Cardiovascular disease (CVD) and frailty have been linked at the mechanistic and epidemiological levels. Our goal is to identify if subclinical markers such as atherosclerosis, body composition, and fibrofatty infiltration measured from non-contrast whole-body magnetic resonance imaging (MRI) are markers of physical frailty. Community dwelling older adults with frailty status ascertained by Fried measurement are being recruited from an aging studies registry. MRI is performed using a Canon Galan3T with dedicated coils. Preliminary analysis from 4 frail individuals (86±15 years, 3 female, BMI=22±3kg/m2) and 2 age-matched robust controls (86±1 years, 1 female, BMI=28±0.2kg/m2) is presented. Of 4 frail one had a prior heart attack; one was previously diagnosed with heart failure. Mean atheroma score from 28 vessel segments (0.42±0.26 vs 0.18±0.10) and aortic tortuosity (2.3±0.4 vs 2.1±0.1) were higher in frail compared to robust indicative of higher atherosclerotic burden and vascular stiffness. Mean subcutaneous and visceral adipose tissue volumes were lower in frail compared to robust. However, mean myocardial (1113±27 vs 1089±2), liver (729±92 vs 683±104) and skeletal muscle (1106±25 vs 1072±64) T1 times (milliseconds) were each higher indicative of greater diffuse interstitial fibrosis. Averaged intramuscular fat percent measured across the pelvis, forearm, pectus, thigh, and calf was higher in frail compared to robust (14.8±4.1% vs 8.5±2.3%) indicative of higher fatty infiltration. Although these early results do not reach statistical significance, they support further study to determine cardiovascular and tissue related differences between physically frail and robust older adults, which in turn may inform intervention developments for frailty and CVD.

β-GPA: AN AMPK ACTIVATOR WITH POTENTIAL EFFECTS ON HEALTHSPAN AND FUNCTION

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β-Guanidinopropionic acid (β-GPA) is a naturally occurring compound reported to activate AMP Activated Protein Kinase (AMPK) signaling in vivo. Acute administration of β-GPA in young animals has been reported to improve multiple functional measures including a switch to oxidative fatigue-resistant muscle fibers, improved glucose uptake, and increased mitochondrial biogenesis. However, it is unknown if β-GPA may promote healthy aging or prevent late-life functional decline. To address this knowledge gap, we tested the effects of β-GPA on mitochondrial energetics and cellular function in young and old genetically heterogenous mice (HET3). Both age groups were fed either 1% β-GPA or control chow for ~5 months and basic functional parameters including metabolism were assessed. β-GPA treatment decreased lean and fat mass in young males, but prevented late-life losses in these parameters in old animals. Notably, glycated hemoglobin (HbA1c) levels were lower in treated young and old males suggesting improved glucose homeostasis. Citrate synthase activity was also higher in old males fed β-GPA suggesting increased mitochondrial biogenesis. At the molecular level, mitochondrial Complex I expression decreased with β-GPA treatment in old males versus controls. High resolution respirometry revealed generally decreased respiration in old animals compared to young and decreased Complex 1 coupled respiration in soleus of β-GPA treated young but not old males. These findings indicate that the mitochondrial effects attributed to β-GPA may be mediated by its action on Complex I. While treatment outcomes varied in young and old males these results suggest β-GPA may prove beneficial in combating age-related declines in function.

AGE, SEX, AND FRAILTY INFLUENCE AGE-DEPENDENT CHANGES IN VENTRICULAR STRUCTURE AND FUNCTION IN C57BL/6 MICE

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The heart undergoes maladaptive changes during aging that set the stage for cardiovascular diseases, but frail older individuals are most likely to develop such diseases. We investigated the impact of frailty on left ventricular (LV) remodeling in male and female mice (aged 9-23 mos). Ventricular function/structure and frailty were assessed with echocardiography (Vevo 2100) and a frailty index (FI) tool. Fractional shortening (systolic function) increased with age (9 vs 23 mos) in males (27.7±2.6 vs 38.4±1.6%; $p<0.05$) and females (26.9±1.4 vs 32.5±1.8%; $p<0.05$); similar results were seen with ejection fraction. Conversely, E/A ratios (diastolic function) declined with age in males (1.9±0.1 vs 1.3±0.1; $p<0.05$) and females (2.1±0.3 vs 1.6±0.1; $p<0.05$). LV mass and LV internal diameter (diastole) increased with age in females but not in males, while intraventricular septum (diastole) increased in males only. As age-dependent changes were heterogeneous, we stratified the data by FI scores. Interestingly, fractional shortening ($r=0.52$; $p=0.006$) and ejection fraction ($r=0.52$; $p<0.0001$) were graded by FI score, but only in males. By contrast, LV mass was graded by frailty, but only in females ($r=0.55$; $p<0.0001$). Thus, diastolic function declines with age in both sexes while systolic function actually increases. Aging females display increased LV mass and LV dilation whereas older males exhibit septal thickening. These maladaptive changes are graded by frailty, suggesting that cardiac aging is prominent in those with poor overall health. Age, sex and frailty influence cardiac aging, which may predispose frail older men and women to develop different cardiovascular diseases as they age.

