1

Fasting to Ferroptosis

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Cardiology

Minneapolis
Heart Institute
Foundation

2

Disclosures

CO-Investigator R01

1R01HL162927

3

Objectives

- Intermittent fasting and RV function
- Ferroptosis in pulmonary hypertension
- Development of targeted therapy for RV failure

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An Engine Out of Fuel

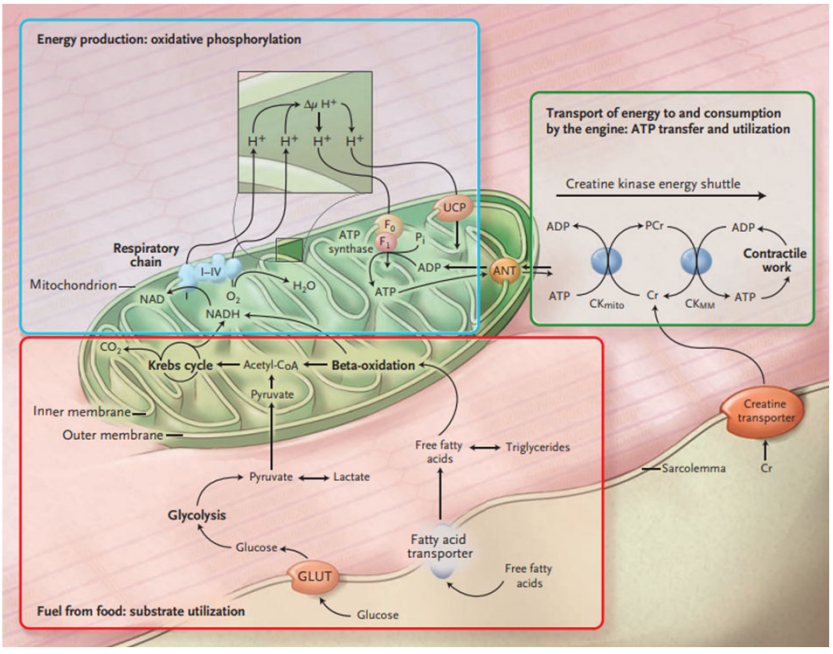
THE CHEMICAL NATURE OF HEART FAILURE*

By GEORGE HERRMANN, M.D., F.A.C.P., and GEORGE M. DECHERD, JR., M.D., F.A.C.P., *Galveston, Texas*

Herrmann *et al*, 1939

5

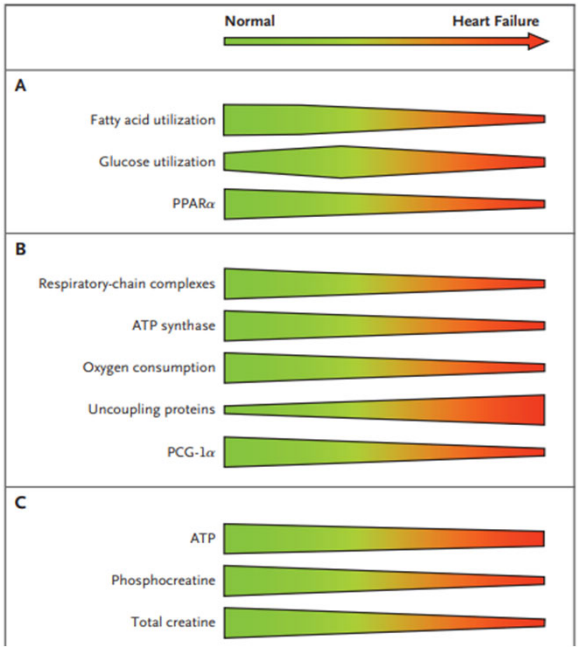
Myocardial Energetics



Neubauer *et al*, 2007

6

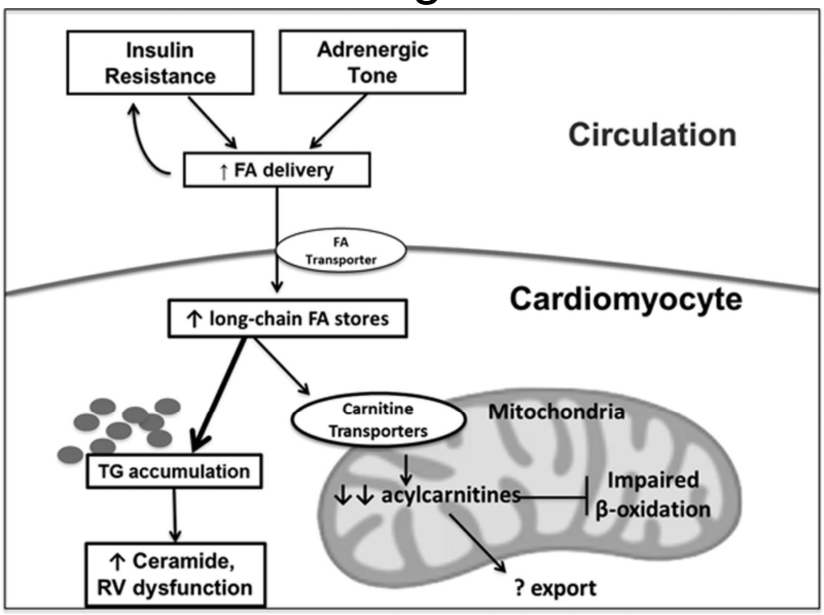
Myocardial Energetics



Neubauer *et al*, 2007

7

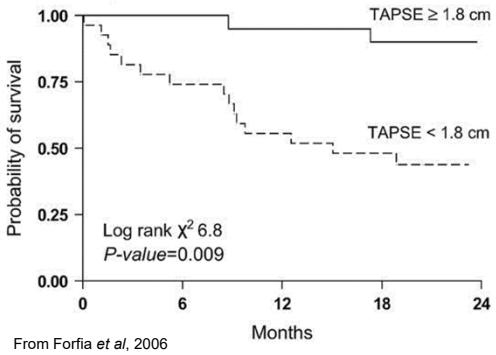
RV Bioenergetics in PAH



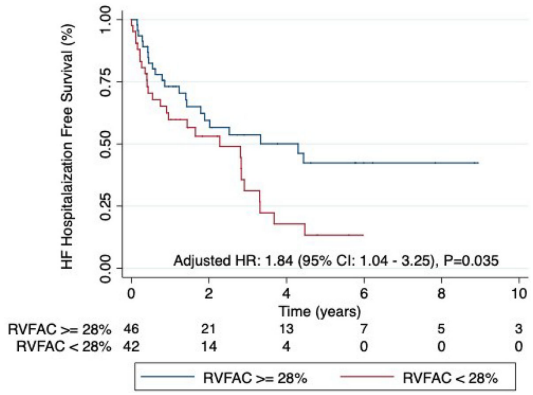
Brittain *et al,* Circulation 2016

8

RV Failure and Mortality



From Forfia *et al*, 2006



From Prins *et al*, 2019

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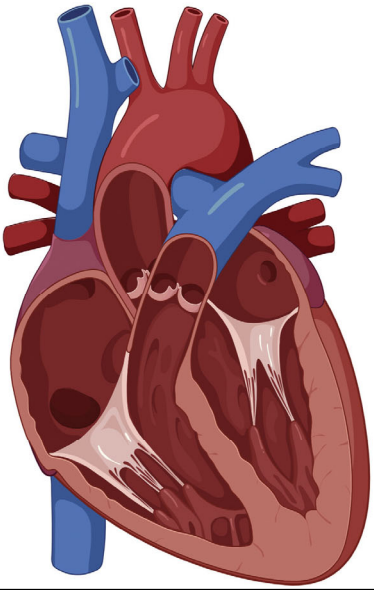
Major Clinical Problem with Little Treatment Options

Right Ventricle
- Derived from secondary heart field
- 2 cell layers with most contractility leading to longitudinal shortening
- Thin walled, crescent shaped chamber
- Low pressure system
- Better adapted to volume overload
- Perfusion occurs during systole and diastole
- α1-receptor signaling decreases inotropy in pressure overload
- Does not develop hypertrophy following norepinephrine infusion
- Lower β-MHC content
- Higher macrophage and dendritic cell content
- Higher ECM content
- ER-α stimulation most beneficial



Left Ventricle
- Originates from primary heart field
- 3 cell layers and most contractility is circumferential
- Thick walled, bullet shaped chamber
- High pressure chamber
- Better adapted to pressure overload
- Perfusion occurs during diastole
- Higher afterload reserve
- α1-receptor signaling increases inotropy in pressure overload
- Develops hypertrophy following norepinephrine infusion
- Higher β-MHC content
- ER-β stimulation most beneficial

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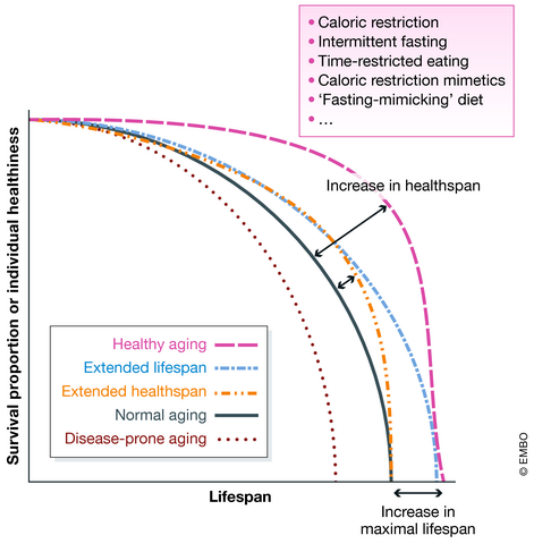
Intermittent Fasting



