

EDITORIAL COMMENT

The Detrimental Effects of Alcohol and Cannabinoids on Cardiovascular Function*



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People used to binge alcohol drinking or/and smoking marijuana to enjoy the weekend are likely not aware of their increased risk of developing acute cardiovascular (CV) dysfunction, cardiac arrhythmias, and other life-threatening conditions affecting the liver and brain (1). In their study in this issue of *JACC: Basic to Translational Science*, Paloczi et al. (2) described how exaggerated alcohol assumption, even in a single shot, may induce severe CV dysfunction in mice.

SEE PAGE 625

It is noteworthy that the authors recognized the up-regulation of the endogenous cannabinoid (also referred to as endocannabinoid) anandamide as a leading mechanism underlying alcohol-induced CV dysfunction (3). Such results strongly suggest how the concomitant assumption of alcohol and cannabinoids may synergistically determine CV dysfunction.

Although those observations raise a warning for public health, especially involving young people, any translation to human beings still remains

highly speculative, and caution should be used. Our recommendation is justified by the following reasons already acknowledged by the authors in their article:

- 1) The study might suggest that both alcohol- and cannabinoid-mediated effects on CV dysfunction might trigger common pathways. Such evidence is limited to the animal model, whereas further data are needed to confirm a relevance for human beings. Indeed, mouse and human pathophysiology show several differences, especially concerning metabolism and the toxicity of exogenous compounds. Therefore, it often happens that intriguing evidence in mice is no longer confirmed in humans.
- 2) The mouse model might be distant from real life of human beings. Ethylic alcohol concentration may be correctly estimated in mice but not in humans. Indeed, wine, beer, and other alcoholic beverages combine ethylic alcohol with other “cardioprotective” compounds, such as polyphenols (3). Especially concerning moderate assumption of red wine, several studies in past decades investigated its antioxidant properties, which may partially balance alcohol toxicity. We need studies investigating whether this so-called “French paradox” might have a role in limiting the negative acute effects of binge alcohol drinking (3).
- 3) Concomitant administration of exogenous cannabinoids together with alcohol was not explored. Therefore, we cannot conclude about a potential synergistic toxicity of alcohol and cannabinoids on cardiac function.
- 4) Additional mechanisms, such as increased inflammation (elevated levels of macrophage migration inhibitory factor [MIF], interleukin 1 β ,

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and interleukin-6), autophagy, and overt cardiac apoptosis, potentially impacting acute CV dysfunction were only partially explored, suggesting that further studies are needed to better clarify the relationship of alcohol and endocannabinoids on CV dysfunction.

Therefore, much remains to discover and clarify. Certainly, the authors might have identified an additional negative effect of excessive alcohol consumption that should further discourage people to abuse. In line with this, not only chronic alcohol abuse but also acute alcohol intoxication would have a detrimental role in triggering devastating complications (4).

Another strength of this study is the demonstration that alcohol-induced cardiac dysfunction is dependent on cannabinoid type 1 receptor (CB1) activation. Being ubiquitously expressed in several tissues (including brain, heart, vascular, and inflammatory cells), CB1 has been extensively studied in the last decade. Its activation has been associated with organ dysfunction in different CV disease models. A specific CB1 antagonist rimonabant was also proved to effectively reduce body weight and CV risk in humans in clinical trials, but the high rate of severe psychiatric adverse effects imposed withdrawal from the market (4).

The results provided by Paloczi et al. are in line with previous evidence indicating a pathophysiological role of CB1 in CV injury. This is an intriguing issue because beneficial effects of CB1 inhibition and/or

CB2 activation were already demonstrated in other CV disease models, including atherosclerosis and related life-threatening complications (5). Ultimately, this study should stimulate further efforts in developing new CB1 pharmacological antagonists that do not pass the blood-brain barrier and therefore are better tolerated. Because CB2 was recently demonstrated to have anti-inflammatory activities circulating inflammatory cells, it would be of particular interest to develop compounds that simultaneously inhibit CB1 and activate CB2 at the same time (5).

Finally, we would stress future perspectives for endocannabinoids and their transmembrane receptors in CV research. The authors involved in this study are recognized as experts in this field of research and some of them (i.e., Pal Pacher, George Kunos, and Thomas Schindler) recently paved the way for analyzing the cannabinoid system by using cannabinoid tracers for cardiac nuclear imaging. We believe that this exciting route would be a very successful approach for translating mouse discoveries in human beings and for performing therapeutic strategies to limit alcohol-induced CV toxicity.

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