

Article

# Physiological Effects of Cold Stress On Cardiac Function

Raghad Hasan Nafal<sup>1</sup>, Mohammed Hayder Asker<sup>\*2</sup>

1. College of dentistry, Ibn Sina University of Medical and Pharmaceutical sciences, Iraq, Baghdad
2. Basic Science Department, College of dentistry, Mustansiriyah University, Baghdad, Iraq

\*Correspondence: [moh.hayder@uomustansiriyah.edu.iq](mailto:moh.hayder@uomustansiriyah.edu.iq)

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**Abstract:** Cold stress is an important environmental factor which may interfere with the physiological stability in mammals, especially in small animals like rabbits. Rabbits are very sensitive to low temperatures because of the high surface-area to volume ratio, and insulated area, leading to complex thermoregulatory and cardiovascular responses, to maintain the core body temperature. The review is a summary of existing scientific findings on the physiological and molecular actions of cold stress on the cardiac system in rabbit models. Exposure to cold causes significant sympathetic response that causes the heart rate to rise, blood pressure to increase, and the myocardial oxygen demand to increase. Hemodynamic changes, such as raised systemic vascular resistance, and variations in the cardiac output exert heavy burden to the myocardium. Moreover, cold stress has a considerable impact on electrophysiological stability, leading to slowing conduction, QT prolongation, and an excessively high risk of arrhythmias. At the molecular level, low temperatures increase oxidative stress, activate inflammatory signals, impair calcium translocations, and induce apoptosis, which plays a role in structural and functional cardiac changes. Edema, vascular congestion and initial signs of myocardial remodeling are established in histological studies when exposed over a long period. The rabbits are a useful translational model because they have physiological similarities to human beings on autonomic regulation and cardiac electrophysiology. Given these mechanisms, it is possible to mention that the research of environmental cold stress on heart health offers valuable insights into the effect of cold stresses and conditions future studies on protective measures and adaptive mechanisms.

**Keywords:** Cold Stress, Cardiac Physiology, Sympathetic Activation, Oxidative Stress & Apoptosis, Rabbit Model

## Introduction

Cold stress has been identified as one of the most potent environmental determinants which could be able to modify physiological stability of the mammals. Rabbits especially cannot withstand low temperatures; they have a high surface to volume ratio as well as limited insulation ability that combine and make them susceptible to heat loss in cold temperatures (1). The rabbits have a