Hofer *et al*, 2017

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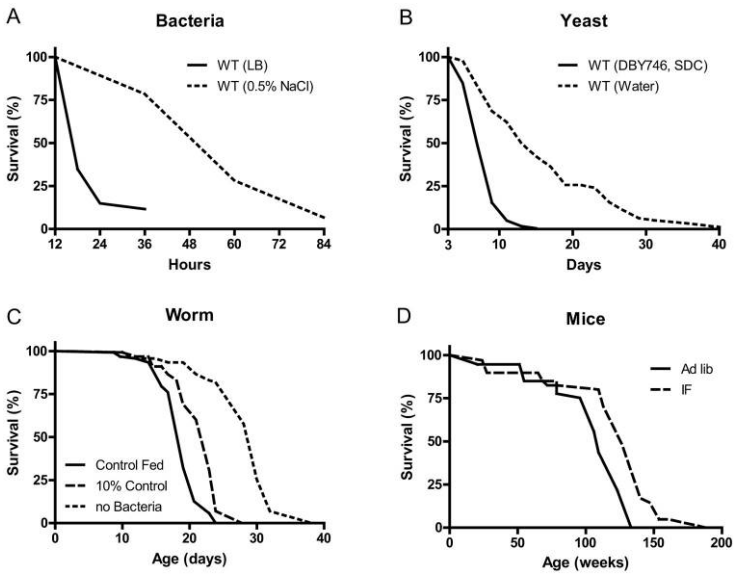
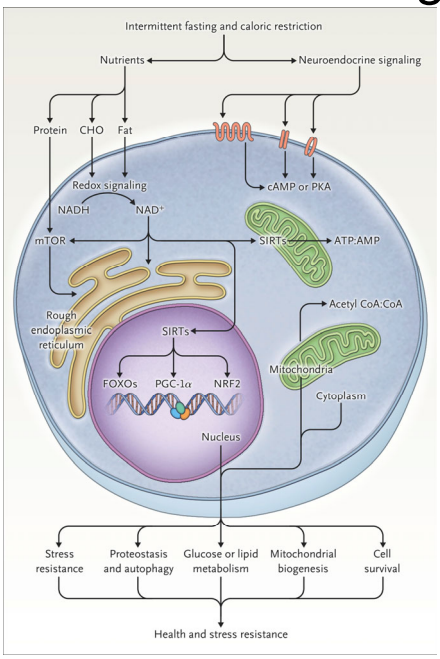
Intermittent Fasting and Lifespan Extension



From Longo *et al*, 2015

12

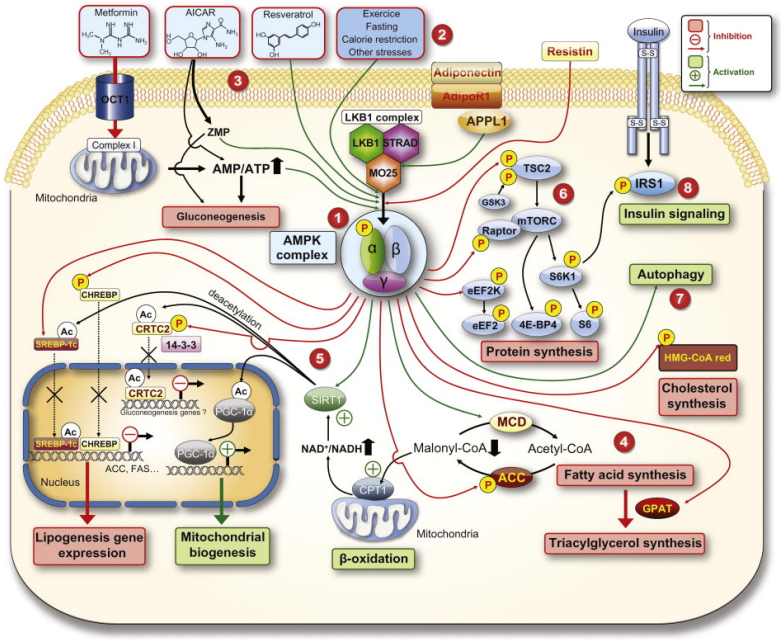
Intermittent Fasting



Acabo *et al*, 2019

13

Intermittent Fasting and AMPK



Foretz *et al*, 2010

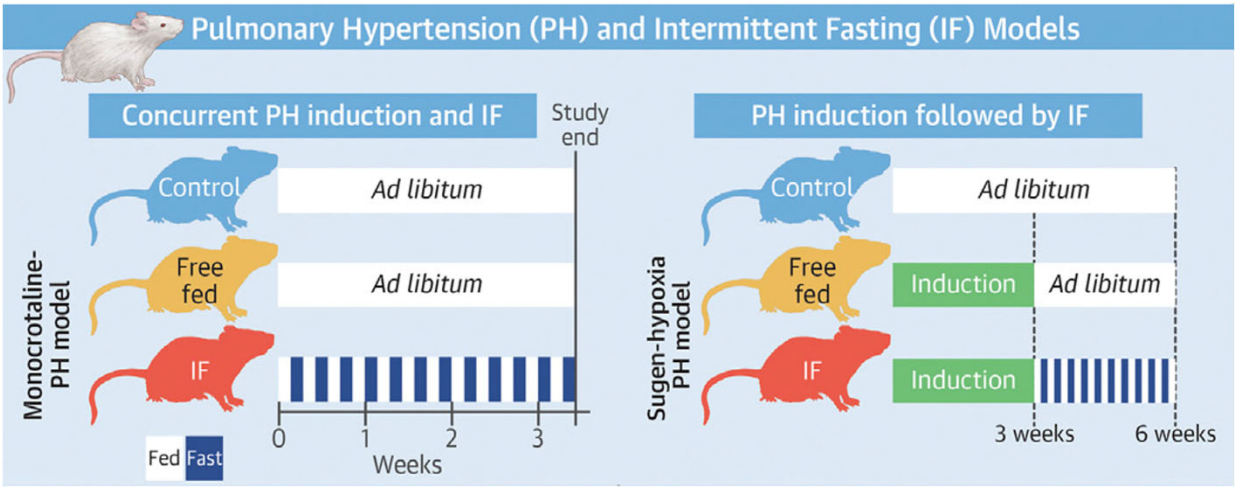
14

Hypothesis

- Intermittent fasting might prevent and/or restore RV maladaptive metabolic changes via AMPK.

15

Methods



Kazmirczak *et al* JACC BTS

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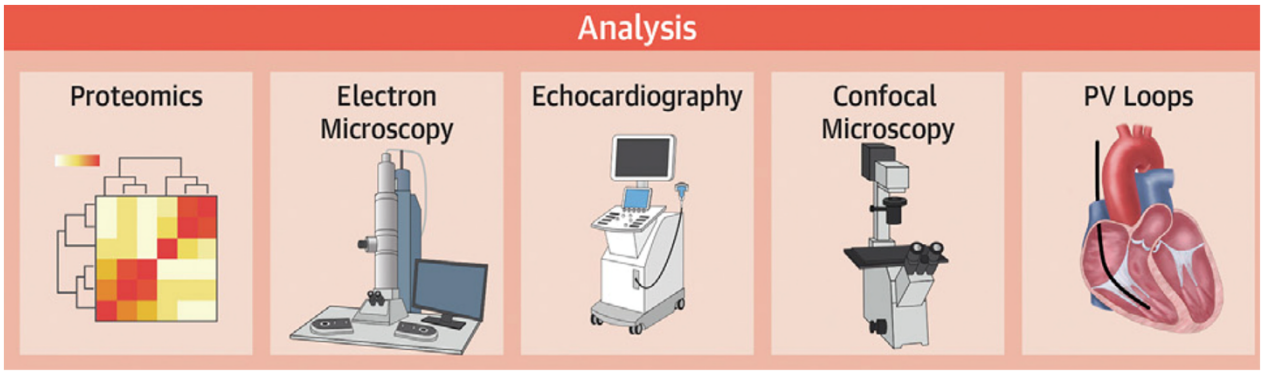
Methods



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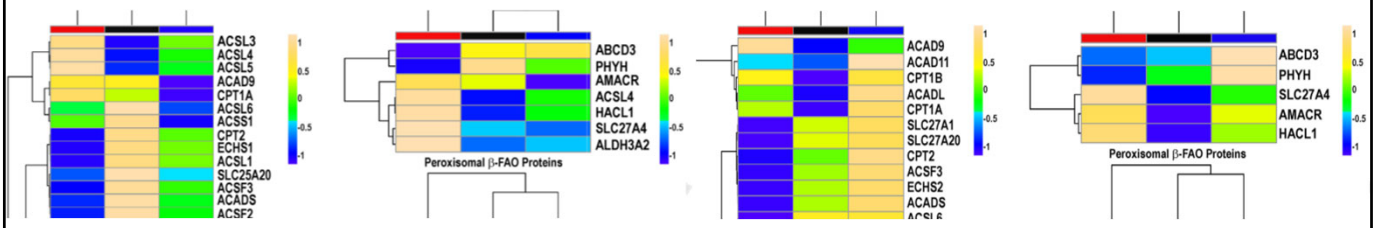
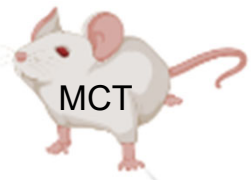
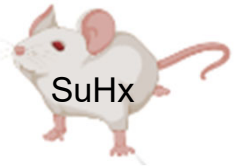
Intermittent Fasting Activates AMPK







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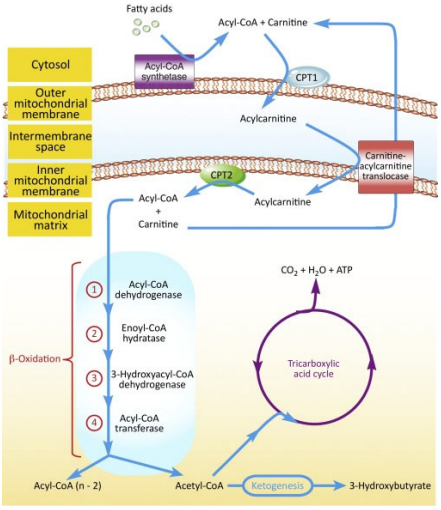
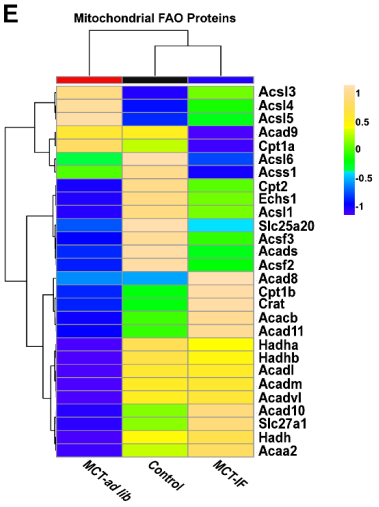
Intermittent Fasting Prevents FAO Protein Downregulation





