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Subchronic Cigarette Smoke Exposure Effects on Cardiomyocytes: A Literature Review

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Abstract

Subchronic exposure to cigarette smoke has been shown to induce pathological changes in various organ systems, including the cardiovascular system. This literature review synthesizes current evidence on the effects of subchronic cigarette smoke exposure on mouse cardiomyocytes, with a focus on oxidative stress, mitochondrial dysfunction, genetic regulation, contractile function, and inflammation. Experimental models typically involve whole-body or nose-only exposure for several weeks, simulating human subchronic exposure patterns. Mechanistic findings reveal increased reactive oxygen species (ROS) production, impaired mitochondrial respiration, and disruption of antioxidant defense systems, particularly involving superoxide dismutase (SOD) and adenine nucleotide translocator (ANT). Gene expression studies demonstrate altered regulation of apoptotic, inflammatory, and metabolic pathways, accompanied by epigenetic modifications such as DNA methylation and microRNA dysregulation. Functional assessments indicate decreased cardiomyocyte viability, reduced contractile activity, and increased cellular senescence. Inflammatory responses are characterized by elevated cytokine production, including TNF-α and IL-6, which may contribute to myocardial remodeling. While evidence strongly suggests a detrimental effect of subchronic cigarette smoke on mouse cardiomyocytes, limitations remain due to the scarcity of long-term follow-up studies and direct translational models in humans. Future research should focus on targeted interventions to mitigate oxidative and inflammatory damage in cardiomyocytes exposed to tobacco smoke.

Keywords: Cigarette Smoke Exposure; Subchronic; Cardiomyocytes; Oxidative Stress; Mitochondrial Dysfunction

1. Introduction

Cigarette smoking remains one of the leading preventable causes of morbidity and mortality worldwide, contributing significantly to cardiovascular diseases, chronic obstructive pulmonary disease, and various cancers (Messner et al., 2014). While the deleterious effects of long-term smoking have been extensively documented, subchronic exposure, typically defined as continuous or repeated exposure over a period ranging from several weeks to a few months has garnered increasing attention for its role in initiating early pathophysiological changes, particularly in cardiac tissue (Parmar et al., 2023). Experimental models using mice have proven valuable for understanding the mechanistic pathways through which cigarette smoke induces cardiac injury, as their cardiovascular physiology and cellular responses share key similarities with humans (Ardiana et al., 2021).

Cardiomyocytes, the contractile cells of the myocardium, are critical for maintaining cardiac output and overall cardiovascular function. These cells are highly metabolically active, relying on robust mitochondrial function to sustain continuous contraction. Subchronic cigarette smoke exposure has been shown to impair cardiomyocyte structure and

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function through multiple mechanisms, including oxidative stress, mitochondrial dysfunction, inflammatory activation, and apoptotic signaling. Reactive oxygen species (ROS) generated from cigarette smoke constituents such as nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons can damage lipids, proteins, and nucleic acids, disrupting cellular homeostasis (Burton et al., 2011).

In addition to oxidative stress, mitochondrial injury plays a pivotal role in the pathogenesis of smoke-induced cardiotoxicity. Studies have reported decreased mitochondrial membrane potential, impaired respiratory chain activity, and altered ATP production in cardiomyocytes exposed to cigarette smoke extract (CSE) (Burton et al., 2011). These mitochondrial alterations often coincide with the activation of apoptotic pathways, including upregulation of pro-apoptotic proteins such as Bax and downregulation of anti-apoptotic proteins like Bcl-2 (He et al., 2017). Moreover, systemic inflammation triggered by smoke exposure can exacerbate myocardial injury through elevated circulating cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contributing to myocardial remodeling and eventual contractile dysfunction (Higashi et al., 2014).

Animal studies using subchronic exposure protocols, such as whole-body inhalation or nose-only exposure chambers, have shown early histopathological changes in the myocardium, including interstitial fibrosis, myofibrillar disarray, and increased collagen deposition (Husna et al., 2019). While these alterations are less severe than those seen in chronic exposure models, they represent early indicators of potential progression toward heart failure if exposure persists. The translational relevance of these findings lies in the fact that even moderate-duration smoking or secondhand smoke exposure may initiate pathological processes in the heart well before clinical symptoms appear (Husna et al., 2019).