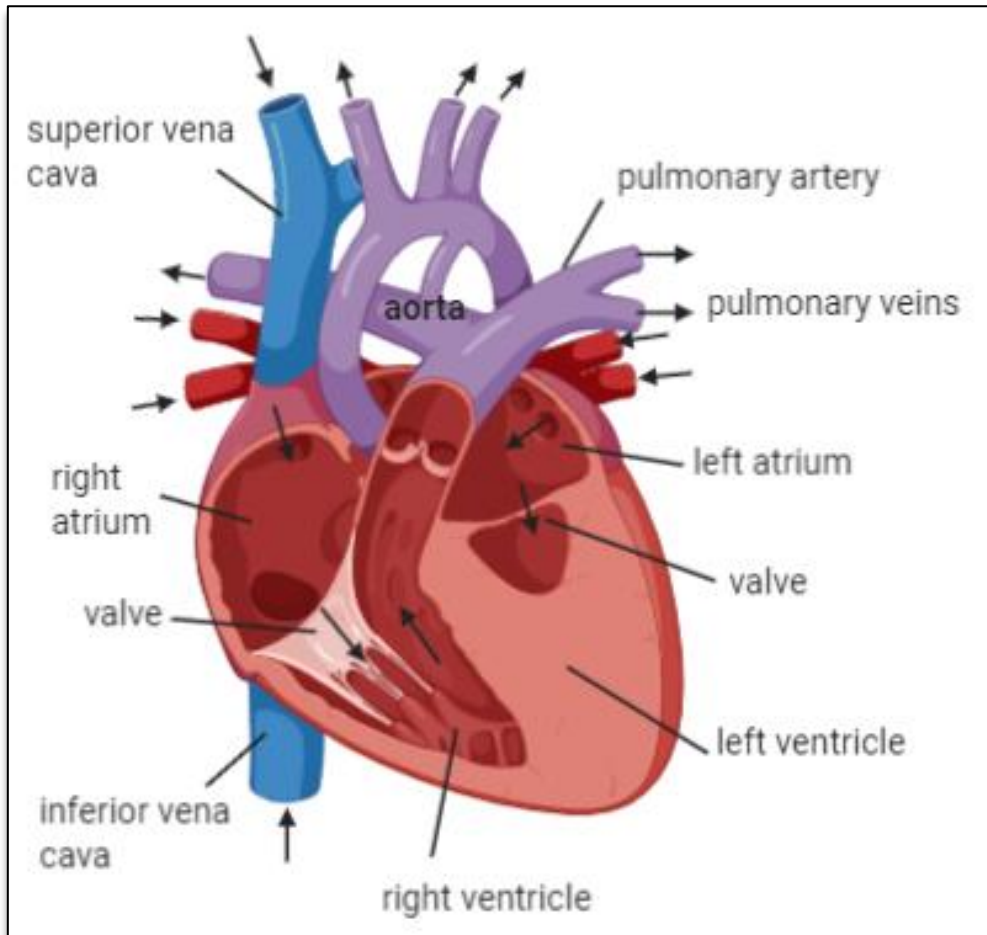
sophisticated network of thermoregulatory pathways that include the nervous, endocrine, metabolic, and cardiovascular systems to balance the internal temperatures when exposed to cold temperatures (2). Cardiovascular system is central and immediate in bringing about adaptive responses that include increased sympathetic activity, metabolic heat generation, and constriction of peripheral blood vessels in an effort to minimize heat loss. Sympathetic stimulation leads to increases in the levels of catecholamines that can greatly alter the heart rate, myocardial contractility, vascular resistance, and the total cardiac workload (3). It is also known that cold stress can affect electrophysiological conduction of the heart, which may endanger arrhythmias and make cardiac rhythm less steady. Recent literature has highlighted that long term or repeated exposure to low temperatures may result in oxidative stress, mitochondrial dysfunction, and inflammatory activation in myocardial tissue, which can lead to structural remodelling or functional impairment of the heart (4,5). New evidence also indicates that cold stress can cause myocardial oxygen demand to increase and coronary blood flow to reduce because of peripheral vasoconstriction. Such a difference between the oxygen supply and demand can precondition the heart to ischemic-like alterations, reduced contractility, and higher vulnerability to arrhythmias (6). In addition, physiological stress related to temperature has been demonstrated to effect on autonomic balance, by altering it towards an increase of sympathetic dominance which in turn impacts cardiac electrophysiology and mechanical performance (7). The rabbits are a good model of study widely used as an experimental model to study the cardiovascular responses to stress factors in the environment. The cardiac structure, myocardial structure and the autonomic control mechanisms of their bodies are similar to those of the human body to a great extent and therefore are applicable in the study of cold-induced cardiac changes (8).

The purpose of this review is therefore to give a general account of the physiological implications of cold stress on the cardiac workings on rabbit models. It emphasizes the effect of cold exposure on the heart rate, the regulation of blood pressure, myocardial oxygen consumption and electrical activity as well as the oxidative, inflammatory, and metabolic processes that play a role in this effect. It also explains the applicability of the rabbit models in experimental cardiology and gives research gaps to be filled in future research.

## Literature Review

### 1. Overview A Cardiac Physiology in Rabbits:

Among the various animal models used in cardiovascular research, rabbit is the most frequently selected one due to the fact that its cardiac anatomy and the corresponding physiological responses share a lot of similarities with those of the human heart (9). Just like the human heart, the rabbit heart contains four chambers, and the presence of mitochondria in large numbers in the myocardium allows for effective aerobic metabolism and thus the rabbit heart's performance can be sustained for long periods. Besides, the Purkinje fiber network is so evolutionary that the rapid electrical conduction facilitated by it renders rabbit ECG patterns to be very much like the human ones (10). Rabbits have high heart rate of 150-300 beats per minute while at rest, which makes them a good model for studying autonomic regulation and cardiac excitability (11). Their reaction to sympathetic and parasympathetic signals is just as similar to that of human vessels as much as autonomic regulation is concerned thus providing the researchers with a chance to investigate the development of arrhythmias and heart modifications to stress under environmental conditions like cold exposure using this model (12). Besides this the rabbit coronary circulation to one vessel is similar to that of human vessels as far as autonomic regulation is concerned which gives the researchers an opportunity to study the development of arrhythmias and heart alterations to stress under environmental pressures such as cold exposure using this model (13).