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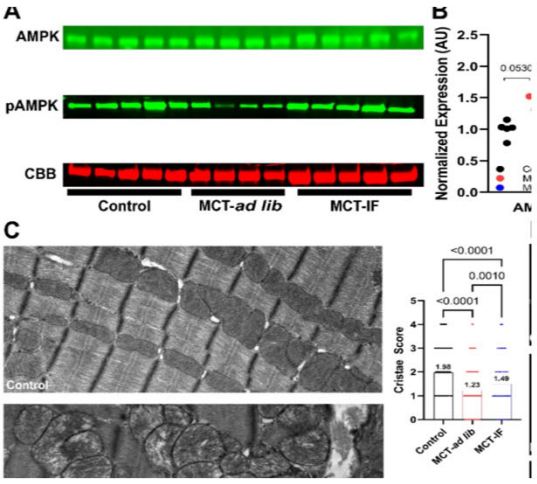
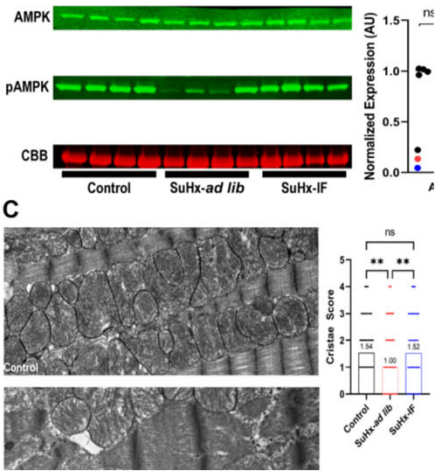
Intermittent Fasting Restores Mitochondrial Cristae Morphology





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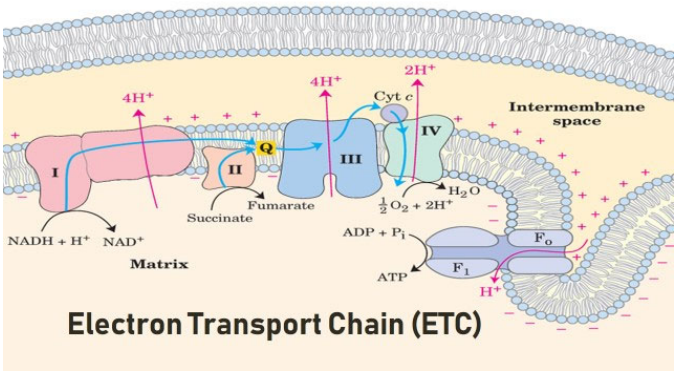
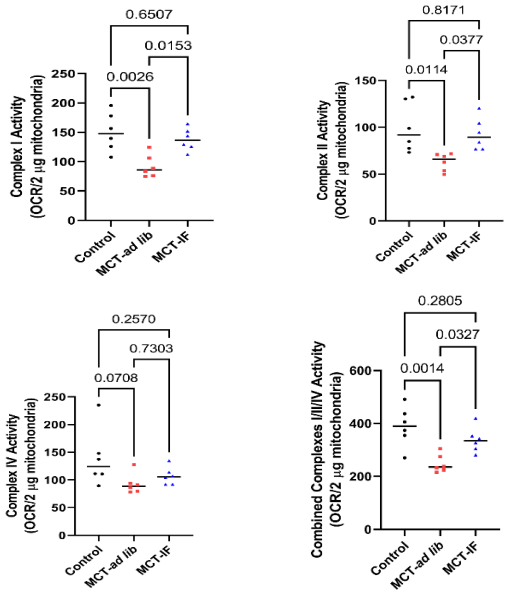
Intermittent Fasting Enhances ETC Activity





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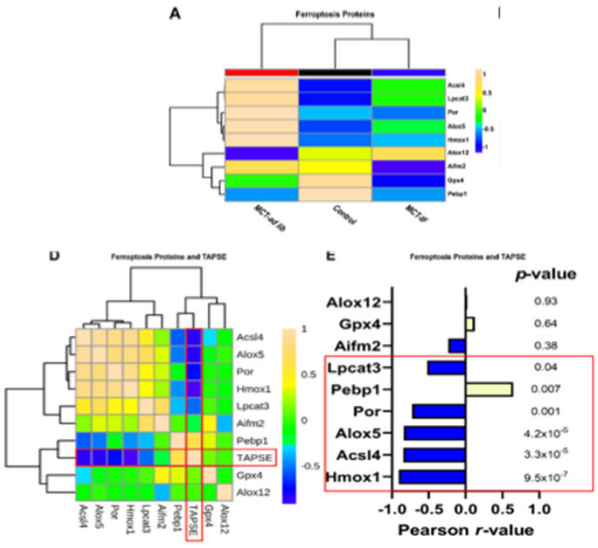
Intermittent Fasting Mitigates Ferroptosis



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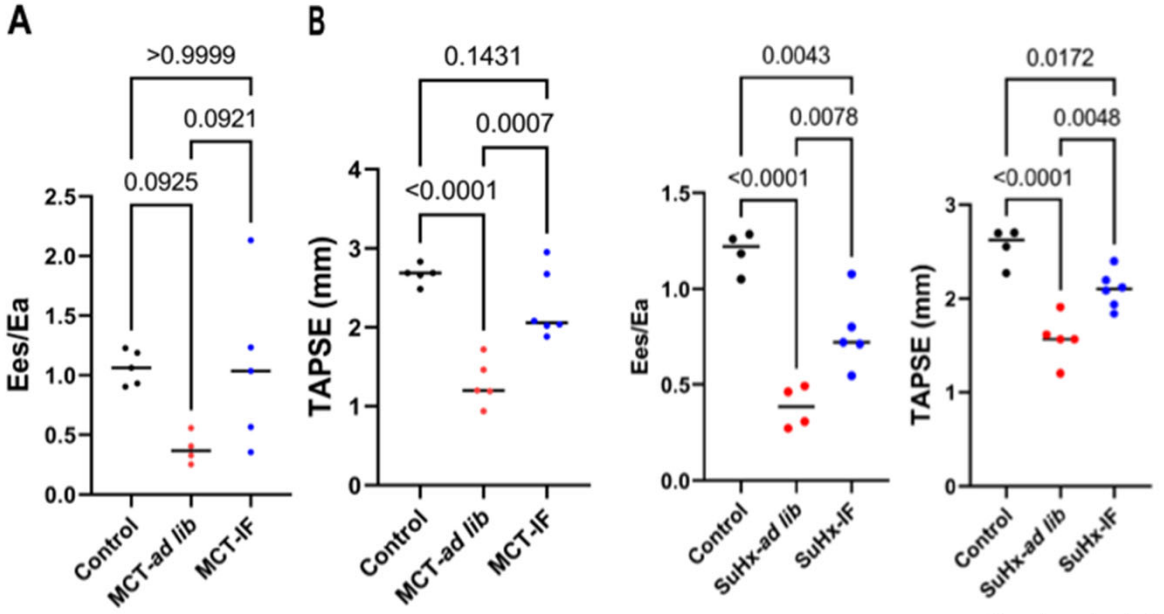
Intermittent Fasting Prevents RVD



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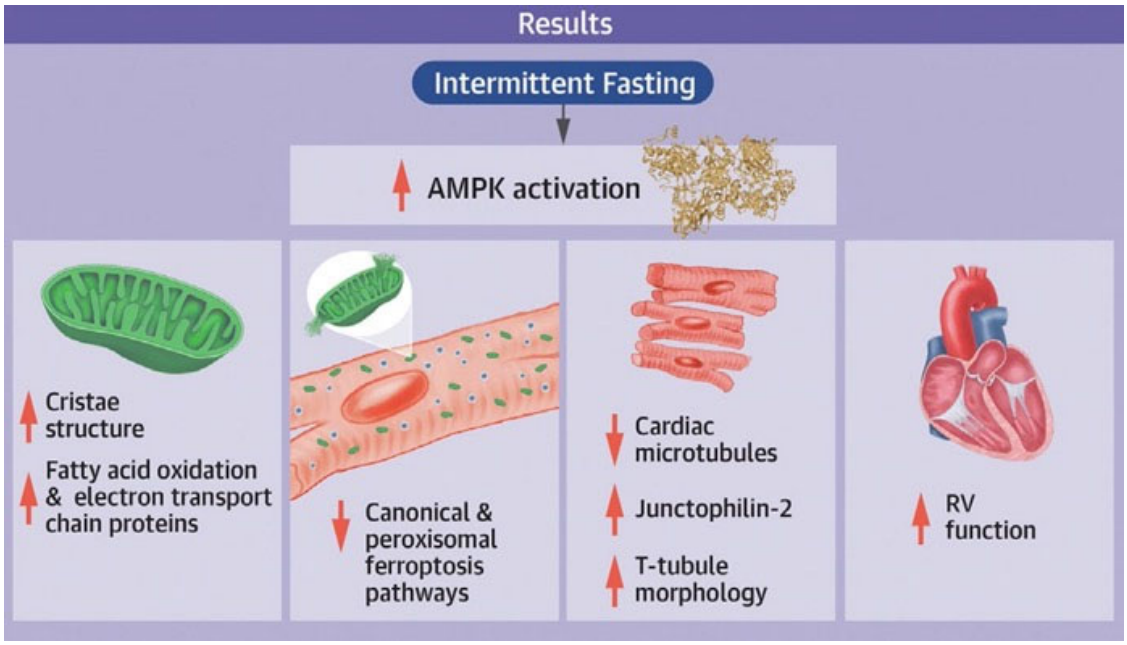
Summary



