Menthol vapes: A cool sensation, a cardiac disruption?

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The widespread adoption of e-cigarettes, particularly among younger populations, has introduced a new array of chemical exposures with uncertain long-term health consequences. While nicotine's cardiovascular effects are well-documented, the impact of non-nicotine additives, especially those designed to enhance flavour and sensation, remains less understood. Clinicians face a growing challenge in counselling patients on the full spectrum of vaping risks.

Emerging evidence suggests that cooling agents commonly found in vape liquids, like menthol and WS-3, could directly interfere with cardiac electrophysiology, potentially leading to arrhythmias. This mechanism presents a distinct concern beyond the established risks of nicotine, demanding closer scrutiny from the medical community.

KEY TAKEAWAYS

- The Pivot: Cooling agents in e-liquids, not just nicotine, directly impair cardiac ion channel function, raising arrhythmia risk.
- The Data: Menthol and WS-3 significantly altered calcium and sodium currents in cardiomyocytes, prolonging action potential duration.
- The Action: Advise patients that even nicotine-free vaping with cooling agents carries potential cardiac risks, particularly for those with pre-existing conditions.

The increasing prevalence of e-cigarette use has brought with it a complex array of chemical exposures, many of which lack comprehensive toxicological profiles. While nicotine's role in cardiovascular disease is a long-standing concern, the vast number of flavouring agents and other additives in e-liquids introduces additional, often uncharacterised, risks. Clinicians have struggled to provide definitive guidance on the safety of these products beyond nicotine cessation, particularly as new formulations enter the market with little pre-market scrutiny.

Among these additives, cooling agents like menthol and WS-3 (N-Ethyl-p-menthane-3-carboxamide) are particularly common, used to impart a sensation of coolness without a minty flavour. These compounds activate transient receptor potential melastatin 8 (TRPM8) channels, which are expressed not only in sensory neurons but also in various other tissues, including the heart. The potential for these agents to interact with cardiac ion channels and alter electrophysiological properties has become a focal point of recent preclinical investigations, moving beyond general pulmonary concerns to specific cardiac risks.

The mechanism of cardiac disruption

Preclinical studies have begun to delineate the specific mechanisms by which cooling agents might disrupt normal cardiac function. Researchers have employed various models, including isolated cardiomyocytes, cardiac tissue preparations, and in vivo animal models, to observe the direct effects of menthol and other cooling compounds. These investigations typically involve exposing cardiac cells or tissues to concentrations of cooling agents comparable to those absorbed during vaping.

One primary area of focus has been the impact on cardiac ion channels, which are critical for the generation and propagation of electrical impulses in the heart. Menthol, for instance, has demonstrated direct effects on both voltage-gated sodium channels (Nav1.5) and L-type calcium channels (Cav1.2). These channels are fundamental to the cardiac action potential. Disruption of their function can lead to altered excitability and conduction abnormalities, setting the stage for arrhythmias.

Specifically, exposure to menthol has been shown to inhibit Nav1.5 channels, reducing the peak sodium current. This effect can slow the depolarisation phase of the action potential, potentially prolonging the QRS duration on an electrocardiogram. But menthol also affects Cav1.2 channels, which are crucial for calcium influx during the plateau phase of the action potential and for excitation-contraction coupling. Alterations in calcium handling can lead to delayed afterdepolarisations (DADs) or early afterdepolarisations (EADs), both of which are known triggers for ventricular arrhythmias.

The effects are not limited to menthol. Other cooling agents, such as WS-3, also exhibit similar electrophysiological disturbances. Studies have reported that WS-3 can prolong the action potential duration (APD) in isolated cardiomyocytes, a key indicator of repolarisation abnormalities. Prolonged APD, particularly when heterogeneous across the myocardium, increases the risk of re-entrant arrhythmias, including torsades de pointes.

The concentrations of cooling agents required to elicit these effects in preclinical models are often within the range observed in the plasma and tissues of individuals who vape. This suggests a direct translational relevance, indicating that the levels achieved during typical e-cigarette use could be sufficient to induce cardiac electrophysiological changes. The cumulative exposure from chronic vaping, particularly with high-concentration e-liquids, remains an area of significant concern.

The clinical implications of these preclinical findings are substantial. Patients with pre-existing cardiac conditions, such as long QT syndrome, Brugada syndrome, or a history of myocardial infarction, may be particularly vulnerable to these pro-arrhythmic effects. Even in otherwise healthy individuals, chronic exposure to these agents could contribute to an increased risk of cardiac events over time. The lack of comprehensive long-term human data on the cardiovascular effects of these specific additives represents a significant knowledge gap.

The open-label nature of most vaping product use is an obvious caveat. Users often combine various e-liquids, sometimes from different manufacturers, making it challenging to isolate the effects of individual components. Furthermore, the variability in vaping devices, puff topography, and user behaviour means that systemic exposure to cooling agents can differ widely among individuals. These factors complicate the extrapolation of preclinical findings to real-world clinical outcomes, but the underlying biological plausibility remains strong.

Future research must focus on large-scale epidemiological studies to correlate cooling agent exposure from vaping with the incidence of arrhythmias and other adverse cardiac events in human populations. Mechanistic studies in human-derived cardiomyocytes and advanced cardiac models will also be essential to confirm and expand upon

the preclinical observations. Until then, clinicians should advise patients that e-cigarettes, even those marketed as nicotine-free, contain additives that may pose direct cardiac risks.

CLINICAL IMPLICATIONS

The emerging data on cooling agents in vapes should prompt a re-evaluation of how clinicians counsel patients about e-cigarette use. It is no longer sufficient to focus solely on nicotine addiction and its well-known cardiovascular risks. The direct electrophysiological effects of compounds like menthol and WS-3 on cardiac ion channels present a distinct and concerning mechanism of harm.

For patients with pre-existing cardiac conditions, particularly those prone to arrhythmias, the use of e-liquids containing cooling agents should be strongly discouraged. The potential for these additives to prolong action potential duration or disrupt calcium handling could exacerbate underlying vulnerabilities, increasing the risk of serious cardiac events. This applies even to individuals using nicotine-free products, as the cooling agents themselves appear to be the culprits.

The industry's continued introduction of novel flavouring and sensation-enhancing additives, often without rigorous safety testing, places an undue burden on public health. Regulatory bodies must move beyond a reactive stance and demand comprehensive toxicological data for all e-liquid components before they reach the market. This includes detailed cardiovascular safety assessments, not just pulmonary toxicology.

Clinicians should proactively inquire about the specific types of e-liquids patients use, including the presence of cooling agents, and educate them on these under-recognised risks. Until more definitive human data are available, the safest advice remains complete cessation of all e-cigarette products.

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