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Advances in understanding cold-related hemodynamic changes in the cardiovascular system

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Abstract

Cold exposure induces significant hemodynamic disturbances that contribute to increased morbidity and mortality from cardiovascular disease (CVD). This review explores the physiological and molecular mechanisms by which cold stress affects blood pressure regulation, vascular resistance, and wall shear stress (WSS), and how these alterations promote CVD development. Cold exposure elevates blood pressure primarily through activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). These neurohumoral pathways enhance vasoconstriction and increase blood viscosity, thereby elevating peripheral vascular resistance. Moreover, cold-induced alterations in WSS impair endothelial function, facilitate platelet aggregation, and accelerate atherosclerotic progression. Despite extensive evidence linking cold exposure to hemodynamic and vascular dysfunction, the precise molecular and integrative mechanisms remain incompletely understood. We propose that the SNS-RAAS axis represents a central regulatory pathway underlying cold-induced hemodynamic changes, warranting further investigation to clarify its contribution to cold-related cardiovascular pathology.

Keywords

cold; hemodynamics; blood pressure; blood resistance; blood shear stress

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A growing body of epidemiological evidence indicates that non-optimal ambient temperatures are associated with increased morbidity and mortality from cardiovascular disease. In 2019, approximately 1.69 million global deaths were attributed to non-optimal temperatures, with the health burden of cold exposure far exceeding that of heat-related mortality[1-4]. Despite its clinical significance, a precise and universally accepted definition of “cold exposure” remains lacking[5]. Several studies have operationalized cold exposure using temperature percentiles, typically defining it as two or more consecutive days with a daily mean temperature below the 5th or 10th percentile of historical temperature distributions[6-8]. In experimental animal models, cold exposure is commonly standardized at approximately 5.0 ± 1.0 °C[9-10].

Hemodynamics refers to the study of the mechanical principles governing blood flow within the cardiovascular system, encompassing parameters such as blood pressure, vascular resistance, and shear stress, as well as their interrelationships[11]. Although the precise mechanisms underlying cold-induced cardiovascular injury remain incompletely understood, accumulating evidence suggests that cold exposure perturbs hemodynamic homeostasis, resulting in alterations in blood pressure, flow resistance, and wall shear stress. These changes are thought to contribute to the initiation and progression of cardiovascular diseases. This review summarizes current evidence on the hemodynamic effects of cold exposure, aiming to provide deeper insight into its role in cardiovascular pathology.

1 Effects of cold exposure on blood pressure

1.1 Cold exposure increases blood pressure

An analysis of 1895 outpatients in Urumqi, China, (July 2020-December 2021), revealed an approximately linear relationship between ambient temperature and blood pressure: for every 10 °C decrease, systolic blood pressure increased by 0.84 mmHg, diastolic pressure by 0.56 mmHg, mean arterial pressure by 1.38 mmHg, and pulse pressure by 0.66 mmHg[12]. A Japanese study found that morning home blood pressure (HBP)

was particularly sensitive to indoor temperature, increasing by 8.2 mmHg for every 10 °C decrease, especially among older adults and women[13]. A web-based telemedicine program evaluating HBP in patients with chronic cardiovascular disease, each 1 °C decrease in ambient temperature was associated with a 0.55 mmHg increase in mean blood pressure, a 0.68 mmHg increase in systolic pressure, and a 0.27 mmHg increase in diastolic pressure; notably, antihypertensive therapy—particularly angiotensin receptor blockers—attenuated the temperature effect, whereas diuretics amplified it[14].

1.2 Mechanisms of cold-induced blood pressure elevation

Cold exposure raises blood pressure through several neurohormonal pathways involving the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), nitric oxide (NO), and endothelin.

1.2.1 SNS involvement in cold-induced blood pressure elevation

Cold exposure (6 ± 2 °C) elevates plasma norepinephrine, which increases cardiac output and constricts peripheral vasculature, thereby raising blood pressure. Clinical studies show that acute cold exposure increases plasma norepinephrine, suggesting that SNS activation—rather than adrenal catecholamines per se—plays a central role in cold-induced pressor responses[15-18]. This is supported by evidence that adrenalectomized individuals exhibit blood pressure increases during cold pressor testing comparable to those with intact adrenal glands[19-20]. Even mild cold exposure (19 °C versus 24 °C) has been reported to elicit nearly a threefold rise in plasma and urinary norepinephrine over 12 h[21]. Acute cold exposure may also heighten baroreflex/stress-reflex sensitivity, further augmenting SNS activity[22-24].

