18F-Fluorodeoxyglucose (18F-FDG) was used to examine glucose uptake by PET/MRI imaging (n=6). DOX treatment in Non-Tg male mice caused cardiac dysfunction, whereas expression of M3-SIRT3 and M1-SIRT3 attenuated cardiac remodeling and reduced ejection fraction ($p < 0.05$). Analysis of acetylated peptides revealed that DOX increased the acetylation of several proteins involved in cardiac energy production (e.g. ACO2 and ATP5PB) and lipid metabolism (e.g., HADHA) while M1-SIRT3 expression mitigated these effects. Lipidomic analysis of cardiac tissue identified an increase in proapoptotic lipid markers including gangliosides and phosphatidylserine species and a large decrease in triglyceride lipid species in DOX treated mice. Quantitative PCR identified increases in Cpt1a ($p < 0.05$) and Lipe ($p=0.0518$) in DOX treated Non-Tg mice, but not in M3-SIRT3 and M1-SIRT3 mice. DOX decreased the expression of Fapb3 and Hadha ($p < 0.05$) in all groups. 18F-FDG PET showed increased cardiac glucose uptake in Non-Tg, and M3-SIRT3 DOX treated mice ($p < 0.05$) but remined unchanged in M1-SIRT3 mice.

CONCLUSION: Our data show that increased M1-SIRT3 expression in the heart prevents DOX induced dilated cardiomyopathy. M1-SIRT3 expression altered mitochondrial protein acetylation while DOX decreased cardiac triglycerides and increased glucose uptake indicative of metabolic dysfunction.

Heart and Stroke Foundation of Canada

P023
TARGETING TUMOR NECROSIS FACTOR (TNF) IN ATRIAL STRETCH-DEPENDENT ADVERSE ATRIAL REMODELING AND VALVULAR ATRIAL FIBRILLATION IN A MOUSE MODEL OF AORTIC REGURGITATION

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BACKGROUND: Atrial fibrillation (AF) is the most common sustained supraventricular arrhythmia worldwide with its incidence linked to cardiovascular (CV) disease. Most conditions linked to AF are associated with elevated atrial pressures and atrial stretch, which are powerful stimuli for atrial remodeling. We previously established that the proinflammatory and mechanosensitive cytokine, tumor necrosis factor (TNF), is a key mediator of stretch-related atrial remodeling and AF vulnerability. As TNF is critical factor mediating atrial fibrosis, hypertrophy, inflammation, and arrhythmias in heart disease, we hypothesized that targeting stretch-mediated TNF-dependent signaling may offer a novel therapeutic target in valvular AF patients.

METHODS AND RESULTS: We have developed a clinically relevant mouse model of aortic regurgitation (AR), which is characterized by acute and chronic diastolic volume overload and elevated left ventricular end-diastolic (LVEDPs) and atrial pressures. The effects of pharmacological TNF inhibition with Etanercept (Enbrel®, twice-weekly, 2.5 mg/kg) beginning early (2-days post-AR) or later (1-week post-AR) were examined. Cardiac structure and function as well as electrophysiological properties were assessed using echocardiography, telemetry hemodynamics, histology, immunohistochemistry, in vivo intracardiacs, and ex vivo optical mapping in isolated atria. Results: Four weeks of AR resulted in progressive LV dilatation, functional impairment, and hypertrophy in the absence of ventricular arrhythmias. Moreover, LVEDPs increased acutely and remained elevated with disease progression. In the atria, AR resulted in hypertrophy, fibrosis, and macrophage infiltration as well as decreased conduction velocity, atrial effective refractory periods and action potential durations in wild-type mice. Importantly, AR increased both in vivo and ex vivo AF susceptibility. By contrast, both early and delayed TNF inhibition with Etanercept attenuated AR-induced adverse atrial remodeling and protected against AF inducibility, independent of ventricular changes.

CONCLUSION: Our results establish that stretch-mediated adverse atrial remodeling and AF vulnerability with AR requires TNF, suggesting TNF may offer an important therapeutic target for the prevention and treatment of valvular AF.

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P024
TREADMILL STRESS TEST VENTILATORY PATTERN USING A WEARABLE DEVICE AS AN ADDITIONAL MARKER FOR CV DISEASE

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BACKGROUND: Treadmill stress testing for cardiovascular disease (CVD) is typically done with ECG and blood pressure monitoring alone, with respiratory monitoring via sealed face mask and gas sampling occurring rarely in clinical settings. We sought to examine whether a simple electronic, non-invasive, chest-mounted respiratory monitoring device could successfully be used to reveal clinically useful insights during stress testing.

METHODS AND RESULTS: Twenty-five adult patients referred for treadmill exercise stress testing at an outpatient cardiology clinic were equipped with a small, lightweight, electronic chest band (Airgo, MyAir Inc.) capable of measuring respiratory rate (RR) and minute ventilation (Ve) during completion of an unmodified Bruce protocol stress test. Univariate regression was used to assess patient characteristics such as age, sex, and cardiovascular comorbidities as predictor variables for Ve and RR slope (change in Ve and RR over time). Log transformations were performed for non-normally distributed variables (Ve slope, RR slope, and body mass index, BMI). The mean age of patients was 55.0 years (SD 13.4); 18 males and 7 females. Group mean results (+/- SD): stress test duration 8.6 +/- 3.5