This literature review aims to provide a comprehensive synthesis of current research on the effects of subchronic cigarette smoke exposure on mouse cardiomyocytes. Specifically, it will address the experimental models used to simulate subchronic exposure, the molecular and cellular mechanisms involved, functional consequences on cardiomyocyte performance, and the broader implications for cardiovascular health. By elucidating these pathways, this review seeks to bridge the gap between basic science findings in animal models and potential preventive or therapeutic strategies for smoke-induced cardiac injury in humans.

2. Review Content

2.1. Cardiovascular Disease

Cardiovascular disease (CVD) is the leading cause of death worldwide. CVD encompasses a wide range of disorders, including diseases of the heart muscle and the vascular system that supplies the heart, brain, and other vital organs (Gaziano et al., 2006). Cardiovascular diseases are a group of disorders affecting the heart and blood vessels. They are a heterogeneous series of conditions, with atherosclerosis being the most frequent primary cause of their development. CVDs are chronic diseases that develop gradually over a lifetime and often remain asymptomatic for a long period. Furthermore, CVD is a major cause of morbidity and mortality among patients worldwide (Frąk et al., 2022). Atherosclerosis is the leading cause of cardiovascular-related death globally. It is characterized by the thickening and hardening of arterial walls, which accompanies aging and has a significant negative impact on the cardiovascular system and various other diseases. Increased plasma cholesterol levels (>150 mg/dL) are a major cause of atherosclerosis progression (Frąk et al., 2022).

Coronary artery disease (CAD) is a common heart condition characterized by narrowing or blockage of the main blood vessels, namely the coronary arteries. CAD is most often caused by the formation of plaques within the intimal layer of the vessel wall. These plaques, composed of fatty materials, develop within the intima along with severe inflammation, particularly when the inflammation is chronic. This process impairs the supply of sufficient blood, nutrients, and oxygen to the cardiomyocytes. Consequently, atherosclerotic plaques may erode or rupture, initially leading to thrombosis and subsequently vessel occlusion, resulting in myocardial infarction, stroke, limb ischemia, and death. Other contributing factors include endothelial dysfunction, low-grade inflammation, and lipid accumulation (Frąk et al., 2022).

Arterial hypertension (AH) is one of the most common types of CVD. Arterial hypertension often causes few or no symptoms but is a major risk factor for myocardial infarction, stroke, kidney failure, and peripheral vascular disease. According to the most significant guidelines, AH is diagnosed when a person's office or clinic systolic blood pressure is ≥140 mm Hg and/or diastolic blood pressure is ≥90 mm Hg after repeated measurements. CVDs are caused by multiple factors. Some are non-modifiable, such as age, sex, and genetic background, while others are modifiable and therefore can be reduced (e.g., smoking, lack of physical activity, poor eating habits, increased blood pressure, type 2 diabetes, dyslipidemia, and obesity) (Frąk et al., 2022).

2.2. Cardiac Hypertrophy

Cardiac hypertrophy is the heart's response to various extrinsic factors and intrinsic stimuli that increase biomechanical stress. While hypertrophy can ultimately normalize wall tension, it is associated with unfavorable outcomes, placing affected patients at risk of sudden death or progression to overt heart failure (Frey and Olson, 2003). Pathological hypertrophy is associated with increased cardiomyocyte death and fibrotic remodeling and is characterized by reduced systolic and diastolic function, which often progresses to heart failure. The main triggering events for hypertrophic heart disease are mechanical stress and neurohumoral stimulation, both of which contribute to the modulation of various cellular responses, including gene expression, sarcomere protein synthesis, and cellular metabolism, leading to the development and progression of cardiac hypertrophy (Shimizu and Minamino, 2016). Neurohumoral factors, such as catecholamines or angiotensin II, upregulate calcineurin/NFAT and CaMKII/MEF-2 signaling to induce pathological cardiac hypertrophy. IL-6/gp130/JAK/STAT signaling also promotes pathological hypertrophy. Nitric oxide signaling and natriuretic peptide/cGMP/PKG pathways are anti-hypertrophic, whereas PDE5 and PDE9A promote pathological hypertrophy by suppressing these signaling pathways (Shimizu and Minamino, 2016).

