it stimulates the trigeminal nerve and elicits a non-baroreflex mediated vagal response similar to the diving reflex[18]. Hence, whole-body skin cooling with facial exposure leads to decreased[14,16-17,29-31] or unaltered[13,15,32] HR.

2.3 Myocardial oxygen demand

Cardiac contractibility and cardiac output remain unchanged at rest despite increased pre and afterload by whole-body cold exposure[33]. Increased SBP with lightly altered HR may slightly increase myocardial oxygen demand[29]. The higher myocardial oxygen demand in response to cold results in an increase in coronary blood flow (CBF)[34]. Cold exposure causes dilation of the structurally and functionally normal coronary arteries[35]. This autoregulation is mediated by β-adrenergic vasodilation of coronary resistance vessels to maintain coronary blood flow at a steady state[36].

3 Effect of age on the cardiovascular responses to cold exposure

3.1 Cutaneous vasoconstriction

Cutaneous circulation acts as a variable heat insulator immediately beneath the skin's surface. The initial thermoregulatory response to cold exposure is cutaneous vasoconstriction. The patency of relevant cutaneous vessels is controlled by the autonomic nervous system and numerous endogenous mediators determine how much heat is preserved in a cold environment[37-38]. Cutaneous vasoconstriction in response to both mild[39] and severe[40-42] cold exposure is attenuated with aging, resulting in more significant heat loss and a reduced ability of the elderly to preserve body temperature in cold environments[39-41]. Compared with young adults, the decrease in skin blood in healthy older adults is attenuated by 50% during whole-body cold exposure[43]. The mechanism may involve impaired sympathetic skin response, reduced noradrenergic neurotransmitter synthesis, insufficient noradrenergic transmitters, and altered downstream signaling pathways inside the vascular smooth muscles[44-45]. However, the central ability to increase skin sympathetic nervous activity (SSNA) does not affect older adults in cold stress[44-45]. Moreover, the reduced sympathetic activation in older persons during whole-body cooling is only observed in the skin, as muscle sympathetic nerve activity is intact in older adults[45], suggesting altered afferent signaling or impaired central reception of those signals from skin thermoreceptors.

Apart from a diminished discharge rate of the efferent sympathetic nerve, the presynaptic synthesis and release of noradrenaline (NA) are decreased with aging. The possible mechanisms for the reduced biosynthesis of NA in aged skin include diminished bioavailability of tetrahydrobiopterin (BH4) and L-tyrosine. Tyrosine hydroxylase, the rate-limiting enzyme for NA synthesis, requires sufficient concentrations of the cofactor BH4 and the substrate tyrosine to achieve optimal activity[46-47]. The increased reactive oxygen species (ROS) with advancing age decrease the bioavailability of BH4, the essential cofactor of tyrosine hydroxylase. Consequently, the ability of cutaneous microvascular constriction is diminished in the elderly by increased oxidative stress[48-49]. Therefore, direct injection of BH4[50] or tyrosine[51] or oral ingestion of a pharmacological source of BH4, sapropterin[52] or L-tyrosine[53-54] improved core temperature maintenance and augments the cutaneous reflex vasoconstriction response to cooling in older adults. Collectively, these studies demonstrate that reduced noradrenergic neurotransmitter biosynthesis may blunt reflex

cutaneous vascular response to cold stress in older adults.

Unlike young adults, the sympathetic noradrenergic transmitters do not have a functional role in reflex vasoconstriction in older adults[55]. Although a published study indicated cutaneous skin responsiveness to exogenous NA is reduced in aged skin[56], according to recent research[45], skin blood vessel sensitivity to NA is not impaired in older adults. Only maximal doses of NA can blunt vasoconstrictor response[45,57]. Moreover, the vascular transduction of sympathetic outflow to vasoconstriction of the skin is not changed with aging[45]. Therefore, impaired cutaneous vasoconstriction in older adults might not be associated with reduced vascular responsiveness to noradrenergic stimulation.