1.2.2 RAAS involvement in cold-induced blood pressure elevation

Cold stress stimulates plasma renin activity, increases angiotensin II (Ang II) formation, and activates RAAS. Sun *et al.* reported that the cold-induced increase in blood pressure was markedly smaller in angiotensinogen (AGT) knockout mice (19 ± 3 mmHg) than in wild-type mice (61 ± 5 mmHg) at 1 °C[25]. Inhibiting RAAS activation—by reducing AGT expression or blocking the angiotensin II type 1 receptor (AT1R)—prevented cold-induced blood pressure elevation[26]. Using a recombinant adenovirus carrying rat renin antisense RNA, Wang *et al.* suppressed renin expression and abolished cold-induced increases in total and active plasma renin, Ang II, and plasma/urinary aldosterone, thereby reversing cold-induced hypertension—underscoring RAAS's pivotal role[27].

1.2.3 NO involvement in cold-induced blood pressure elevation

NO, a key endothelium-derived vasodilator, is essential for blood pressure regulation and endothelial function. Cold-exposed animals exhibit reduced plasma and urinary nitrite/nitrate (surrogates of NO production), indicating suppression of NO synthesis by cold[25,28]. Notably, AGT knockout mice did not show this reduction[25], suggesting that RAAS mediates the cold-induced inhibition of NO. Consistently, cold exposure reduced endothelial nitric oxide synthase (eNOS) protein expression in the heart and aorta of wild-type mice, whereas eNOS expression was preserved in AT1R knockout mice, implicating AT1R in the inhibitory effect on eNOS[28]. In rats, eNOS gene transfer increased NO production and blunted cold-induced blood pressure elevation[29]. Interestingly, systemic eNOS delivery also lowered plasma norepinephrine in cold-exposed rats, implying that increased NO may dampen SNS activity; conversely, cold-related NO suppression may accompany SNS activation. Thus, NO is both a downstream effector and a potential modulator of SNS activity in cold-induced hypertension.

1.2.4 Endothelin involvement in cold-induced blood pressure elevation

Endothelins are endothelial-derived vasoconstrictor peptides integral to vascular tone and hemodynamics; endothelin-1 (ET-1) is the most potent known endogenous vasoconstrictor in mammals. ET-1 levels in mesenteric resistance arteries increase significantly after one week of cold exposure, coinciding with rising blood pressure[30]. Experimental studies also show that cold exposure enhances ET-1 metabolism and secretion in human subjects[17]. Cai *et al.* reported that each 1 °C drop in mean temperature was associated with an 8.2% increase in ET-1 levels, further highlighting ET-1 in cold-induced hypertension[31]. Of note, AT1R gene knockdown markedly reduced cardiac ET-1 levels in cold-exposed rats, suggesting that RAAS—*via* AT1R—mediates cold-induced ET-1 upregulation[32].

In summary, the SNS/RAAS axis appears central to cold-induced blood pressure elevation. Cold exposure activates the SNS, increasing norepinephrine release and engaging RAAS, which raises Ang II levels. Ang II then promotes ET-1 production, leading to vasoconstriction and higher blood pressure. In rats, bilateral renal denervation—which disrupts SNS-mediated RAAS activation—abolished cold-induced increases in renin and prevented hypertension, indicating that SNS activation initiates the response, whereas RAAS drives the sustained pressor effect[33]. Pharmacological RAAS blockade at multiple nodes and genetic knockout models consistently delay and attenuate the hypertensive response to cold[25,27-28,34-35]. Concurrent suppression of NO and elevation of

ET-1 illustrate the broader neurohumoral interplay underpinning the pressor effect. Collectively, these findings support the SNS/RAAS axis—modulated by ET-1 and NO—as a key regulator of blood pressure changes during cold exposure.

2 Effect of cold exposure on resistance to blood flow

The resistance to blood flow arises primarily from two sources: internal friction among blood components as blood moves, and the friction between the flowing blood and the vessel wall[36]. According to Poiseuille's law, which estimates flow resistance under laminar conditions in cylindrical vessels, the resistance (R) is expressed as:

$$R = \frac{8\eta L}{\pi a^4}$$

Where η represents blood viscosity (in Poises), L is the vessel length (cm), and a is the blood vessel radius. This equation illustrates that vascular resistance depends strongly on vessel radius (to the fourth power) and on blood viscosity. Cold exposure has been shown to increase both blood viscosity and vascular constriction, thereby increasing total flow resistance and producing hemodynamic disturbances.

2.1 Cold exposure increases blood viscosity

Multiple animal studies have reported a significant increase in blood viscosity with decreasing ambient temperature[37-39]. Keatinge *et al.* reported significant increases in plasma and whole-blood viscosity in healthy men and women after 6 hours of cold exposure, with seasonal analyses showing peak viscosity values during winter months among 16 healthy volunteers[40]. Frohlich *et al.* found that immersion of healthy volunteers (*N* = 10) to mid-sternum in 10 °C water for 90 min resulted in a mean increase of 19% in blood viscosity[41]. Similarly, a population-based study in Germany demonstrated a significant correlation between periods of low temperature and elevated plasma viscosity in the general population[42].

