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Circulating extracellular vesicle characteristics differ between men and women following 12-weeks of concurrent exercise training.

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Concurrent resistance and endurance exercise training (CET) have numerous health benefits; however, hormonal and genetic differences exist that alter responses to CET between sexes. These include greater muscle mass, type II fiber area and higher release of IL-6 and testosterone following exercise in men and greater relative increases in upper body strength in women. Extracellular vesicles (EVs) are small membrane bound signaling factors that contribute to the adaptive signaling environment following exercise. Little is known of the EV response to long term exercise training and whether it differs between men and women. **Purpose**: To determine if EV concentration, subpopulations, miRNA contents, and signaling potential differ between men and women following acute and chronic exercise training. **Methods**: 18 participants (age: 27.3, Body fat: 27.8%, female n=9) underwent 12-weeks of CET consisting of resistance followed by interval training. Prior to and following the 12-week CET, subjects performed an acute bout of heavy resistance exercise (AHRET). Blood draws were taken at rest and following AHRET. EVs were isolated from plasma using size-exclusion chromatography. EV concentration, size, surface markers, and miRNA contents were analyzed via nanosight tracking analysis, imaging flow cytometry, and small RNA sequencing respectively. Data were analyzed via three-way [Sex x AHRET x chronic training] repeated-measures analysis of variance (ANOVA), significance: p=0.05. **Results:** AHRET elevated circulating [EV] (+51%, p=0.04) and EV protein content (+108%, p=0.02) in trained men only. AHRET decreased muscle-derived ($SGCA^{+}$) EVs (1.05% vs 0.52%, p=0.02) and increased microvesicles ($VAMP3^{+}$) EVs (2.5% vs 3.1% p=0.02). There were considerable sex-specific effects of CET on EV miRNAs, highlighted by greater miRNA in women (2,852 pg/ml vs 1,208 pg/ml p=0.01) and a larger variation in differentially expressed EV miRNAs at rest following CET in men (39 vs 12). This pattern was inverted following AHRET (7 vs 32). Pathway analysis predicted that AHRET and 12-weeks of CET in men positively regulates resistance training related pathways (including PI3K/Akt, mTOR, IGF-1 and IL-6 signaling pathways) more so than in women, **Conclusion:** Acute resistance exercise increased EVs following 12 weeks of CET in men only. EV subpopulations are sensitive to acute exercise independent of sex and training. Lastly, EV miRNA contents differ greatly between men and women and exercise training causes miRNA contents to be more supportive of exercise related pathways in men compared to women. **Significance/Novelty:** This report highlights several novel sex-based differences in the EV response to concurrent exercise training between men and women. It is becoming clear that circulating EVs may be important sex-specific adaptive signaling molecules following exercise training. Supported by UKMOD, Award No. WGCC 5.5.6