Lastly, aging increases vascular dysfunction with altered signaling pathways responsible for smooth muscle vasoconstriction. Older adults rely more on ROCK-mediated vasoconstriction during cold stress, as the vasoconstrictor response is significantly attenuated with pharmacological blockade of ROCK in older, but not young, adults[58]. With advancing age, this ROCK-mediated vasoconstriction is upregulated due to increased oxidative stress and angiotensin (AT) II signaling. The reflex vasoconstriction mediated by ROCK depends on the activation of AT receptors only in older adults[59]. However, the vasoconstrictor response to local cooling is well preserved in older adults, but the adrenergically mediated vascular response to cooling is blunted while ROCK-mediated vasoconstriction is increased with age[60]. Although ROCK-mediated vasoconstriction is beneficial for the maintenance of cutaneous vascular response to the cold, overactivation of ROCK is also associated with vascular pathology[61] and might contribute to vascular endothelial dysfunction in the aging population. A recent study demonstrates that the activities of the cold-sensitive transient receptor potential (TRP) A1 and M8 receptors are impaired in mouse skin even with only moderate aging. Aging mice rely more on the activities of cold TRP channels as pharmacological blockade of TRPA1/M8 produces a significantly greater cold-induced cutaneous vascular response in the aged group[62].

3.2 Hemodynamic responses

Elderly persons are particularly susceptible to temperature-related alterations in blood pressure, such as cold-induced increase in blood pressure in winter times[63]. In hypertensive elderly individuals, blood pressure (BP) increases to a higher extent compared to normotensive counterparts[29]. Core body cooling elicits greater pressor responses in the elderly with greater increases in mean and systolic BP than in young adults[64-67]. The peripheral (*i.e.*, brachial) response to moderate cold stress may differ depending on age. This may explain why some studies failed to observe an augmented BP increase in core body temperature-reducing cold stress[39,68]. Because increased arterial stiffness in the elderly tends to affect central BP elevation more than peripheral arteries, greater stress can impose more strain on the heart during cold exposure than is appreciated using brachial BP measurements[69]. Generally, elevated BP in response to skin temperature cooling is induced by cutaneous and visceral vasoconstriction[13]. The greater increase in systolic BP response, but not diastolic one, to cold stress in older adults can be explained by greater central arterial stiffness or diminished baroreflex sensitivity in the elderly[21,70-73]. Aging increases arterial stiffness indexes, including augmentation index as an index of arterial stiffness, wave reflection increases, and pulse wave velocity in response to whole-body skin or facial cooling[21,29,74]. The fact that indexes of central arterial stiffness with aging are associated with the magnitude of the pressor responses to superficial skin cooling can be explained by the reduced ability of the aorta to buffer pressure fluctuations in the cardiac cycle. The aortic structural changes in the elderly result in more significant pulse pressure and systolic BP both at rest and during exercise[75-76]. As another hemodynamic determinant of BP, heart rate is reduced to a lesser degree in the elderly during cold exposure[77]. The dampened heart rate reduction in older adults might be due to blunted baroreflex for maintaining BP[70].

3.3 Myocardial work and oxygen supply

Myocardial oxygen demand may be affected by aging and cold stress[78]. Although cold stress increases BP, central venous pressure, and pulmonary capillary wedge pressure[13,79-82], no significant changes in inotropy (ventricular contractibility), HR, and cardiac output are found in young adults[33]. A possible explanation for this is that a slight increase in afterload is offset by elevated left ventricular filling pressure in young adults. Older adults have an augmented vasoconstrictor response during cooling in vascular beds, but not in the skin, compared with young adults[83], and this augmented pressor response to cooling is not associated with an increase in cardiac output[84]. The ability of older adults to maintain stroke volume is impaired during cold exposure, as older adults can hardly achieve the same degree of increase in left ventricular filling pressure or contractility (ejection fraction, the positive systolic velocity when the mitral ring moved toward the cardiac apex, or myocardial acceleration during isovolumic contraction) to balance the worsening increases in preload and afterload[84]. These findings may explain the associations between cold weather and increased incidence of myocardial infarction as well as all-cause cardiovascular mortality in older adults.