2.2 Mechanisms of increased blood viscosity due to cold exposure

The mechanisms underlying cold-induced elevations in blood viscosity remain incompletely defined. Viscosity is determined primarily by plasma water content and macromolecular constituents such as fibrinogen, lipoproteins, and immunoglobulins[43]. One plausible mechanism involves cold-induced vasoconstriction, which drives a fluid shift from the vascular compartment to interstitial spaces, thereby increasing hematocrit and viscosity, as well as blood pressure. This effect may be compounded by enhanced respiratory water loss and cold-induced diuresis[44-45].

Fibrinogen, a critical clotting factor, is a principal determinant of plasma viscosity[46-48]. Seasonal studies have shown higher fibrinogen concentrations during winters[49-50]. In one comparative study, when skin temperature decreased from 35.5 °C to 29.5 °C, plasma cholesterol and fibrinogen rose from 4.90 mmol/L and 2.97 g/L to 5.45 mmol/L and 3.39 g/L in older adults, and from 3.33 mmol/L and 1.84 g/L to 3.77 mmol/L and 2.07 g/L in younger subjects[51]. Both population-based and laboratory studies have confirmed increases in fibrinogen and other coagulation markers during acute or prolonged cold exposure[52-53]. Thus, fibrinogen elevation likely contributes substantially to the observed rise in plasma viscosity under cold conditions.

2.3 Cold exposure reduces blood vessel diameter

Physiologically , cutaneous vasoconstriction constitutes the primary autonomic defense against excessive body heat loss in cold environments[54]. Zhang *et al.*[55] reported that maximal vasoconstriction between 410 and 460 s after subjects immersed one hand in 4 °C water for 5 min. In mice, reduced blood flow in the tail and rump was also observed following immersion of the lower limbs and rump in 4 °C water for 5 min, confirming that cold exposure induces marked vasoconstriction and narrowing of vascular diameter.

2.4 Mechanisms of cold-induced reduction in blood vessel diameter

Neuromodulatory mechanisms play a major role in cold-induced vasoconstriction, which is mediated by sympathetic neurons releasing norepinephrine and by local vascular effectors that increase cold sensitivity[56]. Activation of sympathetic noradrenergic vasoconstrictor nerves reduces skin blood flow, thereby conserving heat. Additionally, non-noradrenergic co-transmitters such as neuropeptide Y and ATP also participate in reflex vasoconstriction[57].

Beyond neural regulation, non-neuromodulatory mechanisms are also critical. Reactive oxygen species (ROS) have been shown to mediate vasoconstriction following cold exposure. Zhang *et al.* demonstrated that ROS contribute to cold-induced vasoconstriction *via* activation of the ROS/RhoA/ROCK1 pathway in vascular smooth muscle cells and the ROS/PKC/ET-1 pathway in endothelial cells[55].

3 Effect of cold exposure on blood flow shear stress

Blood flow imposes several mechanical stresses on the vasculature: wall shear stress (WSS) generated by flowing blood, circumferential (hoop) stress arising from pulsatile flow and pressure, and longitudinal tensile stress influenced by blood

pressure and surrounding tissues. Among these, WSS plays a central role in vascular physiology and pathology. Extensive evidence links aberrant WSS to atherosclerosis, intimal thickening, plaque formation and rupture, and stroke; however, studies specifically examining how cold exposure modifies WSS remain relatively limited. Taher *et al.* investigated the impact of ambient temperature on anterior cerebral artery flow in patients with cranial prostheses and observed negligible WSS changes at 25 °C and 55 °C in both healthy subjects and patients, whereas at 5 °C, WSS increased to 1.2-fold and 2.9-fold of normothermic levels in healthy subjects and patients, respectively[58]. A Japanese group reported that temperature alone did not significantly alter eNOS activation in endothelial cells, but the combination of shear stress and temperature shifts produced a marked increase in eNOS activation at 37 °C and 28 °C, and a decrease at 4 °C, indicating that cold exposure interacts with shear to regulate vascular function[59]. Other investigators showed that low temperature augments shear-induced platelet aggregation and activation, with significantly greater aggregation at 24 °C, 32 °C, and 35 °C than at 37 °C[60], suggesting that cooling may influence platelet behavior in part *via* WSS-dependent mechanisms.

Collectively, these studies describe cold-related changes in WSS and downstream vascular responses but do not fully elucidate the mechanisms by which cold alters WSS.

