1. No.

   2021G014

2. Title

   Analysis of the effects of smoking related substances on adult and immature myocardium and its difference

3. Period

   2021-2023

4. Summary

Smoking is a risk factor for cardiovascular disease. In recent years, the use of heated cigarettes, which emit no secondhand smoke, has increased in Japan in place of traditional paper cigarettes. However, their direct effects on cardiomyocytes, mechanisms, and effects on human myocardium are unknown. In this study, we investigated the effects of PX80 and IS80 heated tobacco CSEs and RF80 and Hi-Lite paper cigarettes on cultured rat cardiomyocytes, isolated cardiomyocytes, and human iPS cell-derived cardiomyocytes (iPS-CM). The results showed that all CSEs decreased cardiomyocyte viability and contractile function, and their toxicity was in the order of RF80>IS80>PX80. To elucidate the mechanism, we used Hi-Lite CSE and found that both rat cardiomyocytes and human iPS-CMs exhibited reduced cardiac function and cell death. On the other hand, intracellular $Ca^{2+}$ levels were elevated, and abnormal kinetics were observed. In addition, various responses indicative of mitochondrial dysfunction (ROS production, decreased membrane potential, mPTP opening, cytochrome c release, etc.) were elicited. These results indicate that cigarette CSE directly impairs rat and human cardiomyocytes by inducing contractile dysfunction and cell death due to abnormal intracellular $Ca^{2+}$ dynamics and subsequent mitochondrial dysfunction that may cause decreased ATP synthesis and activation of cell death pathway.