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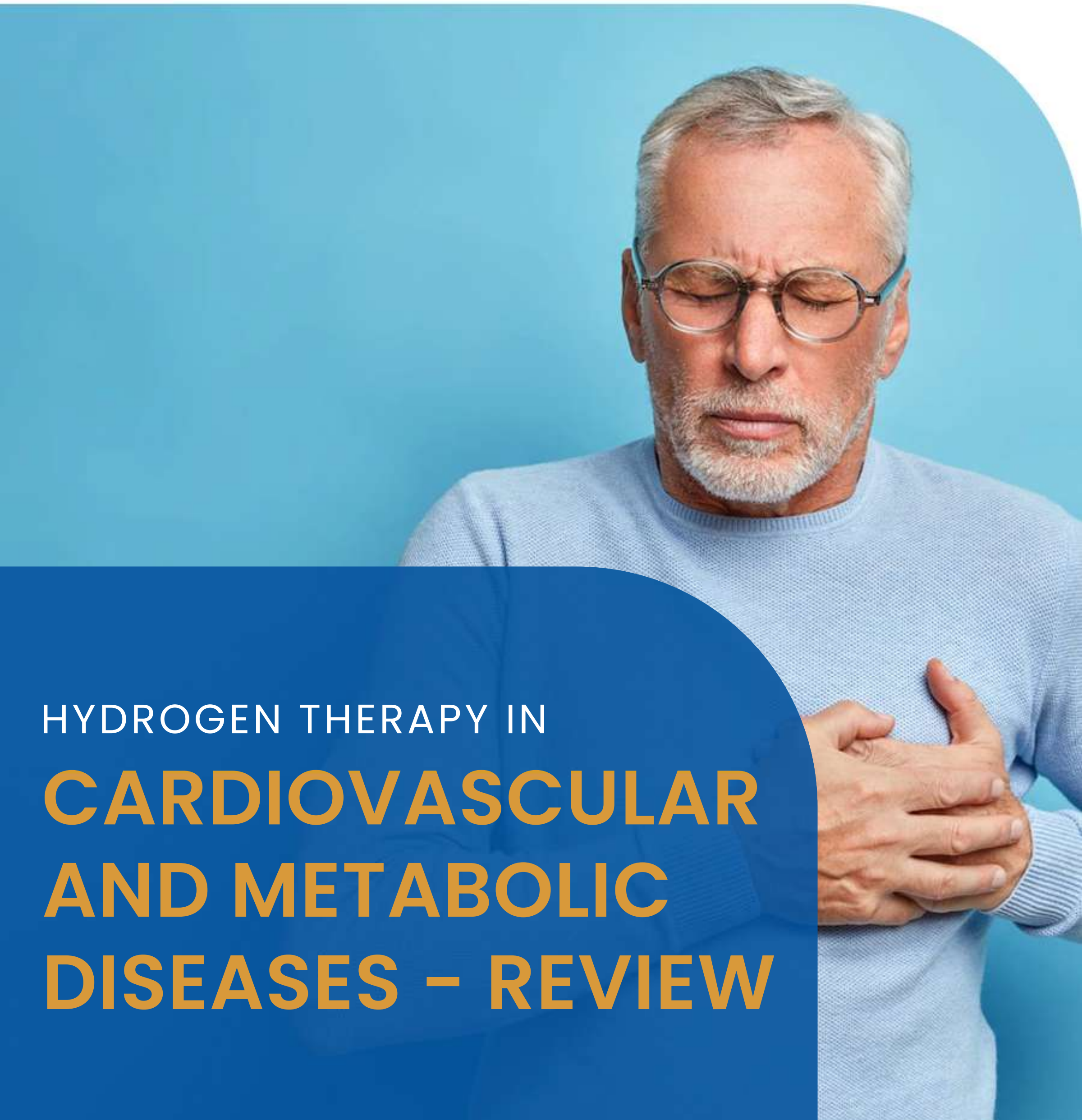

HYDROGEN THERAPY IN CARDIOVASCULAR AND METABOLIC DISEASES – REVIEW

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INTRODUCTION

H2 is produced by mammals by the intestinal bacteria hydrogen, and the earth's atmosphere comprises less than 1 part per million (ppm) of H2. H2 is a highly combustible diatomic gas when activated by a catalyst or heat. It takes 527 °C of temperature for H2 to be flammable, and it can explode with a chain reaction with O2 when the H2 concentration ranges from 4% to 75% vol/vol. Moreover, at approximately .8mM (1.6 ppm, wt./vol) and 1 atmospheric pressure H2 is soluble in water.