**Figure 1.** Anatomical Structure of the Rabbit Heart Showing Major Chambers and Blood Vessels.

## 2. Thermoregulation in Rabbits

The thermoregulatory system is highly effective in providing rabbits with the ability to maintain a stable temperature of the core body even when the environment changes. Since they are small mammals and have a high surface-area-volume ratio, they lose heat faster than larger mammals, so they must regulate themselves thermoregulatively very carefully to survive (14). Normal body temperature of rabbit is 38.5 -40 o C and even slight changes in ambient temperature may cause instant physiological reactions (15). The hypothalamus plays the role of a central controller of thermal balance. Upon detection of cold by the peripheral thermoreceptors in the skin, the hypothalamus triggers the sympathetic functions to trigger the heat conservation and heat production processes (16). Heat conservation is achieved primarily through peripheral vasoconstriction, reducing blood flow to the skin and extremities to minimize heat loss. At the same time metabolic heat production increases via non-shivering thermogenesis and enhanced cardiovascular activity, which raises oxygen demand and cardiac output (17). Rabbits also rely on behavioral adaptations to regulate temperature, such as curling the body, reducing movement, or seeking shelter. Since they possess limited sweat glands, evaporative heat loss is minimal; thus, their thermoregulation depends mainly on vascular and metabolic adjustments rather than sweating (18).

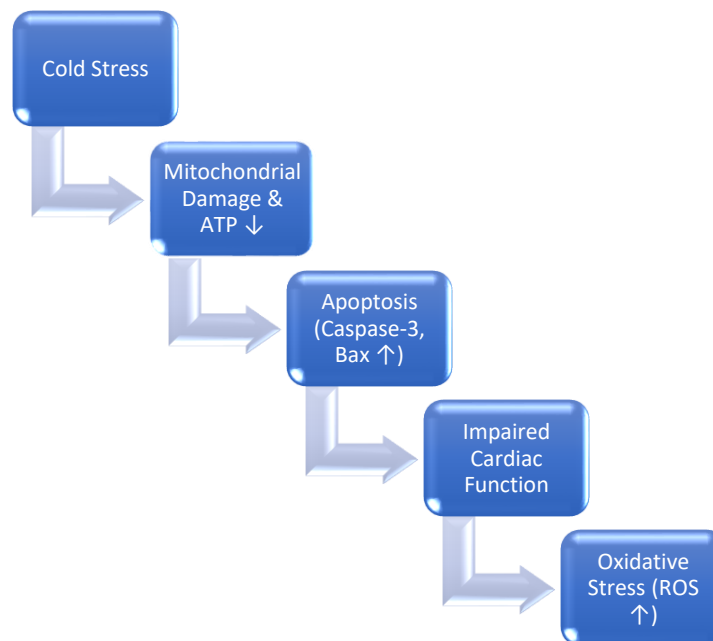
## 3. Effects of Cold Stress on Cardiac Function in Rabbits

Cold stress exposure leads rabbits to undergo several physiological adaptations that notably impact both the cardiac structure and function. The environments characterized by cold temperatures cause the very strong sympathetic system to be activated, which results in the secretion of catecholamines, one being norepinephrine and the other being epinephrine, which, among other things, directly affect the heart rate, the force of contraction, and the demand for oxygen (19). These rapid

changes in the autonomic nervous system put a huge burden on the heart, particularly so in small mammals like rabbits that mainly rely on the heart for their thermogenesis. One of the most profound cardiovascular reactions to cold is the rise in the heart rate (a condition called tachycardia) which is the result of the increased sympathetic activity. This speeding up is to keep the metabolic heat production going but it may also lead to a higher risk of arrhythmias through the modification of the electrical conduction pathways of the heart muscle (20). Besides, blood vessels' contraction due to cold leads to increased resistance against the flow of the blood in the system, thus increasing afterload and requiring the left ventricle to pump with more force. This may over time cause strain on the heart muscle and reduced cardiac output (21). Cold stress causes a change in the balance of oxygen supply and demand in the heart. With the increase in the production of heat, the heart's consumption of oxygen goes up while the blood flow through the coronary arteries may be reduced due to vasoconstriction in the periphery. The very situation of the lack of supply against the high demand can put the heart tissues in the state of ischemic changes, impaired contractility, and lower stroke volume (22). Carried out repetitive exposure to cold also has been recognized as a factor that brings about the oxidative stress and inflammatory signaling within the cardiovascular tissue, hence, contributing to the mitochondrial dysfunction, the altered calcium handling, and the early remodeling of the myocardial fibers (23).

#### 4. Molecular Mechanisms of Cold Stress Affecting Cardiac Function

Cold stress triggers several molecular pathways that directly influence cardiac function in rabbits. One of the primary mechanisms is oxidative stress. Exposure to low temperatures increases the production of reactive oxygen species (ROS) in myocardial cells, leading to mitochondrial dysfunction, lipid peroxidation, and impaired ATP generation (26). This inflammation belongs to the cell stress, abnormal calcium signaling, and the early remodelling of cardiac fibers (27). Cold-induced changes in the heart are also caused by apoptosis. It has been found that there is a caspase-3, Bax sequence that is an apoptotic marker, which is enhanced by long exposure to cold to promote the programmed cell death and reduction of functional cardiomyocytes. That may harm the myocardial structure and decrease the pumping efficiency in the long run (28). The activation of  $\beta$ -adrenergic receptors by an augmented secretion of catecholamine increases the cAMP and influences intracellular calcium current and can predispose the heart to arrhythmias (29).