CASE STUDY EXEMPLAR OF DETECTING SEVERE DIASTOLIC DYSFUNCTION USING BALLISTOCARDIOGRAM

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The specific aim of this case study was to describe how monitoring ballistocardiogram (BCG) waveforms can detect early heart failure (HF) changes. HF significantly impairs quality of life and is the principal cause for hospital readmissions in older adults. HF prevalence in American adults aged

65 years and older is expected to increase over 70% by 2030. Detecting worsening HF is challenging. Invasive arterial waveforms display blood pressure changes with each heartbeat; BCG waveforms display repetitive body motions resulting from ejection of blood into the great vessels. BCG waveforms change as cardiac function changes. Currently, BCG signals can be captured non-invasively using sensors placed under a bed mattress and provide heart and respiratory rates. We have developed a new way to analyze the BCG waveform using an innovative closed-loop physiological model of the cardiovascular system. The subject, a 94-year old female with hypertension, presented to her physician with symptoms associated with a new diagnosis of acute mixed congestive HF. Mean heart and respiratory rate trends obtained from her bed sensor in the prior two months did not indicate HF. We simulated cardiac cycles using normal cardiac function data, mildly impaired diastolic function data, and the subject's echocardiography data. The results demonstrated BCG waveform changes that correlated with decreasing cardiac output related to worsening diastolic function. New methods for clinically interpreting BCG waveforms present a significant opportunity for improving early HF detection and improving outcomes. Working on a clinical problem from an engineering perspective merges two disciplines, creating a new methodology.

GAIT SLOWING AMONG FRAIL OLDER ADULTS: IS HIGHER DOPAMINERGIC SIGNALING PROTECTIVE?

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Strategies to reduce gait slowing in frail older adults are urgently needed. Higher dopaminergic (DA) signaling is emerging as a protecting factor against age-related gait slowing, in the absence of Parkinson's Disease (PD). DA signaling is potentially modifiable, thereby offering promising novel strategies to reduce gait slowing. In 3,752 PD-free participants of the Cardiovascular Health Study (72.3 years, 81% white, 39% male), we measured gait speed (usual pace, 15 feet), frailty (Fried definition), and genetic polymorphism of Catechol-O-methyltransferase (COMT, rs4680), an enzyme regulating tonic brain DA levels. Multivariable linear regression models of COMT predicting gait speed were adjusted for age, gender, BMI, ankle-arm index, vision, and arthritis. Strength, education, medications, pulmonary, cardio- and cerebro-vascular diseases, diabetes, mood, and cognition were considered as additional covariates. We examined the full cohort and the subgroup with frailty (n=222), without and with race-stratification to address racial differences in allele frequencies. Average (SE) gait speed was 0.88 (0.003) and 0.58 (0.01) m/sec in the full cohort and the frail subgroup, respectively. COMT was linearly associated with gait speed; gait was faster for met/met (higher DA signaling) and slower for val/val (lower DA signaling) participants. In adjusted models, differences between these two groups were: 0.02 (0.01) m/sec in the full cohort (p=0.4); 0.07(0.02) m/sec in the frail subgroup (p=0.02); 0.10 (0.02) m/sec in white with frailty (p=0.01). COMT genotyping may help identify frail adults who are less vulnerable to gait impairments. Studies of frailty should examine whether higher DA signaling offers resilience against age-related gait slowing.

WHOLE-BODY TAU-KNOCKOUT MICE DEVELOP AGE-ASSOCIATED METABOLIC DYSFUNCTION AND OBESITY

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The microtubule associated tau protein (MAPT) is expressed in multiple tissues; however, the primary focus has been its role in neurodegenerative diseases such as Alzheimer's disease. Few efforts have been made to investigate tau protein function outside of the nervous system. We previously noted that aged (20 mo.) Mapt-KO mice had significantly greater body mass than either age-matched wild-type mice or a Mapt-KO/rTg4510 mouse model of late stage neurodegeneration. We hypothesize that endogenous tau contributes to normal metabolic function and sought to characterize potential metabolic alterations in whole body Mapt-KO mice. In 2-3 month-old wild type (WT) and Mapt-KO mice fed ad lib chow diet, we observed no significant difference in glucose or insulin tolerance. However, in 16 month-old Mapt-KO mice fed ad lib chow, we observed glucose intolerance ($p<0.05$) and increased body mass (1.45-fold, $p<0.001$) compared to WT. In this aged cohort, we evaluated body composition by quantitative magnetic resonance, spontaneous activity and running, grip strength and Rotarod performance, nest building, and performed high resolution respirometry in hippocampus and soleus. Mapt-KO shows significant increases in lean and fat mass (1.18-fold, 2.97-fold, $p<0.05$) and nest building (Deacon Score, $p <0.05$), and reductions in ambulatory activity ($p<0.01$) and rotarod balancing ($p<0.0001$) despite an ability to learn the task. No significant changes were seen in grip strength, spontaneous running, or mitochondrial respiration, although there was a trend of reduced maximum uncoupled respiration in Mapt-KO hippocampus ($p<0.1$). This study concludes that Mapt plays an important role in glucose homeostasis and body weight regulation.

LOSS OF HYPOXIA SIGNALING LIMITS SKELETAL MUSCLE RESPONSE TO AEROBIC EXERCISE IN AGING

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Skeletal muscle function declines with aging. Physical activity improves muscle function, but may require upregulation