Hydrogen (H2), a colorless, odorless, and lightest gas molecule, has been found to be impactful in regulating the homeostasis of the cardiovascular system and metabolic activity. H2, when introduced into a human body through different methods, helps treat cardiometabolic diseases like vascular injury, ischemic or hypertrophic ventricular remodeling, atherosclerosis, intermittent hypoxia, heart transplantation-induced heart injury, obesity, and diabetes in animal models or in clinical trials. The H2 review was conducted by Zhang Y., Tan S., Xu J., and Wang T., to explain the chemical and physical properties of hydrogen, its therapeutic potential, and the molecular mechanisms involved in the diseases mentioned above.

Several clinical and basic studies in the last year have revealed that H2 is a critical pathophysiological regulatory factor with anti-oxidative, anti-inflammatory, and anti-apoptotic effects on cells and organs.

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The Impact of H2 on Vascular Diseases

The vessel walls made of vascular smooth muscle cells (VSMCs) in the tunica media, the middle portion of the vessel wall that contains smooth muscle cells and connective tissues, and endothelial cells (ECs) in the tunica intima, the innermost tunica (layer) of an artery or vein, can sometimes suffer harmful effects due to sedentary lifestyle.

Moreover, adventitia, the outermost layer of the wall of a blood vessel, is essential for maintaining vessel wall homeostasis via regulating immune and inflammatory responses.

Due to various vascular stresses like disrupted flow with oscillatory and reduced shear stress, hypertension, high fat diet (HFD), and mechanical injury, the blood vessels undergo several structural changes by responding through inflammation and endothelial nitric oxide synthase (eNOS) uncoupling, leading to endothelial cell dysfunction, multiplication, and migration of vascular smooth muscle cells (VSMCs) and fibroblast activation. H2 has been reported to regulate these cellular events in vessel walls through their native antioxidant functions directly, or via lipid regulation, cell death, and growth.

The Effects of H2 in Vascular Disease Models

In their research, Ikuroh Ohsawa revealed that "drinking H2-rich water for 4 months reduced atherosclerotic lesion in apolipoprotein E knockout mice (ApoE-/- mice). H2-rich water intake also prevents lipid deposition in the rat aorta induced by periodontitis by decreasing serum ox-LDL levels and aortic oxidative stress. A series of studies from the Qin Shucun group indicated that the anti-atherosclerotic effect of H2 is achieved by suppressing NF-κB activation and subsequently blocking cytokine-induced lectin-like oxidized LDL receptor-1 (LOX-1) gene expression in ECs; decreasing plasma LDL cholesterol and apolipoprotein B100 and apo B48 levels in LDL, and

improving HDL functions, including the capacity to enhance cellular cholesterol efflux and anti-oxidative properties.

More importantly H2 can enhance plaque stability in low-density lipoprotein receptor-knockout (LDLR-/-) mice by increasing levels of collagen and numbers of regulatory T cells, reducing macrophages, dendritic cells numbers and lipid levels in plaques, as well as inhibiting endoplasmic reticulum stress and activating the NF-E2-related factor-2 (Nrf2) antioxidant pathway. In vitro studies also support the antioxidant functions of H2. H2-rich medium has long-lasting antioxidant and anti-aging effects on ECs through the Nrf2 pathway, even after transient exposure to H2.

Recent study indicates that intraperitoneal injection of H2 (99.999%, 1 ml/100 g/ day) prevents abdominal aortic coarctation (AAC)-induced vascular hypertrophy in vivo. However, H2 had no effect on circulating angiotensin II (Ang II) levels, thereby the protective effect of H2 on vascular hypertrophy is possibly by blocking circulating Ang II actions on vessels (especially targeting in VSMCs) rather than inhibiting its synthesis and secretion. Similarly, intraperitoneal (the area that contains the abdominal organs) injection of H2-rich saline has been reported to ameliorate aortic hypertrophy and improve endothelium-dependent vascular relaxation and baroreflex function in spontaneously hypertensive rats (SHR).

Drinking H2-rich water reduced endothelial denudation, macrophage infiltration, and neointimal formation in vein grafts by reducing the activation of p38 MAPK inflammatory cascades, and decreasing the expression and activity of MMP-2 and MMP-9. H2-rich saline also prevents neointimal hyperplasia induced by carotid balloon injury in rat by suppressing ROS and the TNF-α/NF-κB signaling pathway, and inactivating the Ras-MEK1/2 - extracellular signal-regulated kinase1/2 (ERK1/2) and Akt signaling pathways. In addition, H2-rich saline protects cerebral microvascular endothelial cells from apoptosis after hypoxia/reoxygenation via inhibiting PI3K/Akt/GSK3

Moreover, H2 can also influence VSMCs proliferation and migration in vitro. H2-rich medium inhibits PDGF-BB-induced VSMCs proliferation and 10% FBS-induced VSMCs proliferation and migration, and blocks FBS-induced progression from the G0/G1 to the S-phase and increases the apoptosis of VSMCs. H2-rich medium inhibits Ang II-induced proliferation and migration of VSMCs in vitro by blocking ROS-dependent ERK1/2, p38 MAPK, c-Jun NH2-terminal kinase (JNK) and ezrin/radixin/moesin signaling. However, the Atsunori Nakao group indicated that H2-rich medium inhibits VSMCs migration with or without FBS, but has no effects on proliferation.

