Dysregulation of Skeletal Muscle Mitochondrial Function following Critical Illness: a Translational Approach
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OBJECTIVES/GOALS: The objective of the study was to determine whether CLP altered genes associated with mitochondrial function in the diaphragm. METHODS/STUDY POPULATION: A rodent cecal-ligation and puncture (CLP) model used to mimic sepsis-induced critical illness. The CLP model involved ligation of 50% of the cecum below the ileocecal valve in adult C57BL6 mice, followed by needle puncture of the cecum resulting in mid-grade sepsis. Mice survived for 48 hours or more, following injury. Diaphragm and limb muscles were harvested 24 hours following CLP (N = 6) and following a sham CLP procedure (N = 6). RESULTS/ANTICIPATED RESULTS: Gene expression of mitochondrial related genes (mef2c, myh1, pgc1-α), were significantly decreased in the diaphragm of CLP injured animals when compared to controls. In addition, ubiquitin ligases, genes associated with skeletal muscle atrophy murf1 and atrogin were increased in the diaphragm of CLP injured animals when compared to controls. CLP injury decreases skeletal muscle mitochondrial function. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results indicate that sepsis-induced critical illness significantly impacts the expression of genes implicated in mitochondrial function. Further, these findings underscore the importance of sepsis-induced critical illness in contributing to the development of critical illness-related muscle wasting.
HIV-Associated Myocardial Diastolic Dysfunction and Soluble ST2 Concentration in Tanzanian Adults: A Cross-Sectional Study

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OBJECTIVES/GOALS: To determine the prevalence of myocardial diastolic dysfunction (DD) and association of serum concentration of the cardiac biomarker serum soluble ST2 in HIV-infected as compared to uninfected Tanzanian adults at the time of HIV diagnosis. METHODS/STUDY POPULATION: In this cross-sectional study we consecutively enrolled HIV-infected participants and uninfected controls at a large, referral HIV clinic in Mwanza, Tanzania. Standardized history, physical examination, echocardiography and serum samples were obtained. The primary outcome was prevalence of myocardial diastolic dysfunction in HIV-infected as compared to uninfected adults. The secondary outcome was the association of baseline serum sST2 concentration with diastolic dysfunction prevalence. Regression models were used to quantify the associations. RESULTS/ANTICIPATED RESULTS: We enrolled 388 HIV-infected, ART naive and 461 HIV-uninfected controls. Participants with HIV had a higher prevalence of DD (OR = 2.44, p = 0.001, controlled for age, sex, hypertension and BMI) and more severe dysfunction (66.7% vs 42.5%, p = 0.056) at an earlier age. Baseline serum sST2 concentration was significantly associated with DD in HIV-infected but not uninfected participants (p = 0.04 and 0.90, respectively). More HIV-infected adults with concurrent DD exceeded the threshold of 35ng/mL as compared to controls (15.7% vs 5.3%, p<0.0001). Additionally, a significant population level shift to higher sST2 concentration was observed in HIV-infected adults with dysfunction as compared to both HIV-infected without and HIV-uninfected adults with dysfunction (Kolmogrov-Smirnov test: p = 0.02 and 0.04). DISCUSSION/SIGNIFICANCE OF IMPACT: In a large population of HIV-infected adults in sub-Saharan Africa, HIV infection is associated with myocardial diastolic dysfunction. This dysfunction is associated with higher sST2 concentrations. Therefore, we conclude that the sST2 pathway may provide insight into the pathophysiologic mechanisms of dysfunction in HIV-infected adults.