Therefore, the heart of older population is less able to properly adjustment to meet increased myocardial oxygen demand caused by cold exposure due to reduced left ventricular compliance and diastolic function with advancing age[85-88]. Studies found SBP and HR are increased in young persons, and thus the rate pressure product (RPP), a surrogate marker for myocardial oxygen demand is elevated during the cold pressor test[23,26,89] or cold air inhalation[24]. Therefore, myocardial oxygen demand is further increased[84] with aging during whole-body cold exposure[29] due to greater increases of afterload in the elderly and virtually no change of HR.

In response to cold stress, the coronary blood flow (CBF) increases to meet the higher myocardial oxygen demand[13]. This autoregulation driven by the sympathetic system causes vasodilation of coronary arteries to ensure constant coronary blood flow[41,52-55]. The physically and functionally normal coronary arteries dilate in response to cold exposure[55]. In contrast, cold air inhalation impairs the coronary supply-to-demand ratio in healthy persons, whereas inhalation of neutral temperature air does not[34,50]. Inhaling cold air while exercising can further augment RPP and reduce coronary hyperemia. The mechanism may be associated with impaired efferent control of coronary blood flow in normal persons. Studies have shown that aging desensitizes β1-adrenergic receptor which mediates β-adrenergic vasodilation when the myocardial oxygen demand is raised to maintain coronary flow control. Treatment with an adipose-derived stromal vascular fraction (SVF) improves βAR-mediated coronary flow reserve (CFR) and restores the function of isolated coronary artery dilation to β-AR agonists[83,90-91]. Therefore, it is possible that β-AR signaling is blunted in response to cold stress in older adults. Beta-blockers or cell therapy with SVF might be a promising treatment option for restoring the cold-related coronary microvascular dysfunction in the aged population.

In summary, the ability and capacity of older persons, particularly individuals over 60 years, to elicit a normal cardiovascular response to preserve core temperature during cold challenge are weakened relative to younger individuals (Fig. 1). Especially, our knowledge about how cold stress modifies cardiovascular responses in the very old subjects (≥80 years) is largely lacking. As aging leads to a nonreversible decline of homeostatic regulation, it is reasonable to speculate that cold-induced thermoregulation may be further mitigated in the very old group.