Under laminar conditions, WSS can be approximated by the following relationship[61]:

$$WSS = \frac{blood\ viscosity \times blood\ flow\ velocity}{intravascular\ diameter}$$

Because hemodynamic determinants are interdependent, and because cold exposure can increase blood viscosity and reduce vessel diameter (*via* vasoconstriction), WSS would be expected to rise under cold conditions. We therefore hypothesize that the principal bridge between cold exposure and altered WSS is the concurrent increase in blood viscosity and decrease in vessel caliber, a proposition that warrants confirmation in future mechanistic and *in vivo* studies.

4 Summary and outlook

Hemodynamic disturbances likely constitute a key intermediate link between cold exposure and increased CVD mortality. Curren evidence indicates that, although the precise contribution of blood pressure requires more quantitative resolution, the excess CVD risk associated with cold mediated in part by significant increases in blood pressure[62-63]. In parallel, increased blood viscosity—which augments flow resistance—has been associated with higher d CVD morbidity and mortality and may serve as a prognostic marker for cardiovascular disease outcomes[64]. Blood viscosity also contributes to the progression of ischemic heart disease, myocardial infarction, and atherosclerosis. Moreover, WSS connects hemodynamics to vascular biology: both low and high WSS have been implicated in endothelial misalignment, enhanced low-density lipoprotein retention, aberrant smooth-muscle cell proliferation and apoptosis, increased expression of inflammatory mediators and adhesion molecules, and dysregulated platelet activation, thereby promoting atherogenesis and its complications[65] (Fig. 1).

Alterations in blood pressure, flow resistance, and WSS therefore appear to be critical steps in cold-related cardiovascular pathophysiology. Nevertheless, major gaps remain in our understanding of how cold perturbs these hemodynamic factors at molecular, cellular, and systems levels.Given the prominent role of the SNS and RAAS in the cold response—and the interdependence among hemodynamic determinants—we hypothesize that the SNS/RAAS axis is not only central to blood pressure elevation but also a core driver of broader hemodynamic dysregulation, with other changes occurring

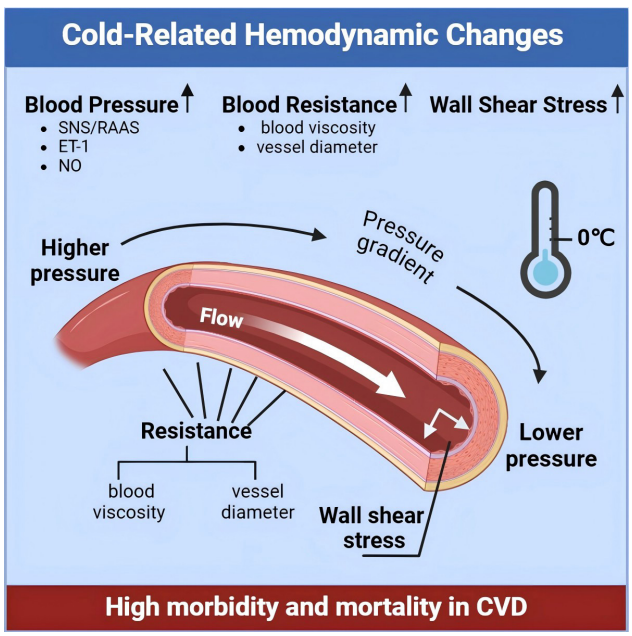

Fig. 1 Schematic representation of the effects of cold exposure on hemodynamic factors Created in BioRender.com

Cold exposure activates the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), leading to vasoconstriction, increased blood viscosity, and elevated blood pressure. These changes collectively alter vascular resistance and wall shear stress (WSS), resulting in endothelial dysfunction, enhanced platelet aggregation, and acceleration of atherosclerosis. The SNS/RAAS axis serves as the central regulator linking cold exposure to hemodynamic and cardiovascular disturbances. CVD, cardiovascular diseases; SNS/RAAS, sympathetic nervous system and renin-angiotensin-aldosterone system; ET, Endothelin.

downstream of axis activation. Targeted studies integrating neurohumoral profiling with high-resolution hemodynamic measurements and vascular biology are warranted to delineate causal mechanisms and to identify actionable nodes for prevention and therapy.

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Research ethics

Not applicable.

Informed consent

Not applicable.

Author contributions

Wu P: Writing original draft; Wang Y; literature search; Wang Z: Investigation; Yu B: Supervision; Fang S: Funding acquisition.

Use of large language models, AI and machine learning tools

No large language models, AI or machine learning tool was used for any part of the present study.

Conflicts of Interests

Yu B is a member of the Editorial Board of the journal. The manuscript was handled in accordance with the journal's standard editorial procedures, and the peer review process was conducted independently of this author and his research group.

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Data availability

All relevant data are within the manuscript.

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