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

min, peak Ve (expressed as % of baseline at rest) 489 +/- 297%, resting RR 17.0 +/- 3.8 breaths per minute, peak RR 35.5 +/- 6.9 breaths per minute, resting heart rate (HR) 78.4 +/- 15.5 bpm, peak HR 156.7 +/- 19.7 bpm, stress test positivity: 1 out of 25 patients. Presence of CVD (defined as current or previous HTN, angina, CVA, A-fib, or sleep apnea) was found to be a significant predictor of both Ve (Figure 1) and RR response over time to exercise (p=0.004, 0.002, respectively, Table 1), with patients having comorbid CVD demonstrating a mean 124% (95%CI 32.2-280%) higher Ve slope and 71.0% (95%CI 23.7-139%) higher RR slope versus patients without these comorbidities. None of age, sex, body mass index (BMI), stress test duration, or delta HR were significant predictors of Ve slope; BMI and stress test duration were found to be significantly associated with RR slope (p=0.001 and 0.007, respectively).

CONCLUSION: Non-invasive chest-mounted electronic respiratory monitoring may provide a useful supplement to current routinely gathered data during treadmill stress testing and may identify morbidity not seen with standard measures.

Figure 1. Per-patient slope of Ve during treadmill stress testing

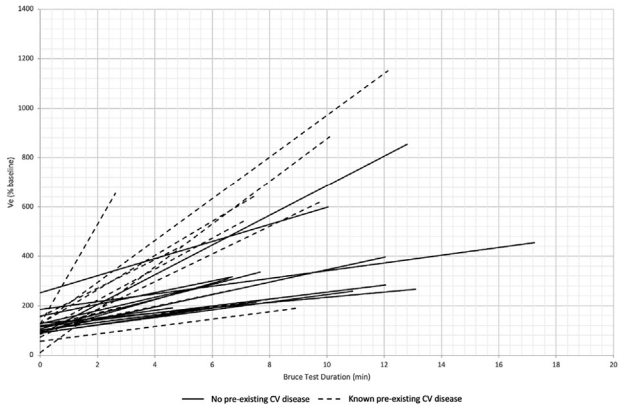

Table 1. Relationship between patient characteristics and respiratory parameters

Patient characteristics	Slope of Ve (%) vs time		Slope of RR (bpm) vs time	
	Beta coefficient	% increase in mean slope (95% CI)	Beta coefficient	% increase in mean slope (95% CI)
Age	-0.022	-	0.087	-
Sex	-0.336	-	-0.086	-
BMI	0.378	-	**0.603****	**15.6 (6.43 – 25.7)****††
Stress test duration	-0.258	-	**-0.526***	**-6.95 (-11.5 – -2.18)***‡
Presence of CVD	**0.550****	**124 (32.2 – 280)****†	**0.579****	**71.9 (23.7 – 139)****†
Delta HR	0.105	-	-0.233	-

*statistically significant, p<0.05
**statistically significant, p<0.005
†represents % increase in mean slope for presence versus absence of patient characteristic
††represents % increase in mean slope for every 10% increase in patient characteristic
‡represents % increase in mean slope for every 1 minute increase in patient characteristic

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P025
A COMPARATIVE ANALYSIS OF ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION BETWEEN CANADA AND THE UNITED STATES FROM THE NORTH AMERICAN COVID-19 STEMI REGISTRY

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BACKGROUND: Important healthcare differences exist between the US and Canada. The goal of this investigation is to compare clinical characteristics, treatment strategies and clinical outcomes of STEMI patients with COVID-19 infection treated in the US versus Canada.

METHODS AND RESULTS: The North American COVID-19 Myocardial Infarction (NACMI) registry is a prospective, investigator-initiated study enrolling STEMI patients with documented COVID infection in the US and Canada. The primary end-point is in-hospital mortality. The secondary end-points include stroke, reinfarction and a composite of death, stroke or reinfarction. Of the 767 STEMI-COVID patients, 67 (9%) were from Canada and 669 (91%) from the US. Patients enrolled in Canada were more likely to present with chest pain (79% vs. 54%, p< 0.001), otherwise patients across both countries had comparable presenting demographics (Table 1). The proportion of patients not undergoing coronary angiography was significantly lower in Canada compared with the US (9% vs. 19%, p=0.039); of those who underwent angiography, no significant differences in reperfusion modalities were noted. Compared with the US, patients in Canada had a significantly lower unadjusted risk for in-hospital mortality (15% vs. 29%, p=0.016) and the risk for the composite of death, stroke or re-infarction (15% vs. 31%, p=0.006). Vaccination status was available in Canada 26 / 67 patients (unvaccinated 13, vaccinated 13) and US 328/ 669 patients (unvaccinated 282, vaccinated 46); a strong association between vaccination and adverse clinical composite is noted in both countries (Canada: 3/13, 23% (unvaccinated) vs. 0/13, 0% (vaccinated), p=0.22; and, US: 75/282, 27% (unvaccinated) vs. 6/46, 13% (vaccinated), p=0.048).

CONCLUSION: Among patients with STEMI and COVID-19 infection those treated in Canada had higher proportions undergoing angiography and a lower risk of death, stroke or reinfarction. Regardless of geography, vaccination was associated with significantly lower risk of mortality in both countries.