**Figure 2.** Molecular Mechanisms of Cold Stress Affecting Cardiac Function.

#### 5. Hemodynamic Responses to Cold Stress

Peripheral vasoconstriction is among the initial responses and it reduces blood supply to the extremities and increases the vascular resistance in the blood system (30). Further, cold stress has the typical effect of moderate increases in the blood pressure of the arteries and compensatory tachycardia to maintain adequate cardiac output (31). Such alterations of hemodynamics might be causal in the long term, which includes contributory strain of the ventricles and diminished effectiveness, along with alterations in the perfusion patterns altering myocardial oxygen balance.

### 6. Electrophysiological Alterations Under Cold Exposure

It is experimentally established that low temperature can elevate QT and QRS, slow conduction velocity and disrupt the repolarization pathways in rabbits (32). The alterations predispose an individual to arrhythmias, especially ventricular fibrillation and ectopy. Sympathetic hyperstimulation is also known to interfere with electrical activities which deal with the treatment of calcium and 8-adenergetic transmission. All these electrophysiological alterations lead to the heightened arrhythmic danger of cold environments (33).

### 7. Acute vs. Chronic Cold Exposure: Comparative Effects

The acute exposure to cold is traditionally linked with the instant sympathetic reaction, tachycardia, raising of the vascular resistance, and raising of the heat production of the metabolism (34). These changes can be reversed after the animal has been returned to a neutral environment. On the contrary, chronic cold exposure results in more sustained adaptations such as cardiac remodelling, increase of oxidative stress burden, alteration of mitochondrial functional state and possible ventricular thickening of the wall (35).

**Table 1.** Comparison Between Acute and Chronic Cold Exposure Effects on Cardiac Function in Rabbits.

Parameter	Acute Cold Exposure	Chronic Cold Exposure
<b>Duration</b>	Minutes to hours	Days to weeks
<b>Sympathetic Activation</b>	Sharp, immediate ↑	Sustained but may partially adapt
<b>Heart Rate (HR)</b>	Rapid ↑ (tachycardia)	May normalize or ↓ due to autonomic adaptation
<b>Blood Pressure (BP)</b>	Quick ↑ via vasoconstriction	Persistent ↑ or vascular remodeling
<b>Cardiac Output (CO)</b>	Initially ↑ to generate heat	May ↓ with prolonged strain
<b>Metabolic Demand</b>	Sharp ↑	Continually ↑ but with energy conservation mechanisms
<b>Electrophysiology (ECG)</b>	QT prolongation, conduction slowing	Higher risk of arrhythmias and electrical instability
<b>Oxidative Stress</b>	Moderate ↑ ROS	High chronic ↑ ROS → mitochondrial damage
<b>Inflammation</b>	Mild temporary cytokine increase	Chronic inflammatory activation (NF-κB)
<b>Apoptosis</b>	Minimal	Significant ↑ (caspase-3, Bax)
<b>Histological Changes</b>	Reversible mild changes (edema)	Structural remodeling, fibrosis, vessel congestion
<b>Overall Cardiac Stress</b>	Functional, short-lived	Structural + functional, long-term

### 8. Structural and Histological Changes in the Rabbit Heart During Cold Stress

Histological evaluation reveals that the heart under cold stress can exhibit a variety of changes in its structure, such as edema in the interstitial areas, infiltration of inflammatory cells, coronary vessel congestion, and even myocyte hypertrophy or degeneration in the very early stage (36). Oxidative stress and cell death through apoptosis are considered major factors in these events, as they have their ways to harm the cellular structures like membranes and mitochondria. In the case of chronic cold

exposure, the damage becomes more severe and the organization of cardiac fiber is disturbed along with the possibility of fibrous tissue formation (37).

## Conclusion

The heart of rabbits is clearly affected by cold stress according to this review. The exposure of the rabbits to coldness causes their body to react as quickly as possible to protect the core temperature which, however, makes the heart work even harder. Changes in heart rate, blood pressure, and electrical activity can occur as a result of prolonged cold exposure. Cold stress at the cellular level means more oxidative and inflammatory signals and possibly earlier signs of tissue damage or remodeling. These effects are part of the reason why the heart becomes less efficient when exposed to cold for a long time. Rabbits are considered a good model for the study of cold's impact on human cardiovascular health since there are notable physiological similarities between the two species. There is still a need for more research to come up with ways to protect the heart from the negative impacts of cold stress.

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