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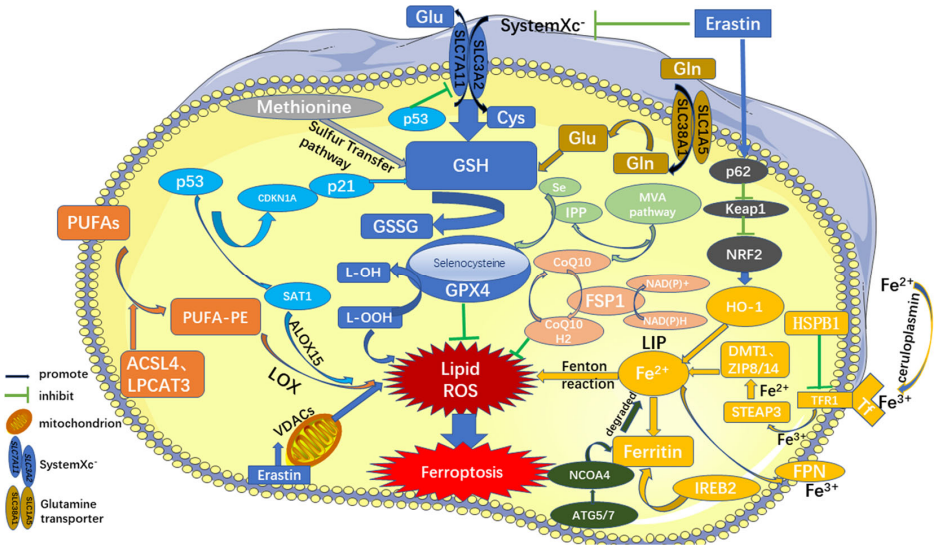
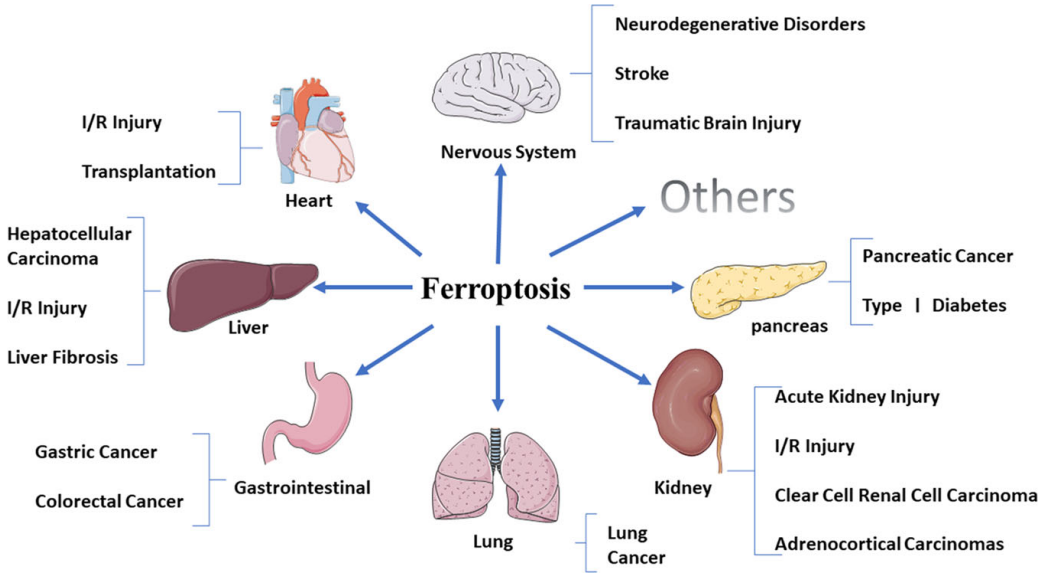
Ferroptosis



Li *et al.* Nature Cell Death & Disease 2020

25

Ferroptosis



Li *et al.* Nature Cell Death & Disease 2020

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Circulation Research

ORIGINAL RESEARCH

Ferroptosis-Mediated Inflammation Promotes Pulmonary Hypertension

Felipe Kazmirczak,* Neal T. Vogel,* Sasha Z. Prisco,* Michael T. Patterson, Jeffrey Annis, Ryan T. Moon, Lynn M. Hartweck, Jenna B. Mendelson, Minwoo Kim, Natalia Calixto Mancipe, Todd Markowski, LeeAnn Higgins, Candace Guerrero, Ben Kremer, Madelyn L. Blake, Christopher J. Rhodes, Jesse W. Williams, Evan L. Brittain, Kurt W. Prins

Kazmirczak *et al* Circulation Res

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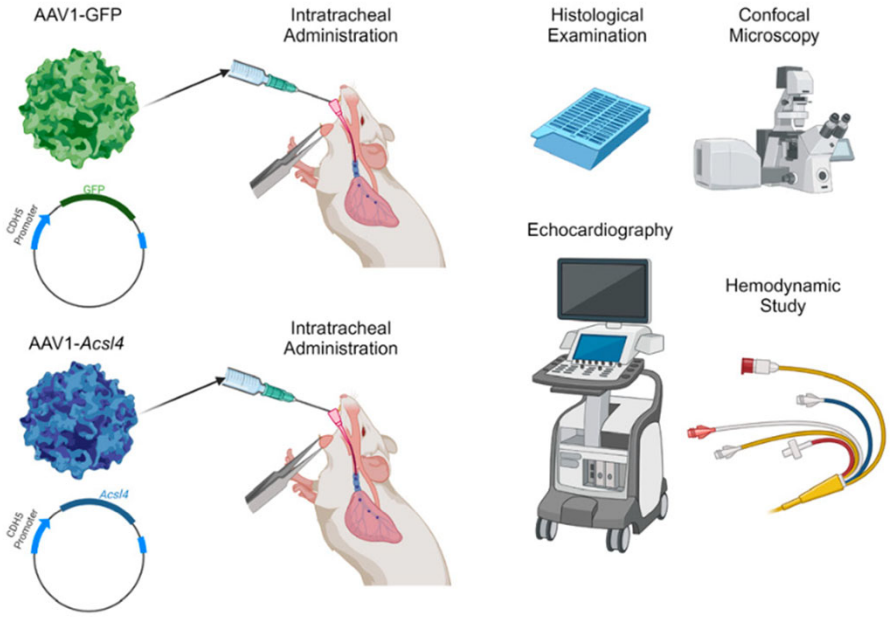
Methods



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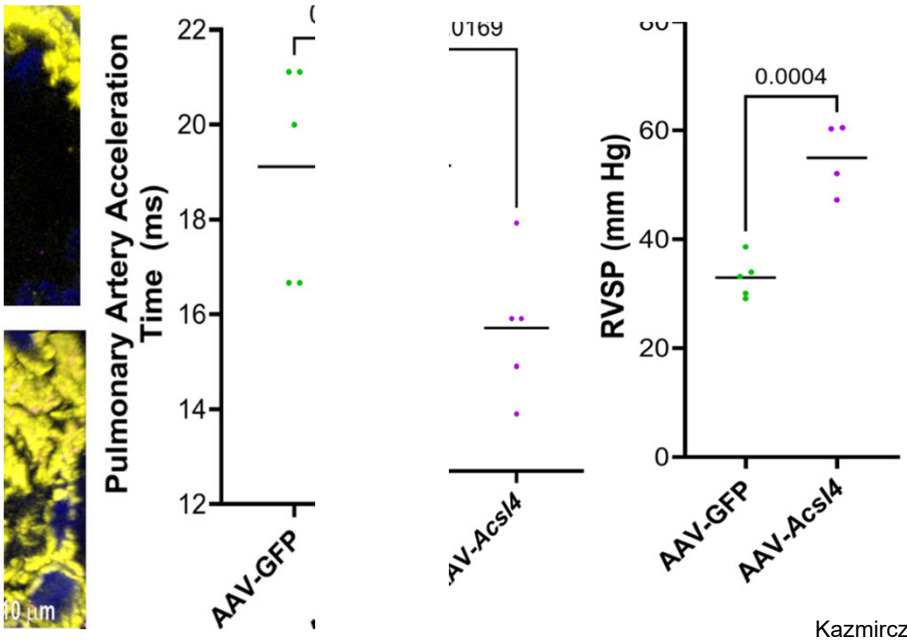
Complement Deposit with Ferroptosis



Kazmirczak *et al* Circulation Res

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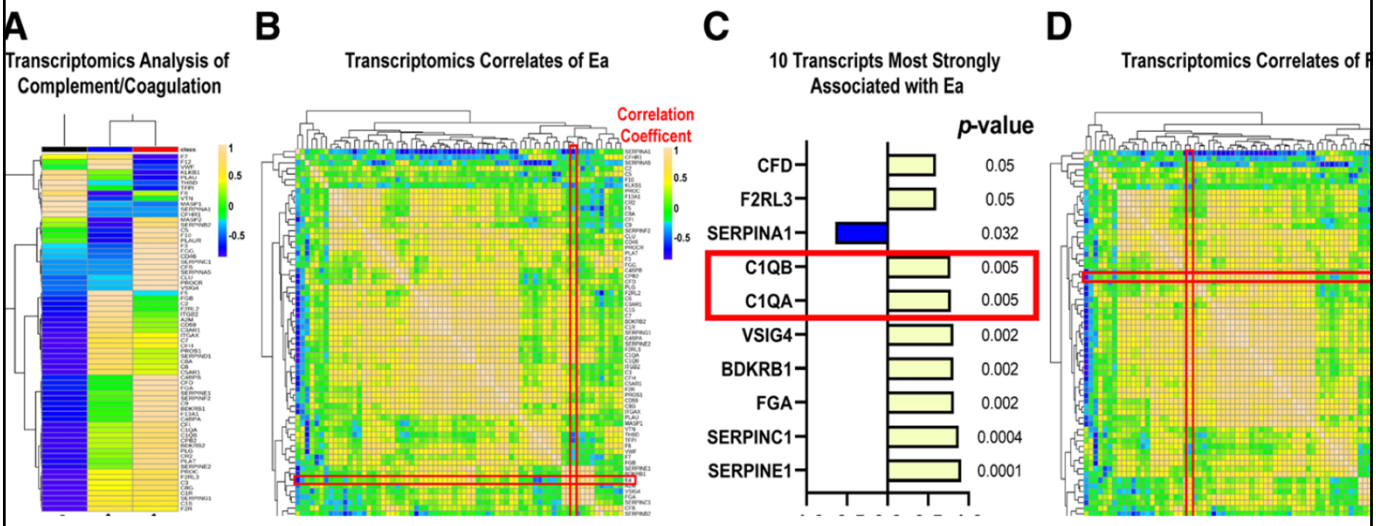
Inhibition of Ferroptosis



