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"Female Mice are Protected from Chronic Inhaled Nicotine-Induced Pulmonary Hypertension via a Sex Hormone-Independent Mechanism"

Introduction: Cigarette smoking has declined in the United States, but e-cigarettes use increased by 46.2% in young adults and 77.8% in high school students between 2017-2018. Little is known about the long-term health implications of these nicotine-containing devices, but cigarette smoking is a major risk factor for cardiovascular and pulmonary diseases, which are the primary cause of death in industrialized countries. Our group previously demonstrated that chronic inhaled nicotine induces pulmonary hypertension (PH) and right ventricular (RV) remodeling in male mice, but female mice exposed to nicotine failed to develop PH, suggesting a sex difference. This led us to hypothesize that *females are protected against the nicotine-induced effects on RV systolic pressure (RVSP) by a sex hormone-dependent mechanism*. Here, we studied intact and ovariectomized (OVX) female mice to assess the role of female sex hormones in nicotine-induced PH.

Methods: Female mice were OVX one week prior to nicotine exposure. Then, intact and OVX C57BL/6J mice were exposed to inhaled nicotine using a vaporization chamber or standard cages (air control) for 12 hours per day for 8 weeks. Nicotine exposure level was comparable to human cigarette smokers or e-cigarette users (serum cotinine of 371±61 ng/mL). Cardiac structure and function were assessed using echocardiography and RV catheterization. Heart rate was maintained between 400 and 500 BPM during echocardiography. Data were analyzed by two-way ANOVA followed by Tukey's multiple comparison test; a p-value of less than 0.05 was considered significant.

Results: Chronic inhaled nicotine in female mice did not significantly increase RVSP (22.7±0.4mmHg, n=9) versus air exposure (24.0±0.5mmHg, n=7). RVSP was unaffected by OVX of air-exposed mice (24.4±0.9 mmHg, n=9) and nicotine-exposed mice (23.6±0.6 mmHg, n=10). RV free wall thickness during diastole (RVFWT;d) was not significantly different between air-control mice (0.328±0.023 mm, n=8), nicotine-control mice (0.292±0.015 mm, n=10), air-OVX mice (0.315±0.021 mm, n=8), and nicotine-OVX mice (0.293±0.013 mm, n=10). RV internal diameter during diastole (RVID;d) was, likewise, not significantly different between air-control mice (1.30±0.03 mm, n=8), nicotine-control mice (1.34±0.04 mm, n=10), air-OVX mice (1.23±0.05 mm, n=8), and nicotine-OVX mice (1.24±0.05 mm, n=10). Neither nicotine nor OVX resulted in changes to left ventricular structure and function.

Conclusion: These findings led us to conclude that female cardiopulmonary protection against nicotine-induced PH and RV remodeling is not mediated by sex hormones. Further studies are required to elucidate the mechanisms underlying protection from nicotine-induced pathology in female mice.