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Biological Sex and Sex-hormones moderate Right Ventricular (RV Dysfunction and Recovery in Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

INTRODUCTION:

CTEPH is a complication of pulmonary embolism and, if untreated, may lead to right ventricular (RV) failure and death. Similar to PAH, females with CTEPH survive longer than males. In PAH, this finding is attributed to sex- and sex hormone-mediated superior adaptation of the right ventricle (RV) to pressure overload and more robust recovery with treatment, but this has not been studied in CTEPH.

BACKGROUND:

Women have a higher RV ejection fraction (RVEF) than men in health, PAH and other groups of pulmonary hypertension but this has not been examined in CTEPH. Multiple lines of evidence indicate that sex hormones and related signaling pathways and metabolites are responsible for these observed sex differences in RV function. Estradiol (E2) demonstrates RV protective effects in experimental PH and attenuates the maladaptive RV response. Higher E2 levels are associated with an increased RVEF in health, and there are menstrual phase-dependent correlations between E2 and dehydroepiandrosterone sulfate (DHEA-S) and measures of RV function in PAH. Hormonal modulation is being studied in Phase II trials to treat PAH. No human studies have linked sex hormones to RV function in CTEPH. CTEPH presents a unique and innovative opportunity to study the effects of sex and sex hormones on the RV. Compared to PAH, CTEPH cohorts are more balanced with respect to biological sex. Furthermore, pulmonary thromboendarterectomy (PTE) surgery often results in a discrete and drastic reduction in afterload, providing an ideal model to examine RV recovery. At present, it is entirely unknown to what extent observed survival differences in CTEPH are driven by sex or sex hormone effects on RV function during disease development, progression, and recovery after PTE. There is a critical need to understand the impact of biological sex and related hormones on RV function in CTEPH. Without this understanding, our ability to leverage sex hormones to design therapeutics and improve outcomes in CTEPH, and other causes of RV failure, remains limited.

HYPOTHESIS AND SPECIFIC AIMS:

Our objectives are to define sex and sex hormone-related differences in RV function and recovery after PTE and determine whether these differences mediate sex-related survival disparities. We hypothesize that females, and patients with increased estrogen and DHEA-S signaling, exhibit superior RV function and recovery after PTE.