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"Cardiovascular Effects of Chronic-*Plus*-Binge Drinking in Adult and Aged Mice"

Alcohol misuse is a persistent public health concern with increasing prevalence among older adults. Epidemiological data indicates that binge and chronic alcohol use has risen significantly in individuals aged ≥50, placing this population at growing risk for alcohol-related morbidity. One area of concern is the risk for non-ischemic alcohol-associated cardiomyopathy (ACM), a cardiac muscle disease that results in the weakening and dilation of the ventricular walls with the potential to lead to heart failure. While ACM is well-characterized in clinical settings, age-specific vulnerability to alcohol-induced cardiovascular dysfunction remains poorly understood. Here, we tested the hypothesis that aging mice will exhibit more severe cardiovascular outcomes in response to chronic-*plus*-binge alcohol exposure compared to their mature adult counterparts.

Male C57BL/6J mice aged 12-16 weeks and 72-76 weeks were subjected to a chronic-*plus*-binge alcohol feeding paradigm. Mice were randomly assigned to four experimental groups: ethanol-fed (EF) and pair-fed (PF) controls, each stratified by age. Following a 5-day acclimation period on the *ad libitum* Lieber-DiCarli liquid diet, mice were fed with or without alcohol (5% in the liquid diet) for 30 days in combination with additional oral gavage of alcohol (5g/kg) or maltodextrin (9g/kg), respectively, on days 10 and 30. All endpoints were assessed 24 hours following the final gavage. Cardiac function was evaluated using echocardiography and terminal pressure-volume (PV) catheterization. Additionally, vascular tone was assessed *ex vivo* on thoracic aortic rings by wire myography.

We found that chronic-*plus*-binge alcohol exposure induced in aging mice tends to increase vascular tone by potentially impairing nitric oxide-dependent vasodilation. This elevated vascular tone promotes morphological changes in the myocardium of aging mice, resulting in the deterioration of diastolic function.

These findings suggest that chronic-*plus*-binge alcohol exposure exacerbates age-related vascular dysfunction in mice by impairing vascular nitric oxide-mediated vasodilation and increasing vascular stiffness. This hemodynamic stress further drives myocardial remodeling and accelerates diastolic dysfunction in the aging hearts.