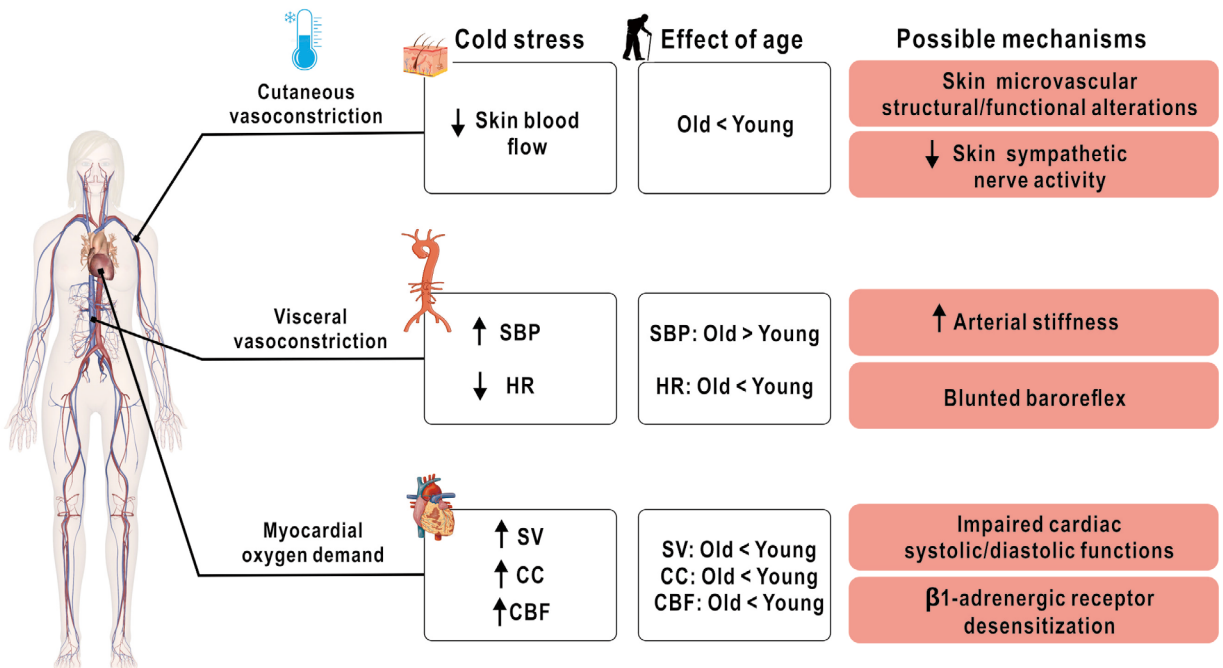

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Fig. 1 Summary of recent research advances in the cardiovascular response to cold stress of older adults

This figure schematically depicts the following points: (1) the cardiovascular response to cold stress in healthy young adults; (2) how these responses differ in healthy older adults; and (3) possible mechanisms mediating age-related differences. SBP, systolic blood pressure; HR, heart rate; SV, stroke volume; CC, cardiac contractility; CBF, coronary blood flow.

4 Cardiovascular responses in older persons with cardiovascular diseases

4.1 Hypertension

Patients with hypertension are more susceptible to cold-related cardiovascular events due to the cold-induced sudden rise of BP during the cold season[2,92]. One may hypothesize that exaggerated cardiovascular responses are related to acute cold exposure due to dysregulated autonomic control and sympathetic overactivation in hypertension. The disrupted autonomic regulation may also affect cardiac electrical function among untreated middle-aged hypertensive patients, resulting in a prolonged T-peak to T-end interval and higher T-wave amplitude during a short-term cold exposure[30]. Hypertension is related to increased arterial stiffness and endothelial dysfunction, resulting in elevated basal vascular tone and overreaction to cold exposure[93]. Moreover, aging-related hypertension may worsen the central arterial stiffness and cold-induced pressor response[21].

Previous studies have examined how hypertension alters cardiovascular responses to cooling, of which the studies that recruited older persons demonstrated greater pressor responses to cold stimulation with increased SBP, BP, and central aortic blood pressure than the ones involving younger persons. Greaney *et al*.[94] found that hypertensive patients (mean age 58 years old) had a greater increase in BP and muscle sympathetic nerve activity (MSNA) than in normotensive subjects. This study also demonstrated that baroreflex sensitivity (BRS) that dominantly controls short-term BP and buffers the increases in BP induced by cooling, is diminished in hypertension compared with that in normotensive controls (mean age 53 years old)[94]. Another study revealed that the hypertensive patients had greater magnitudes of increases in SSNA and skin cutaneous vasoconstrictor response to cooling[95]. Interestingly, the observed aggravation of vasoconstriction is not caused by cutaneous adrenergic sensitivity. Based on these findings, the authors reached a conclusion that non-adrenergic neurotransmitters have a greater contribution to the increased skin sympathetic outflow[95]. Similarly, in a study involving older adults, Jarvis *et al*.[25] reported significant increases in HR, SBP, DBP, and MSNA in a cold pressor test, yet the cardioprotective mechanisms of BRS are preserved in the hypertension group. However, in a study employing young individuals, Zalewski *et al*.[96] found the opposite result with decreased SBP and HR during whole-body cooling in the hypertension group (mean age 30 years old), and there were no significant differences in cardiac contractility between the hypertensive and normotensive groups. The studies mentioned above showed contrasting cardiovascular responses to cold exposure between young and older adults, suggesting age can potentiate the magnitude of cold-induced increases in BP in patients with hypertension.