H2 inhibits vascular remodeling by improving ECs and lipid function, suppressing VSMCs proliferation and migration, and attenuating inflammatory cell accumulation. Therefore, to design a kind of intravascular stent which can release H2 might be a good strategy for suppressing restenosis.

The Effects of H2 in Heart Diseases

In response to pathophysiological stimuli, such as myocardial I/R, hypertension, or neurohumoral triggers, multiple molecular and cellular processes contribute to changes in the size, shape, structure, and function of the heart (ventricular remodeling). The increased production of endothelin-1 (ET-1), Ang II, catecholamines, and pro-inflammatory cytokines activates their cognate receptors and downstream signaling events, which leads to cardiomyocyte necrosis, apoptosis, autophagy, or hypertrophy; and promotes fibroblast activation to produce collagen and other proteins that cause fibrosis (the thickening and scarring of connective tissues). Recently, it was shown that H2 can prevent various heart diseases through blocking parts of the molecular and cellular signaling events described above.

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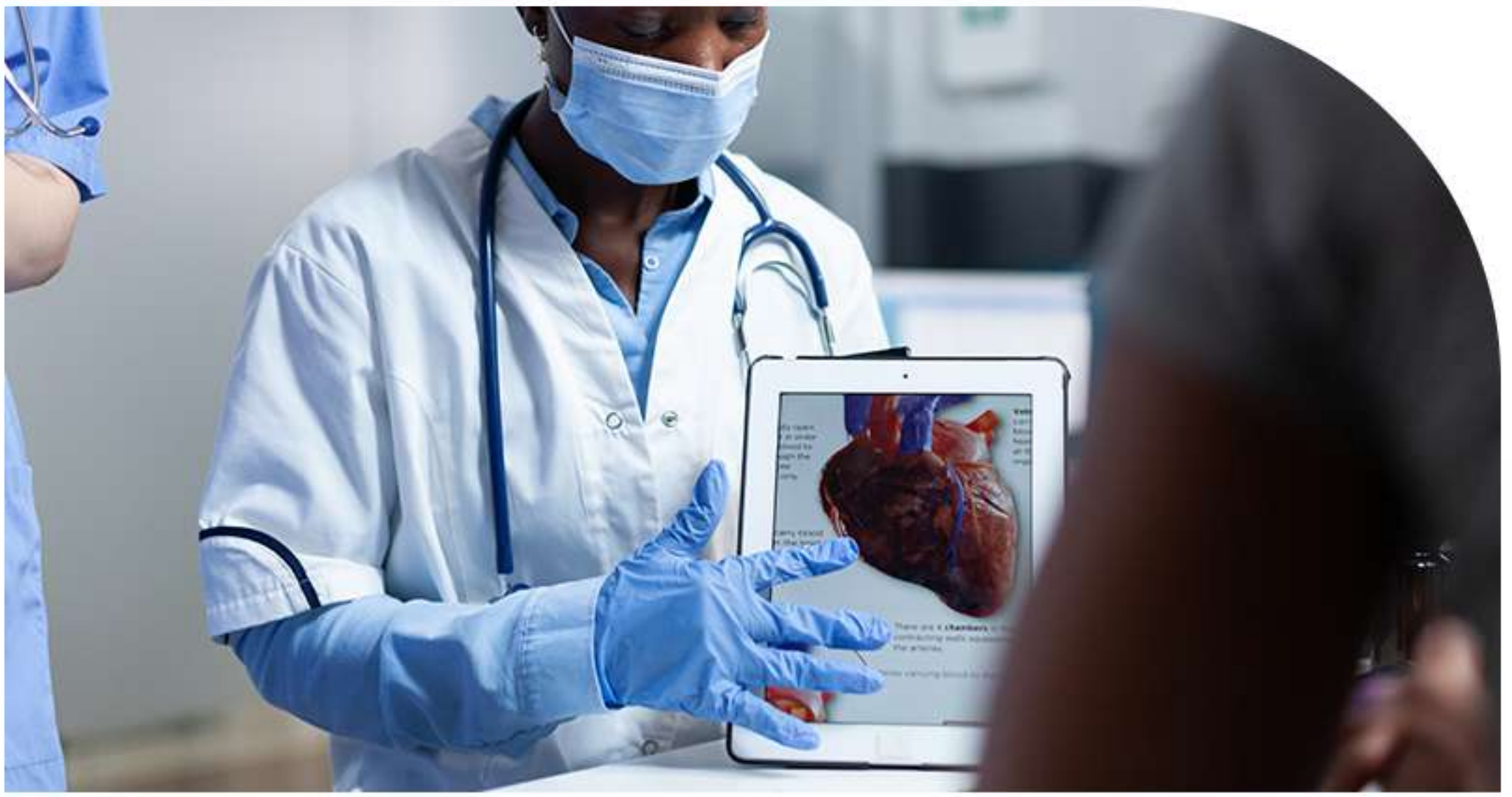
Understanding the Impact of H2 in Heart Disease Models