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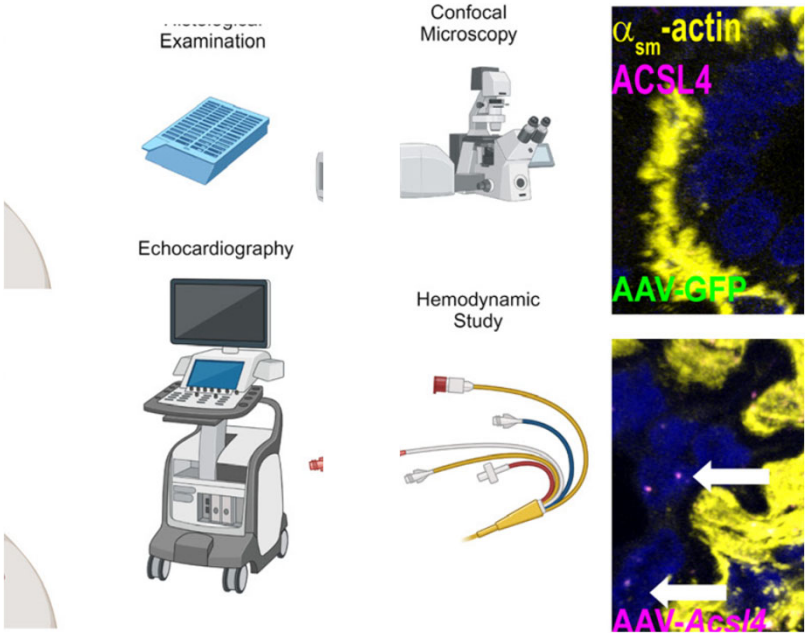
Medial Thickness with Ferroptosis



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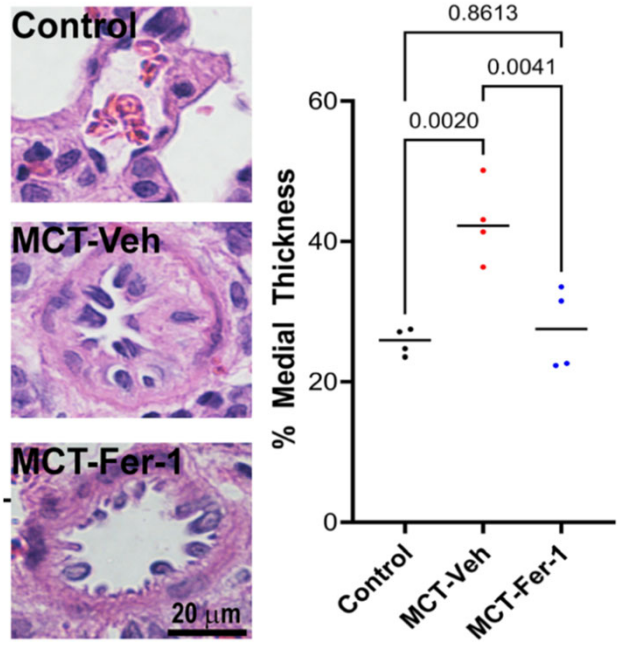
Medial Thickness Ferroptosis inhibition



Kazmirczak *et al* Circulation Res

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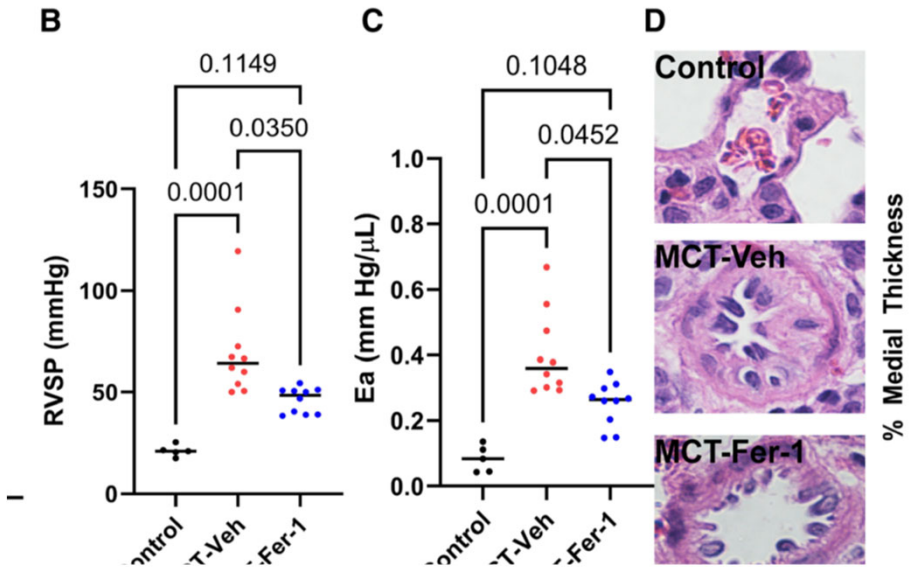
RV function with Fer-1



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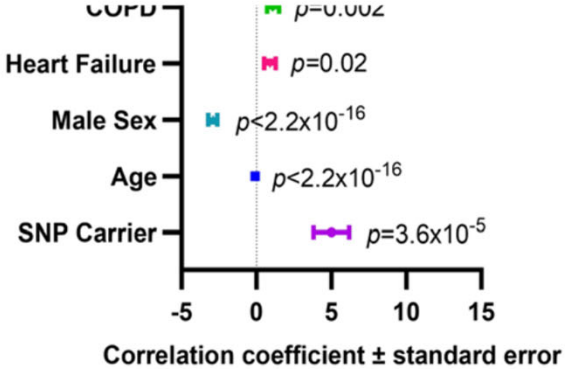
What about humans?



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PVR Multi-Variate Model

VANDERBILT UNIVERSITY
MEDICAL CENTER
Department of Medicine

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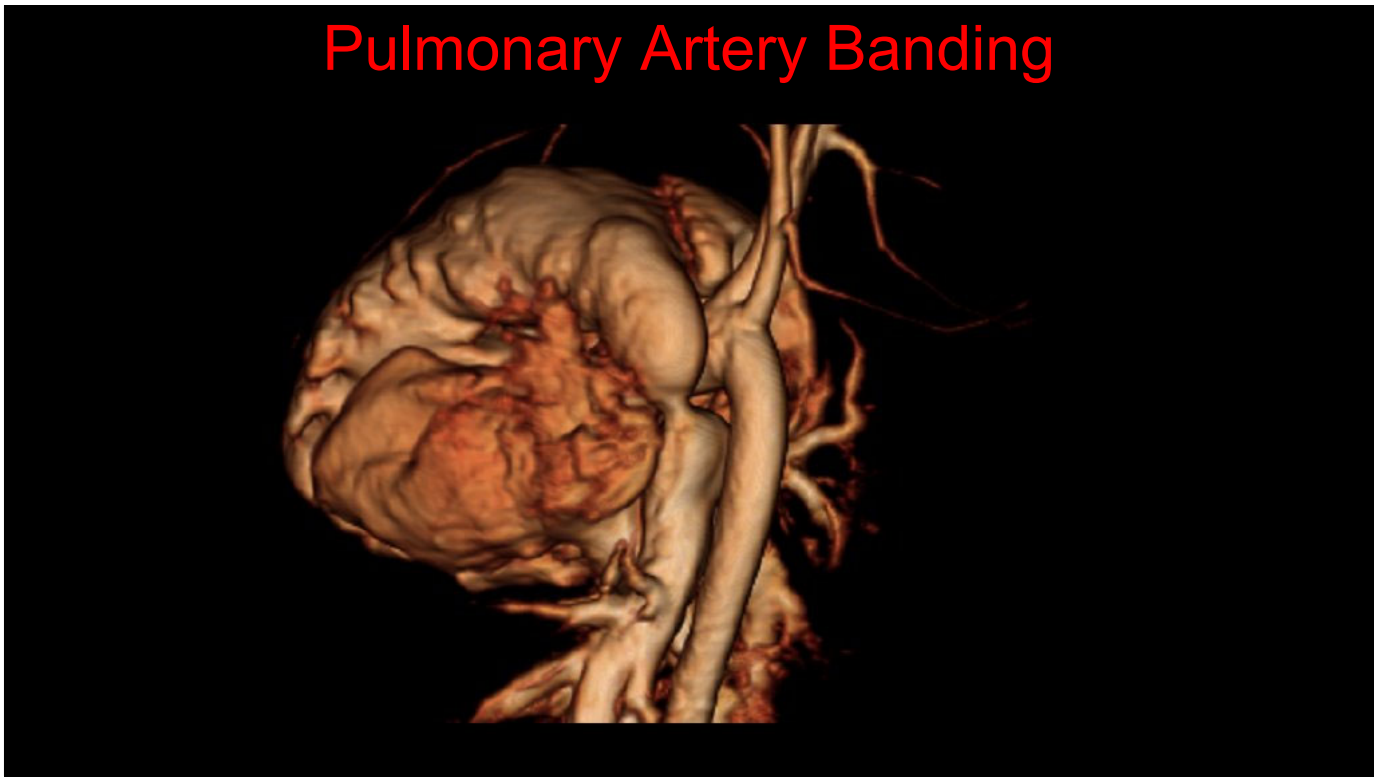