2.3. ROS and Cardiovascular Diseases

Reactive oxygen species (ROS) are highly reactive molecules produced primarily by oxidase systems, and they play a pivotal role in the initiation and progression of cardiovascular diseases (CVD). These molecules can cause profound biological effects because of their ability to oxidize lipids, proteins, and nucleic acids, thereby impairing normal cell function. One of the key mechanisms through which ROS exert their deleterious effects is by disrupting mitochondrial function and altering intracellular calcium (Ca^{2+}) homeostasis. This imbalance in mitochondrial dynamics and Ca^{2+} regulation leads to cellular injury, apoptosis, and functional deterioration within the cardiovascular system (Fei et al., 2022). Among the diverse types of ROS involved in the induction or progression of CVD, the most notable are superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), and hydroxyl radical (HO•). O_2^- and H_2O_2 are considered enzymatically produced ROS, and they participate in both physiological signaling pathways such as vascular tone regulation and pathological processes, including vascular inflammation and fibrosis. O_2^- can be spontaneously dismutated into H_2O_2 by the enzymatic action of superoxide dismutase (SOD), a critical antioxidant defense mechanism in the body. In contrast, $ONOO^-$ and HO• are generally not regarded as ROS signaling molecules due to their extreme reactivity and short half-life. HO•, for instance, is formed via the catalytic conversion of H_2O_2 often through the Fenton reaction and is capable of initiating chain reactions that damage cellular membranes and DNA. Glutathione, a major intracellular antioxidant, serves as an important defense system by neutralizing HO• and preventing further oxidative injury. $ONOO^-$ is generated through the reaction between O_2^- and nitric oxide (NO), and it is particularly damaging because it not only depletes NO but also impairs endothelial nitric oxide synthase (eNOS) function. This leads to a self-perpetuating cycle of reduced NO bioavailability, increased vascular oxidative stress, and progressive endothelial dysfunction. The primary enzymatic and non-enzymatic sources of CVD-related ROS include mitochondrial electron transport chain components, NADPH oxidases (NOX), xanthine oxidase (XO), lipoxygenases (LO), and myeloperoxidases (MPO). Notably, there is a phenomenon known as **ROS source cross-talk**, in which different ROS sources can activate each other, amplifying oxidative stress. For example, H_2O_2 can stimulate NOX activity and promote the conversion of xanthine dehydrogenase into its ROS-producing form, XO. Similarly, $ONOO^-$ can enhance O_2^- generation, further intensifying oxidative damage. In addition, mitochondria and NOX systems engage in bidirectional interactions, creating a feed-forward **oxidative cycling** loop that exacerbates the overall redox imbalance in cardiovascular tissues (Gracia et al., 2017).

2.4. Cigarette Smoke

Cigarette smoke is divided into two phases: the tar phase and the gas phase. The tar or particulate phase is defined as the material trapped when the mainstream smoke is passed through a Cambridge glass fiber filter that retains 99.9% of all particulate matter with a size >0.1 μm. The gas phase consists of material that passes through the filter. The particulate (tar) phase contains 10^{17} free radicals per gram, while the gas phase contains 10^{15} free radicals per puff. Radicals associated with the tar phase are long-lived (hours to months), whereas radicals associated with the gas phase have a shorter lifespan (Ardiana et al., 2021). Cigarette smoke inhaled from tobacco into the smoker's mouth is called mainstream smoke. Sidestream smoke is the smoke emitted from the burning end of the cigarette. Mainstream smoke consists of 8% tar and 92% gas components. Environmental tobacco smoke is produced from a combination of sidestream smoke (85%) and a smaller portion of exhaled mainstream smoke (15%) from the smoker. Sidestream smoke contains relatively higher concentrations of toxic gaseous components compared to mainstream smoke. Among all the known elements, nicotine which found in the tar phase is the addictive substance in cigarette smoke (Ambrose and Barua, 2004). The number of active smokers in Indonesia continues to rise. According to the 2023 Indonesian Health Survey (SKI), conducted by the Ministry of Health (Kemenkes), there are around 70 million active smokers, with 7.4% of them aged between 10 and 18 years. The highest number of smokers is found among children and adolescents.

According to the Global Youth Tobacco Survey (GYTS) 2019, smoking prevalence among school-aged children (13–15 years old) increased from 18.3% (2016) to 19.2% (2019). Meanwhile, the 15–19 age group has the highest smoking rate (56.5%), followed by those aged 10–14 years (18.4%) (Kemenkes, 2024).