Similar to H2, nitric oxide (NO) also has the ability to decrease the infarct size in myocardial I/R injury. However, NO has cytotoxicity by producing reactive nitrogen species (RNS), such as peroxynitrite, which can react with the tyrosine at the active site of vital enzymes (such as Tyr6, Tyr32, and Tyr78 in mouse GST-μ) and cellular components. These adverse effects can be reversed by H2 inhalation. Breathing NO plus H2 can reduce cardiac injury and augment recovery of the left ventricular function, by eliminating the adverse by-products of NO inhalation alone, nitrotyrosine. Besides H2 inhalation, Sun Xuejun Group indicated that intraperitoneal injection of H2-rich saline attenuates myocardial I/R injury and improves cardiac function through anti-oxidative, anti-apoptotic, and anti-inflammatory effects. Recently, Yan Fei Group developed an ultrasound-visible H2 delivery system by loading H2 inside microbubbles (H2-MBs) to prevent

myocardial I/R injury. Moreover, an in vitro study revealed that the cardioprotection induced by hypoxic postconditioning can be augmented by molecular H2 infusion. A clinical study has shown that H2 inhalation (1.3% H2) during primary percutaneous coronary intervention (PCI) is a feasible and safe treatment option for patients with ST-elevated myocardial infarction and may prevent adverse left ventricular remodeling after primary PCI.

Intermittent hypoxia, which is the major feature of sleep apnea syndrome, increases superoxide production and accelerates adverse left ventricular remodeling. Inhalation of H2 at low concentrations (1.3 vol/100 vol) reduces intermittent hypoxia-induced dyslipidemia and oxidative stress, and also prevents cardiomyocyte hypertrophy and perivascular fibrosis in the left ventricular myocardium of C57BL/6J mice. Inhalation of H2 (3.05 vol/100 vol) by cardiomyopathic (CM) hamsters inhibits oxidative stress and decreases embryonic gene BNP, β-MHC, c-Fos and c-Jun expression, thus preserving cardiac function in CM hamsters.

H2 has comprehensive cardiac activities. H2 administration protects against cardiac remodeling and improves cardiac function induced by I/R, intermittent hypoxia, neurohumoral activation, hypertension, and transplantation injury. However, there is still a long way to go to develop H2 into a clinical drug to treat heart failure.

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The Effects of H2 on Metabolic Diseases

Metabolic syndrome (MS), which includes obesity, insulin resistance, hyperglycemia, hypertension, elevated VLDL triglycerides, and low HDL cholesterol, is a primary risk factor for type 2 diabetes and cardiovascular diseases. The pathophysiology of MS appears to be largely due to insulin resistance, with excessive flux of fatty acids being implicated, and a pro-inflammatory state probably also contributes to the syndrome. Moreover, inflammation, insulin resistance, and hepatic steatosis influence one another to form a vicious circle. Therefore, targeting inflammatory responses and lipid metabolism are important strategies to treat metabolic diseases. Interestingly, H2 has the ability to regulate inflammation and lipid metabolism efficiently.

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CONCLUSION

Current studies of H2 focus on anti-oxidation, anti-inflammation, and anti-apoptosis. However, the effective target and the precise molecular mechanisms of H2 are not clear. Recent studies have indicated that H2 can regulate both innate and adaptive immune responses, such as inhibiting lipopolysaccharide/interferon γ-induced NO via blocking Apoptosis signal-regulating kinase (ASK1) and its downstream signaling molecules, p38 and Jun N-terminal kinase (JNK) also known as stress-activated protein kinase, as well as IκBα in macrophages, restoring the L-arginine-induced CD25+Foxp3+ regulatory T cell loss in mice. However, the functions of H2 in regulating cardiovascular immune responses still need further investigation. Moreover, NO, CO, and H2 are important signaling molecules in the cardiovascular system. Breathing NO plus H2 during I/R can reduce the generation of myocardial nitro tyrosine associated with NO inhalation. The combination of H2 and CO can elicit better results than either one alone for inhibiting inflammation and enhancing graft survival. These indicate that H2 can regulate the function of NO and CO. To date, there have been no reported side effects of H2 therapy.

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