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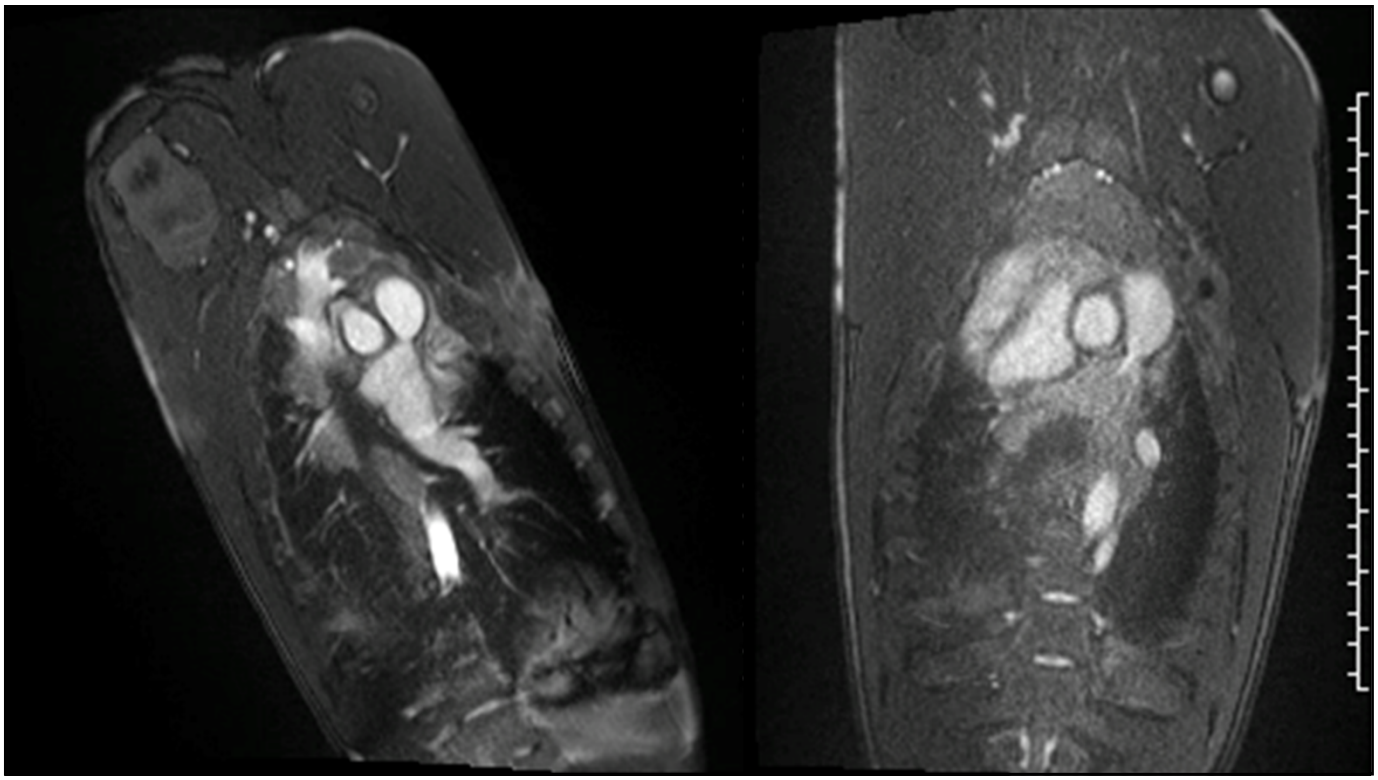

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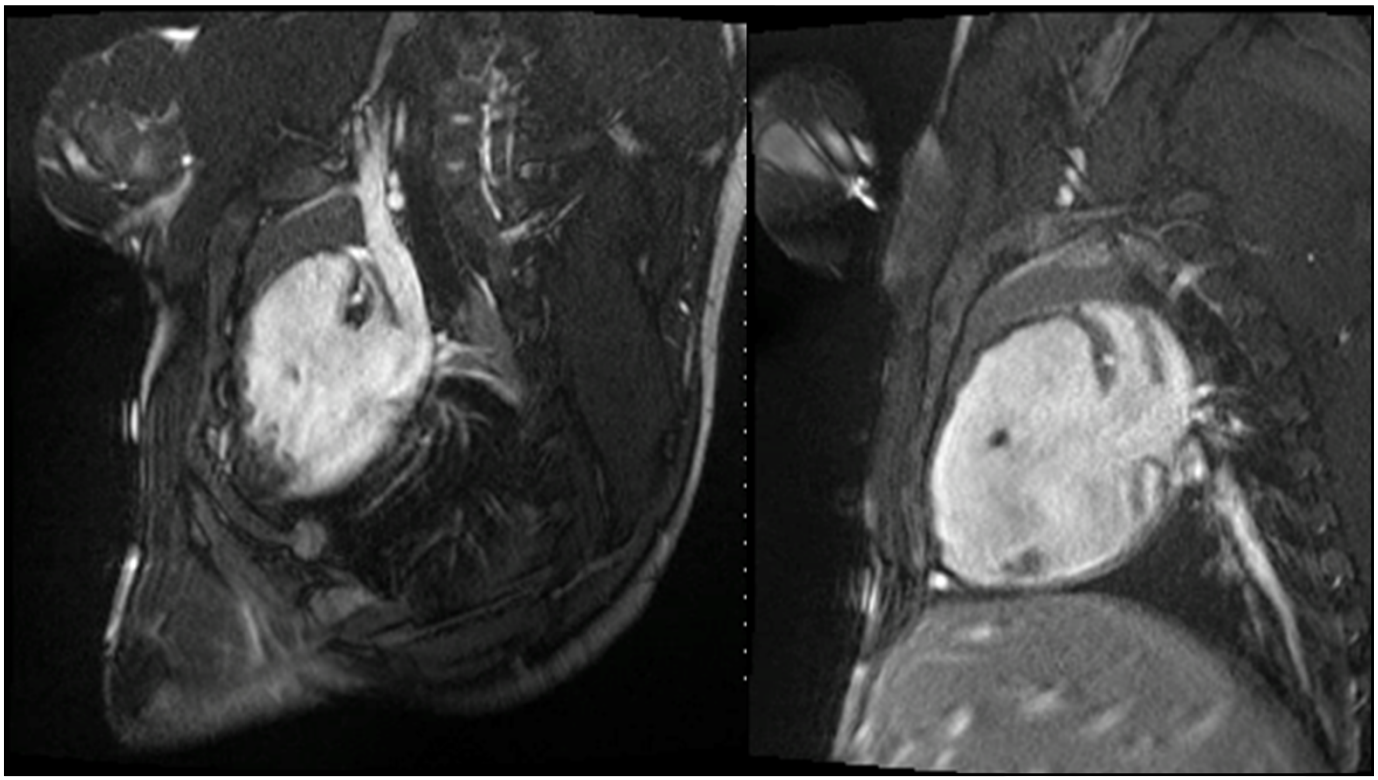

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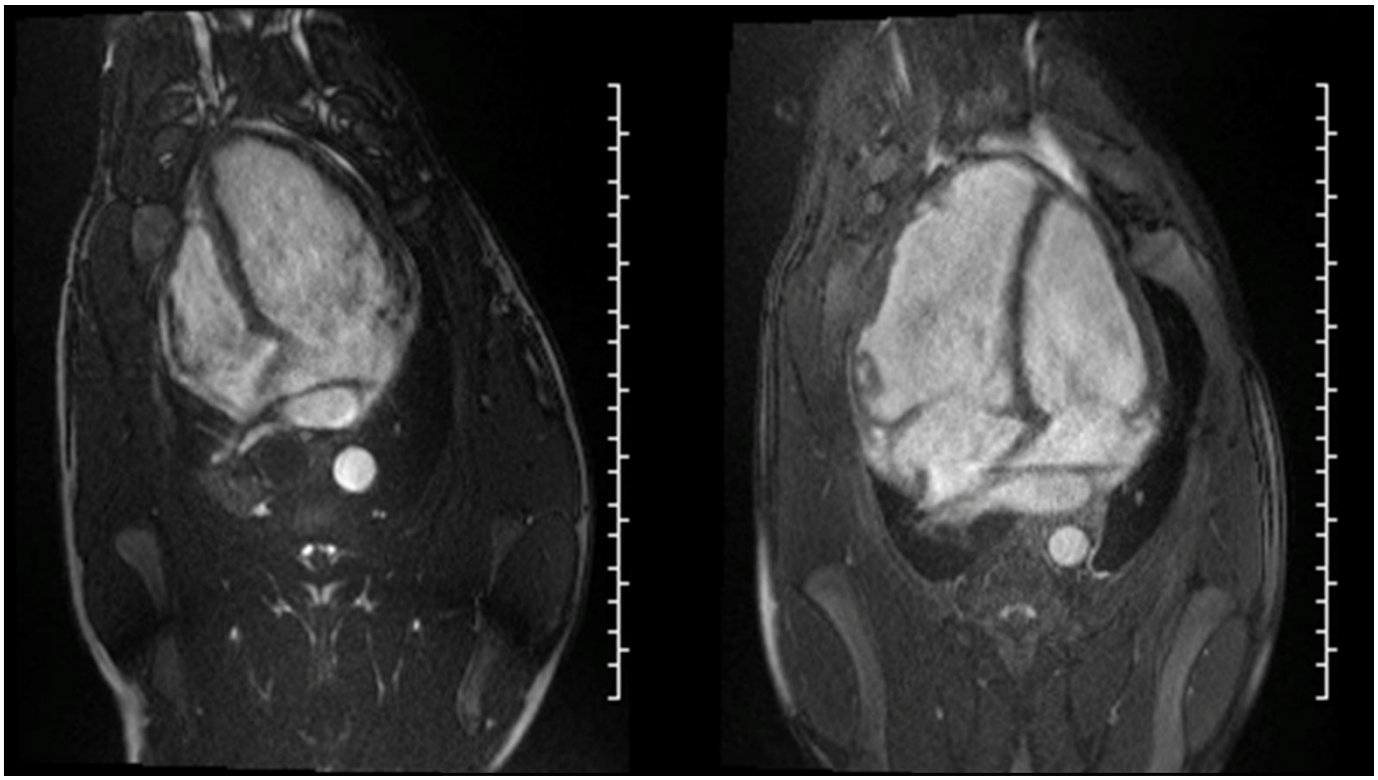

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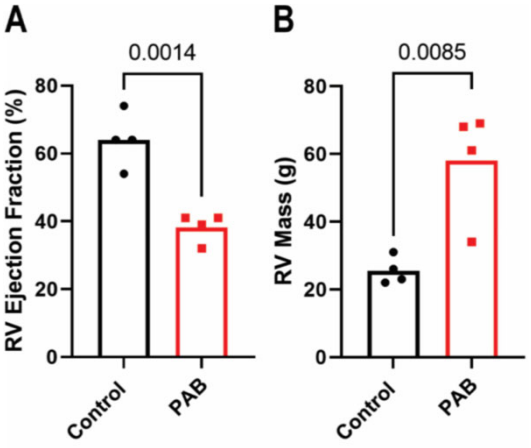
The Journal of Heart and Lung Transplantation
Volume 43, Issue 2, February 2024, Pages 303-313