4.2 Coronary artery disease

Studies on how aging modifies cardiovascular responses to stimuli of the cold in patients with coronary artery disease (CAD) are lacking. Previous studies have shown that coronary blood flow was decreased in healthy persons after cold air inhalation[36] and such an alteration was accentuated with aging[23]. Coronary dilation to skin cooling was found attenuated in older adults[97]. A combination of cold exposure and aging often increases cardiovascular strain compared with cold exposure alone. Several studies used the symptom-limited exercise test to compare myocardial ischemia in CAD patients exposed to cold environment and in those to a thermoneutral environment. A study involving clinical populations including older subjects with CAD showed higher SBP and RPP and lower ischemic threshold and exercise capacity with cold exposure relative to those without cold exposure[98]. However, studies containing younger CAD patients showed better cardiac performance during exercise in cold stress. de Servi *et al*.[99] (mean age 53.5 years old) showed that the increased coronary resistance is offset by metabolic vasodilation during a cold pressor test. So, the overall effect of the cold pressor test in CAD subjects is a reduction in coronary resistance during exercise. Peart *et al*.[100] (mean age 49 years old) reported unaltered RPP in stable CAD patients during cold air exposure compared with that under the thermoneutral condition. These findings suggest that age may augment the deleterious effect of cold exposure on coronary blood supply in the CAD population.

In summary, a cold environment increases cardiac workload during exercise tests in CAD patients. Myocardial oxygen supply may decrease with a higher cardiac strain in older CAD persons, resulting in impaired cardiac performance during exercise.

4.3 Heart failure

Only a few studies show that patients with heart failure (HF) and older ages have reduced maximal and submaximal performance in cold environments[101-102]. Blanchet *et al*.[101] reported that cold exposure caused a 21% reduction in exercise time and significant increase in the level of norepinephrine in HF patients (mean age 60 years old) compared with healthy control subjects, with no significant changes in RPP. Moreover, treatment with beta-blockers such as carvedilol or metoprolol improved the cardiovascular responses to cold stimuli during exercise. Juneau *et al*.[102] found that the maximal exercise time of HF patients (mean age 61 years old) in cold temperature was reduced by 17% with increased RPP, cardiac index, and reduced peripheral vascular resistance. Acute treatment with a low-dose ACE inhibitor for three days remarkably improved

exercise capacity in the cold. Patients with compensated chronic heart failure (age 59-65 years old) tend to have more premature ventricular contractions, making the HF patients more susceptible to malignant ventricular arrhythmias. This can be ascribed to increased sympathetic tone in older HF patients and cold stimulation of the autonomic nervous system[103].

4.4 Geriatric syndromes

Geriatric syndromes are highly prevalent in the elderly. Cold stress may further worsen the condition by increasing the risk of cognitive dysfunction, frailty and depression. A study documented that cognitive functions, including declined working memory, choice reaction time, and executive function are impaired during cold air exposure[104]. A recent study from Japan reported that older adults who felt cold during winter peaks were more susceptible to frailty[105]. Castro *et al*.[106] demonstrated a reduced 5-HT1A receptor responsiveness in the old but not in the young rat during sub-chronic cold stress, suggesting a failure of old rats to adapt their serotonergic responses to cold stimuli, leading to depressive symptoms.

5 Conclusions remarks

Aging includes a broad range of structural, functional, cellular, and molecular alterations[107] in the heart and plays a crucial role in cold-induced cardiovascular responses. The protective mechanisms of cold-induced cutaneous vasoconstriction to maintain thermal homeostasis are impaired in older persons. Moreover, the BP elevation in response to cold stress is exaggerated in older adults. In patients with existing cardiovascular diseases, aging impairs the capacity and mechanisms for proper adjustments to prevent cold injury and further increases the risk of hypothermia- and cardiovascular-related mortality. Thus, future studies are needed to advance our knowledge of the exact mechanisms underlying the aging-related impairments of cold-induced cardiovascular responses and to minimize the mortality burden of cold spells in older adults.

Conflicts of interests

No conflicts of interest, financial or otherwise, are declared by the authors.

Authorship contributions

Cheping Cheng participated in concept and design. Tiankai Li did the literature search. Tiankai Li, Qi Wang and Cheping Cheng wrote or contributed to the manuscript preparation, manuscript editing and manuscript review.

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