2.5. Smoking and Cardiovascular Diseases

An imbalance between the oxidative and antioxidant systems is one of the central mechanisms underlying many chronic diseases, particularly those related to the cardiovascular system. This imbalance is most often associated with the excessive production of reactive oxygen species (ROS), which leads to a state of oxidative stress. Oxidative stress occurs when ROS generation exceeds the body's intrinsic antioxidant defense capacity, resulting in damage to lipids, proteins, and DNA (Gracia et al., 2017). Over time, this damage can compromise cell viability, impair tissue repair mechanisms, and promote chronic inflammation, all of which are critical contributors to cardiovascular pathology. Cigarette smoke is widely recognized as both a direct source of ROS and an indirect trigger of oxidative stress within cells. The smoke contains thousands of chemicals, including free radicals, oxidants, and pro-oxidant compounds, which either directly generate ROS or stimulate endogenous ROS production. This persistent oxidative burden is a well-established causative factor for multiple smoking-related diseases. The oxidative stress induced by smoking initiates a cascade of pathological processes, such as lipid peroxidation, endothelial injury, mitochondrial dysfunction, and chronic inflammation, which collectively accelerate disease progression. The World Health Organization (WHO) reports that active smoking remains one of the leading preventable causes of death worldwide, largely due to the toxic effects of tobacco smoke components on various organ systems. Epidemiological data consistently identify smoking as a major risk factor for cardiovascular diseases (CVD), respiratory disorders, and several forms of cancer (Seo et al., 2023).

Specifically, within the cardiovascular domain, smoking significantly increases the risk of coronary heart disease (CHD) by destabilizing atherosclerotic plaques. This plaque destabilization heightens the likelihood of plaque rupture, which can rapidly lead to thrombus formation at the lesion site. Such thrombi are the primary cause of acute coronary syndrome (ACS), encompassing unstable angina, myocardial infarction, and sudden cardiac death. Beyond plaque-related mechanisms, cigarette smoking also promotes coronary artery spasms, which may occur with or without significant pre-existing narrowing of the coronary arteries. These spasms can acutely reduce blood flow to the myocardium, causing ischemia even in the absence of severe atherosclerosis. Nicotine, a primary psychoactive component of tobacco, exerts potent cardiovascular effects by stimulating sympathetic nerve activity, resulting in vasoconstriction, elevated blood pressure, and increased heart rate. Another critical factor is the elevated carbon monoxide (CO) levels observed in smokers. CO binds to hemoglobin with an affinity more than 200 times greater than oxygen, thereby reducing the oxygen-carrying capacity of blood. This leads to a state of chronic tissue hypoxia, particularly affecting high-demand organs like the heart. In the setting of pre-existing heart disease, this chronic ischemia can significantly worsen heart failure symptoms and prognosis. Furthermore, tobacco smoke exposure is associated with systemic inflammation, as evidenced by increased circulating inflammatory cytokines. It also causes endothelial dysfunction, impairing the ability of blood vessels to dilate appropriately, and contributes to renal impairment, which indirectly increases cardiovascular risk. Together, these factors oxidative stress, inflammation, vascular dysfunction, and end-organ hypoxia explain the disproportionately high prevalence of heart failure among active smokers (Kondo et al., 2019).

3. Conclusion

In conclusion, subchronic exposure to cigarette smoke exerts profound detrimental effects on mouse cardiomyocytes through a complex interplay of oxidative stress, inflammation, endothelial dysfunction, and mitochondrial impairment. The high levels of reactive oxygen species (ROS) generated both directly from cigarette smoke and indirectly via endogenous enzymatic systems disrupt calcium homeostasis, impair mitochondrial bioenergetics, and trigger cell death pathways. These processes collectively compromise cardiac contractility, promote myocardial remodeling, and predispose to the development and progression of cardiovascular diseases. Experimental evidence from murine models highlights the critical role of ROS-mediated oxidative damage and the synergistic interaction between different ROS sources, further amplifying myocardial injury. Moreover, the systemic effects of cigarette smoke including increased sympathetic activity, hypoxia due to carbon monoxide, and heightened inflammatory cytokine production exacerbate cardiovascular dysfunction. Given these multifaceted mechanisms, reducing or eliminating tobacco smoke exposure remains a vital preventive strategy for preserving cardiac function, and further research into targeted antioxidant or anti-inflammatory interventions could offer promising avenues for mitigating smoke-induced cardiac injury.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors report that there are no competing interests to declare.

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