Original Translational Science

Multi-omic and multispecies analysis of right ventricular dysfunction



Prins *et al* JHLT

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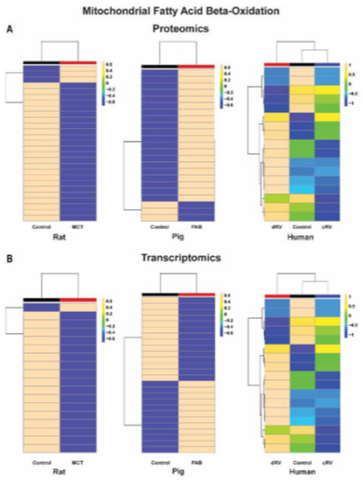
The Journal of Heart and Lung Transplantation
Volume 43, Issue 2, February 2024, Pages 303-313

Original Translational Science

Multi-omic and multispecies analysis of right ventricular dysfunction



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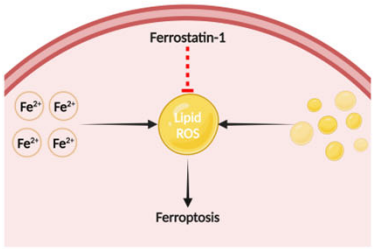
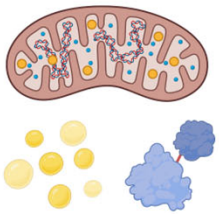
Targeted Therapy for RV Failure

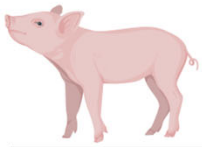
Specific Aim 1: Ferroptosis Inhibition on RV Function

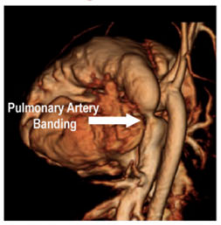


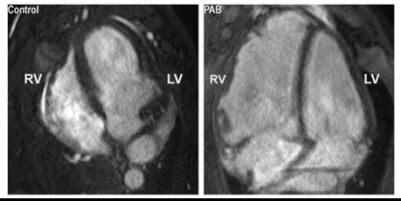
Specific Aim 2: Molecular Effects of Ferroptosis Inhibition



Large Animal Model

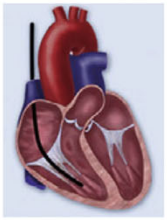






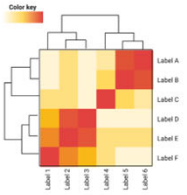
CMR

PV Loops



Electron Microscopy

Lipidomics
Metabolomics
Proteomics



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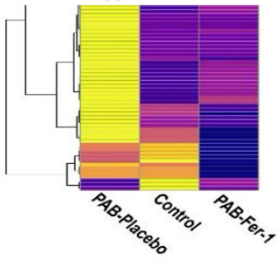
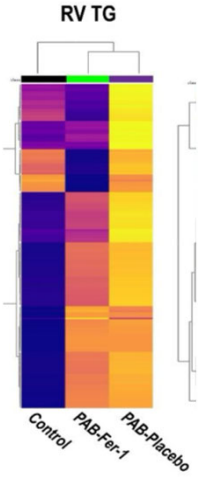
American Journal of Respiratory and Critical Care Medicine

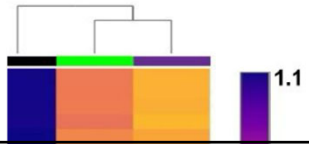
Ferroptosis Inhibition Combats Metabolic Derangements and Improves Cardiac Function in Pulmonary Artery Banded Pigs

Felipe Kazmirczak , Ryan Moon , Neal T. Vogel , Walt Tollison , Matt T. Lahti , John P. Carney , Jenna B. Mendelson , Todd Markowski , LeeAnn Higgins , Kevin Murray , Candace Guerrero , and Kurt W Prins ... Show less





V Acylcarnitine



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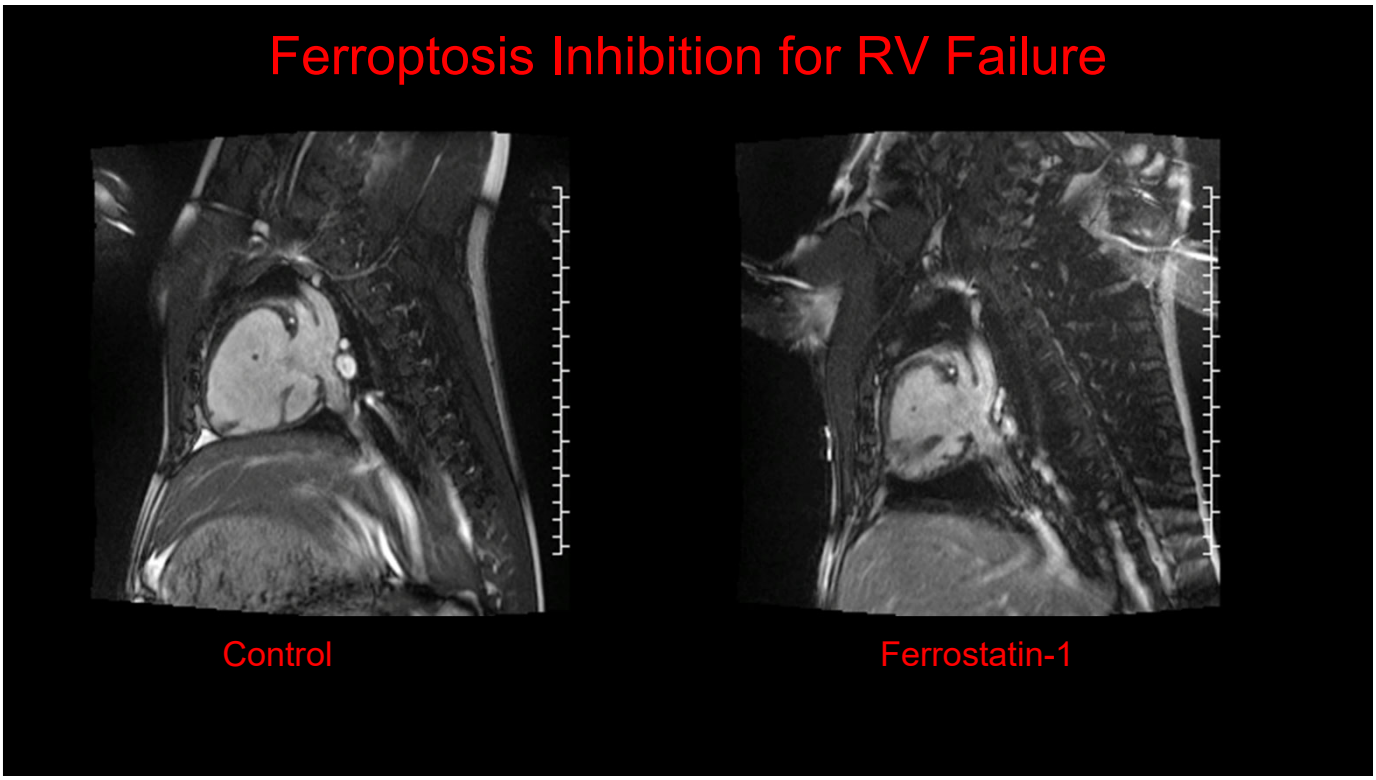
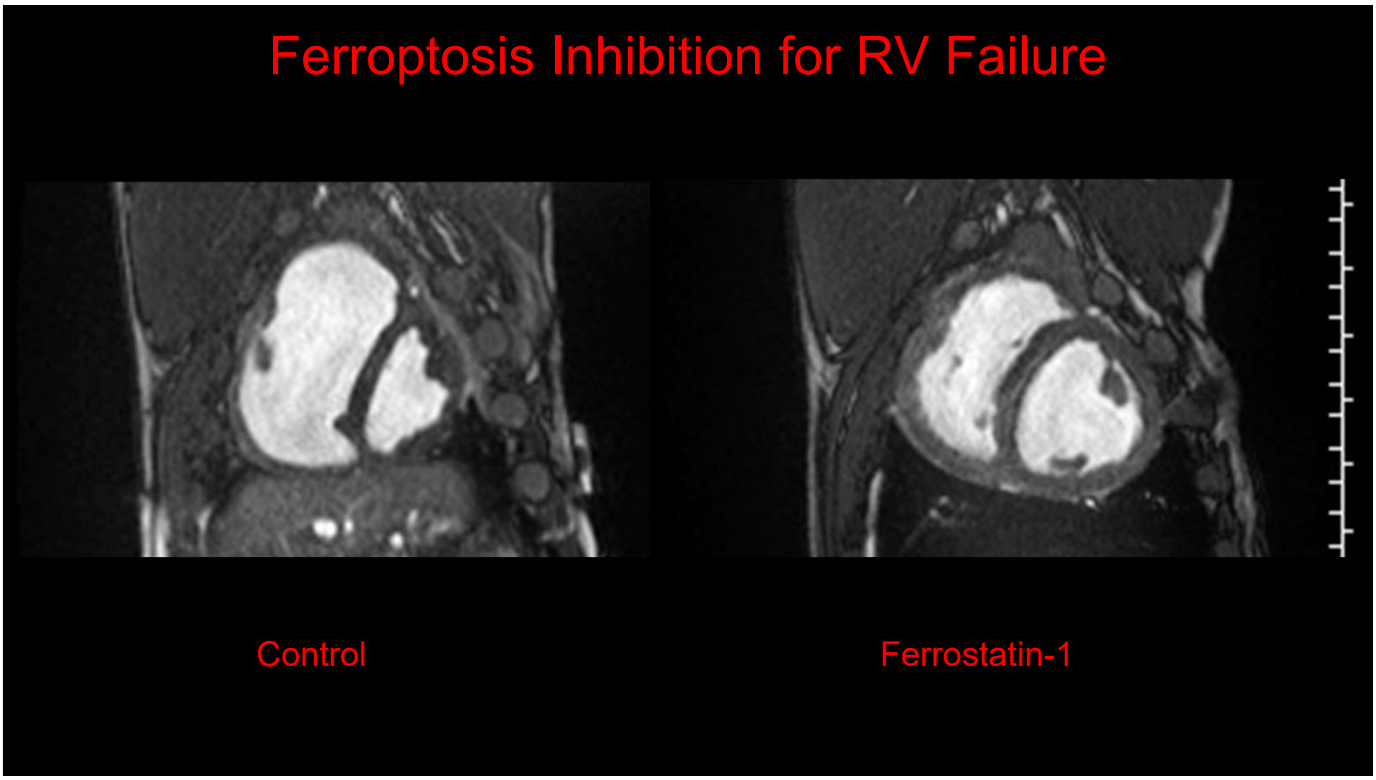

