MRI/S Assessment of Cardiac Morphology/Function and Skeletal Muscle Energetics in Mitochondrial DNA Mutated Mice

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Introduction: Polymerase gamma-deficient (PolG) mice display reduced life spans and premature aging with weight loss, decreased subcutaneous fat and enlarged hearts (1). In this study, we assessed cardiac morphology/function and skeletal muscle energetics in mitochondrial DNA mutated PolG mice that had been either exposed to cigarette smoke, forced air, or room air for 5 months.

Method: All procedures were approved by the Animal Care and Use Committee of our institution and were specifically designed to minimize animal discomfort. 3 different ages of PolG mutant (KI/KI) and wild type (WT) mice (table 1) were exposed to either forced air, 4% cigarette smoke (2 hr/day), or room air. Cardiac MRI and ^{31}P-MRS experiments were performed on a 9.4 Tesla small animal vertical-bore magnet (Bruker Biospin GmbH, Germany) equipped with an 89 mm imaging gradient set (100 gauss/cm). ^{31}P-MRS was performed using a 15 mm ^{31}P surface coil (Bruker Biospin) positioned on the upper hind limb of the mouse and a one Pulse sequence (TR =2 s, NS = 512, SW = 40 ppm,). Cardiac imaging (CMR) was performed on the smoked groups using a birdcage volume coil (Bruker Biospin) with an inner diameter of 30 mm, and an IntraGate Flash sequence was used to acquire long-axis slices and short-axis slices (6-9 slices covering the entire left ventricle, 4 min acquisition time/slice) using the following parameters: TR/TE=8.2/1.8 ms, FOV=2.5X2.5 cm, Matrix =128X128, slice thickness =1 mm, and 10 frames. Cardiac images were analyzed using Analyze 8.1 AVW software (Analyze Direct, Overland Park, KS). At the end of the study, Mt-DNA damage was measured in the 12 month old room air exposed mice for both wild type and PolG mice using q-PCR. Data are presented as Mean ± SEM.

	Wild type 9MO (exposed 21weeks)	KI/KI 9MO (exposed 21weeks)	Wild type 12MO (exposed 32weeks)	KI/KI 12MO (exposed 32weeks)	Wild type 12MO (room air exposed)	KI/KI 12MO (room air exposed)
Smoke exposed	4F & 6M (CMR/MRS)	3F & 2M (CMR/MRS)	3F & 5M (CMR/MRS)	4F & 3M (CMR/MRS)		
Forced Air	5F & 4M (MRS)	4F & 3M (MRS)	3F & 5M (CMR/MRS)	4F & 2M (CMR/MRS)		
Control					3F & 6M (CMR/MRS)	2F & 5M (CMR/MRS)

Table1: different sub groups of wild type mice and PolG KI/KI mice included in the study, where; MO: month old, F: female, M: male.

Results: No mortality was observed in the groups. Skeletal muscle energetic compromise was observed in the PolG mice as reflected by the decrease in PCr/Pi ratio (figures A and C) which is a hallmark for energetic dysfunction (e.g.. decreased ATP synthesis, shift in creatine kinase equilibrium). Initial stages of heart failure appears to be present in the PolG mice compared to the WT mice as reflected by the LV chamber dilation (EDV and ESV increased in all groups) and the increase in the normalized LV mass to body weight (figures B and D). Cardiac function is still preserved in all groups. No differences in gender or smoke exposure were found between groups. Mt-DNA damage in the heart was significantly increased (2.5 fold, *** p≤0.001) in the PolG mice compared to the wild type mice.

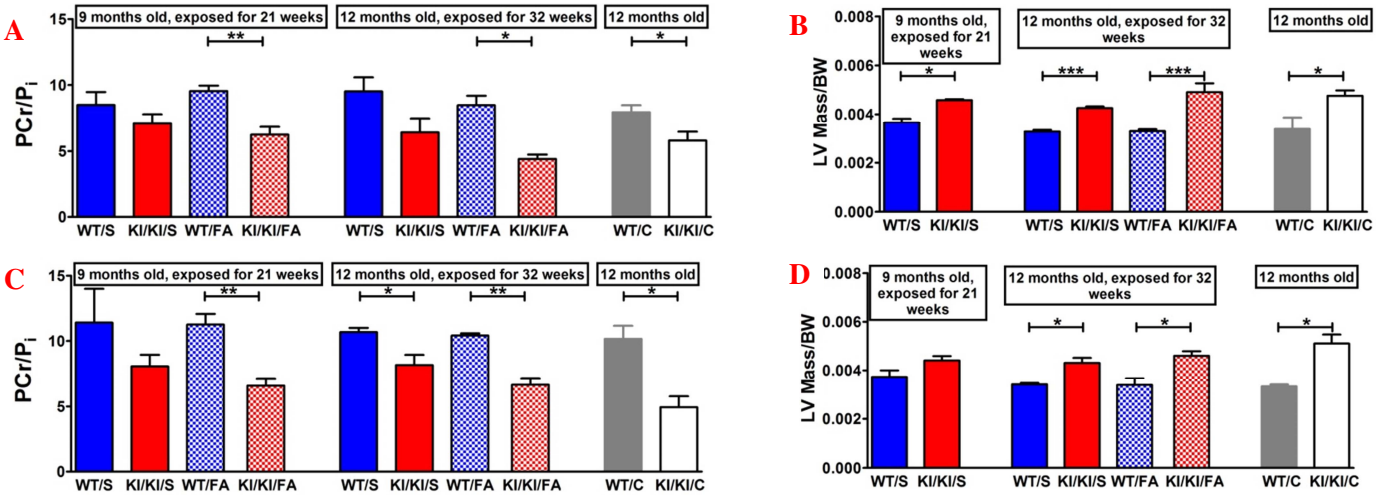

Figure: PCr/Pi ratio and LV Mass to Body weight ratio measurements in male (A, B) and female mice (C, D).
S: smoke exposed, FA: forced air exposed, and C: room air control.

Conclusion: The observed mitochondrial defects in cardiac function and skeletal muscle energetics is consistent with the phenotype that has previously been published (1). However, these differences were not related to gender differences or exacerbated by cigarette smoke exposure.

References: 1- Adeel Safdar A et al. Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice. PNAS, March 8, 2011, 108 (10):4135-4140.