Ferroptosis Inhibition for RV Failure
Control
Ferrostatin-1

43


Ferroptosis Inhibition for RV Failure
Control
Ferrostatin-1

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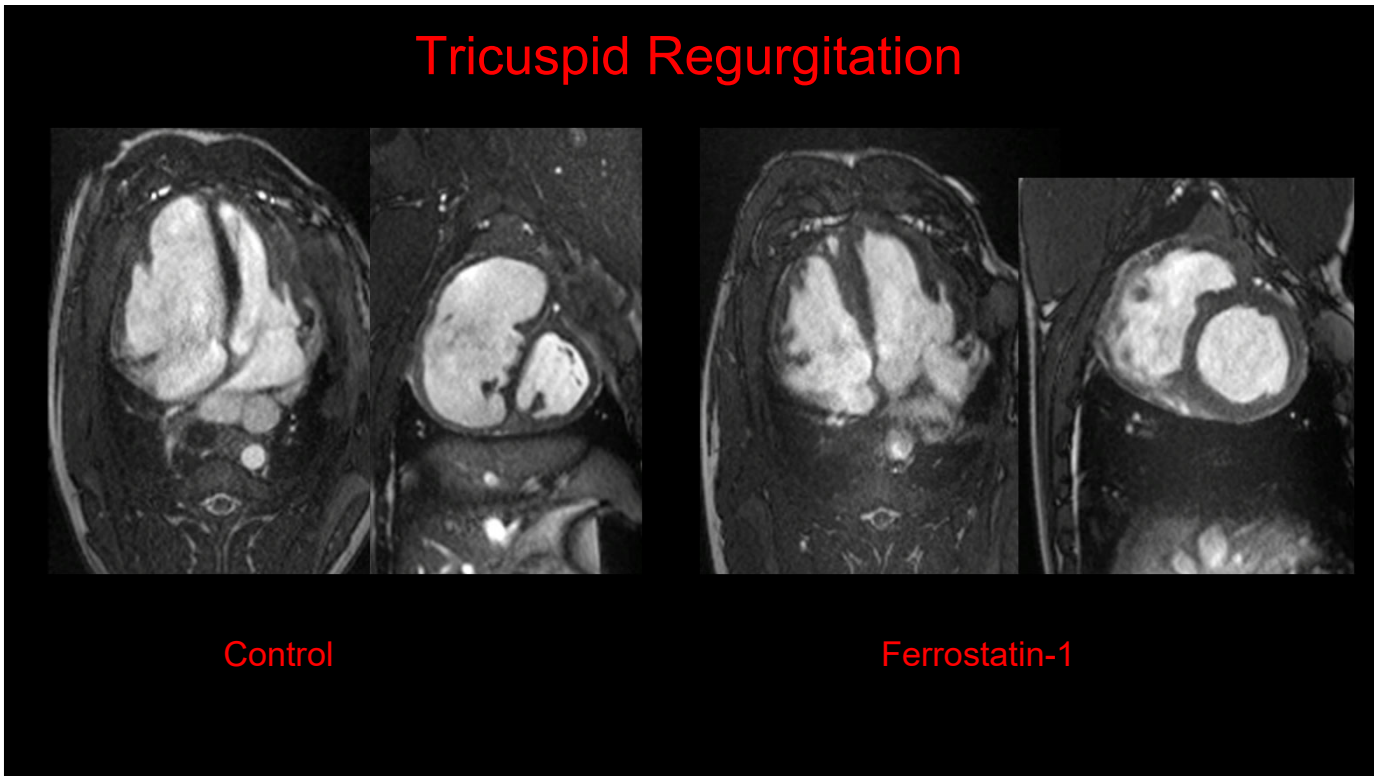
Tricuspid Regurgitation
Control
Ferrostatin-1

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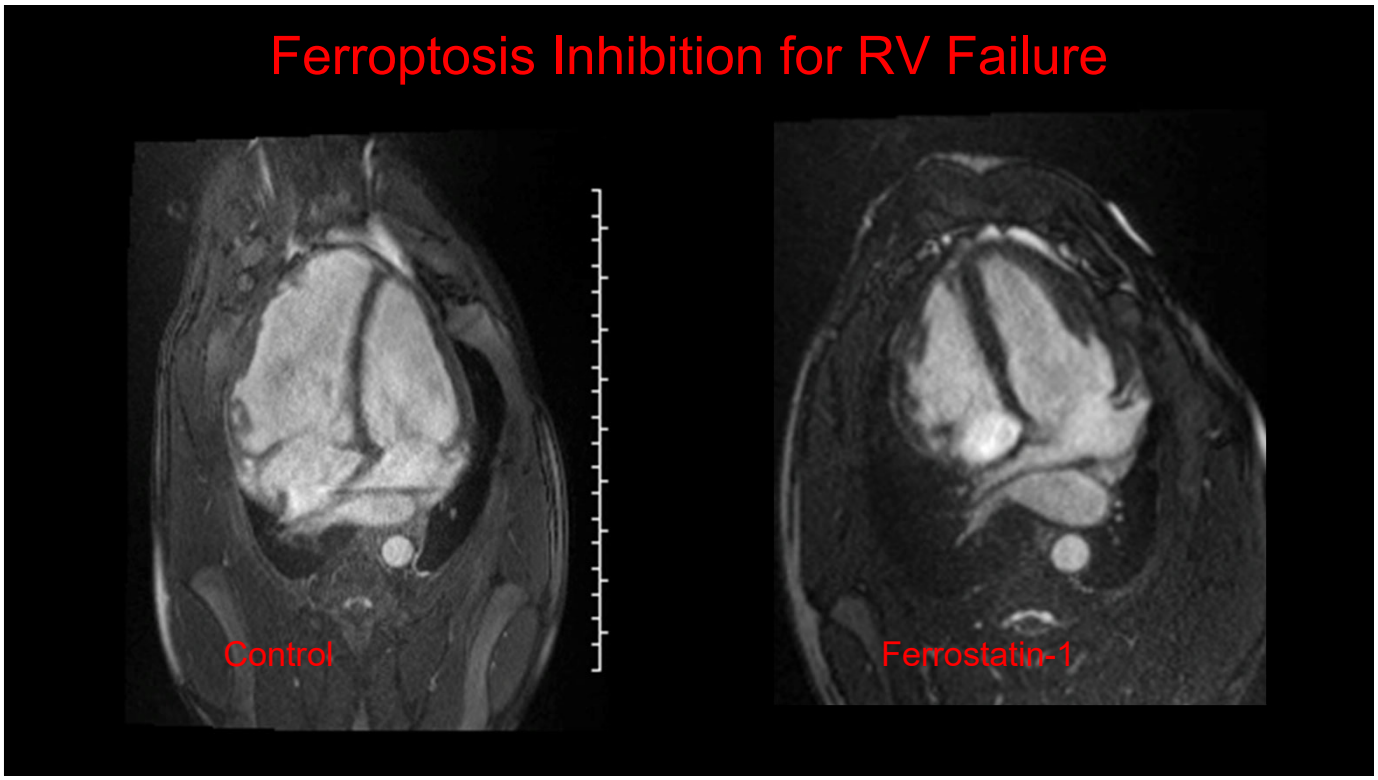
Ferroptosis Inhibition for RV Failure
Control
Ferrostatin-1

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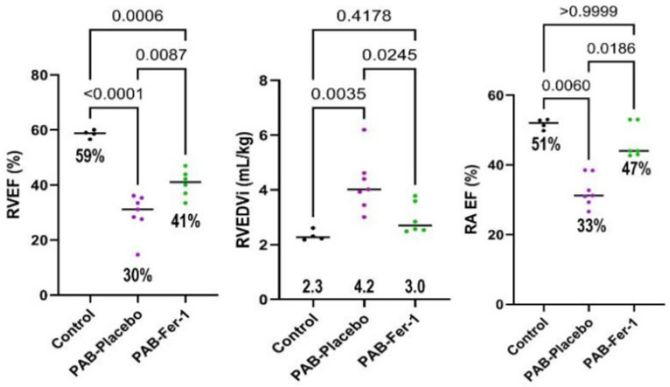
Ferroptosis Inhibition Combats Metabolic Derangements and Improves Cardiac Function in Pulmonary Artery Banded Pigs

Felipe Kazmirczak , Ryan Moon , Neal T. Vogel , Walt Tollison , Matt T. Lahti , John P. Carney , Jenna B. Mendelson , Todd Markowski , LeeAnn Higgins , Kevin Murray , Candace Guerrero , and Kurt W Prins ... Show less



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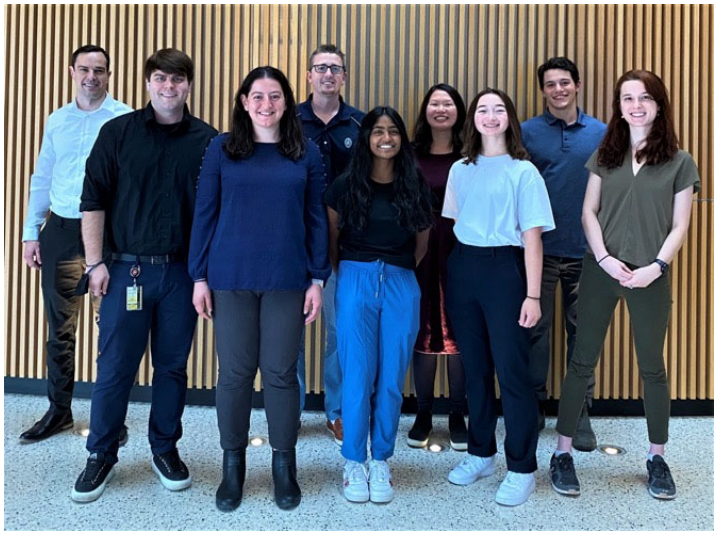
Acknowledgment



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