

Feeding the Failing Heart

Dan Kelly



Disclosures

Scientific Advisory Boards/Consultant:

- Pfizer
- Amgen
- GSK
- BMS

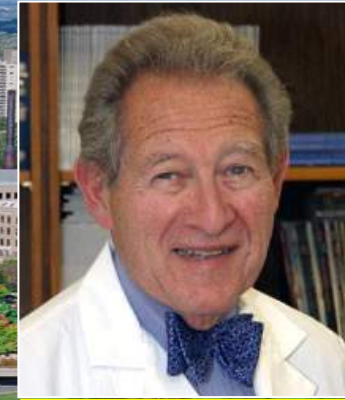
Research Support:

- Amgen
- Pfizer

The Peds-Medicine Connection at Washington University School of Medicine



Arnold Strauss



David Kipnis



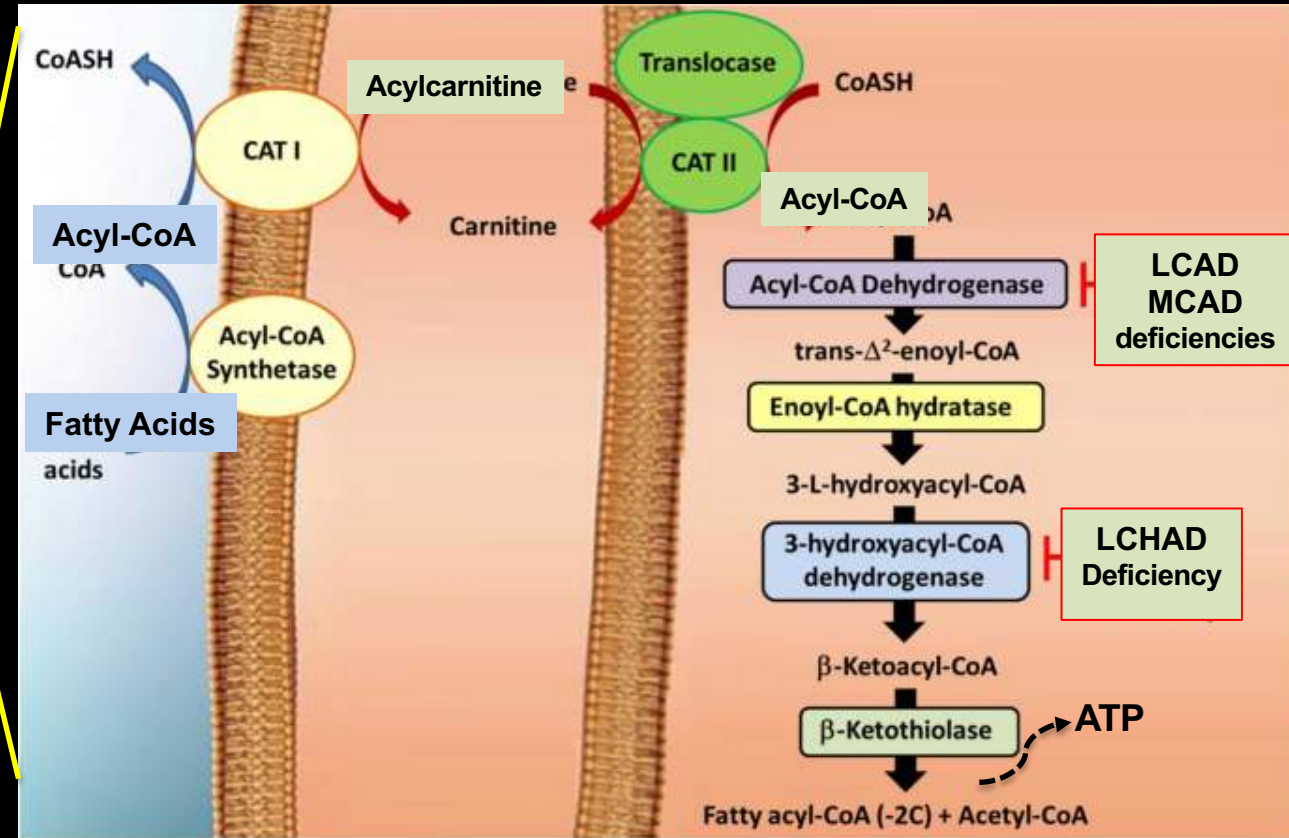
Jeffrey Gordon



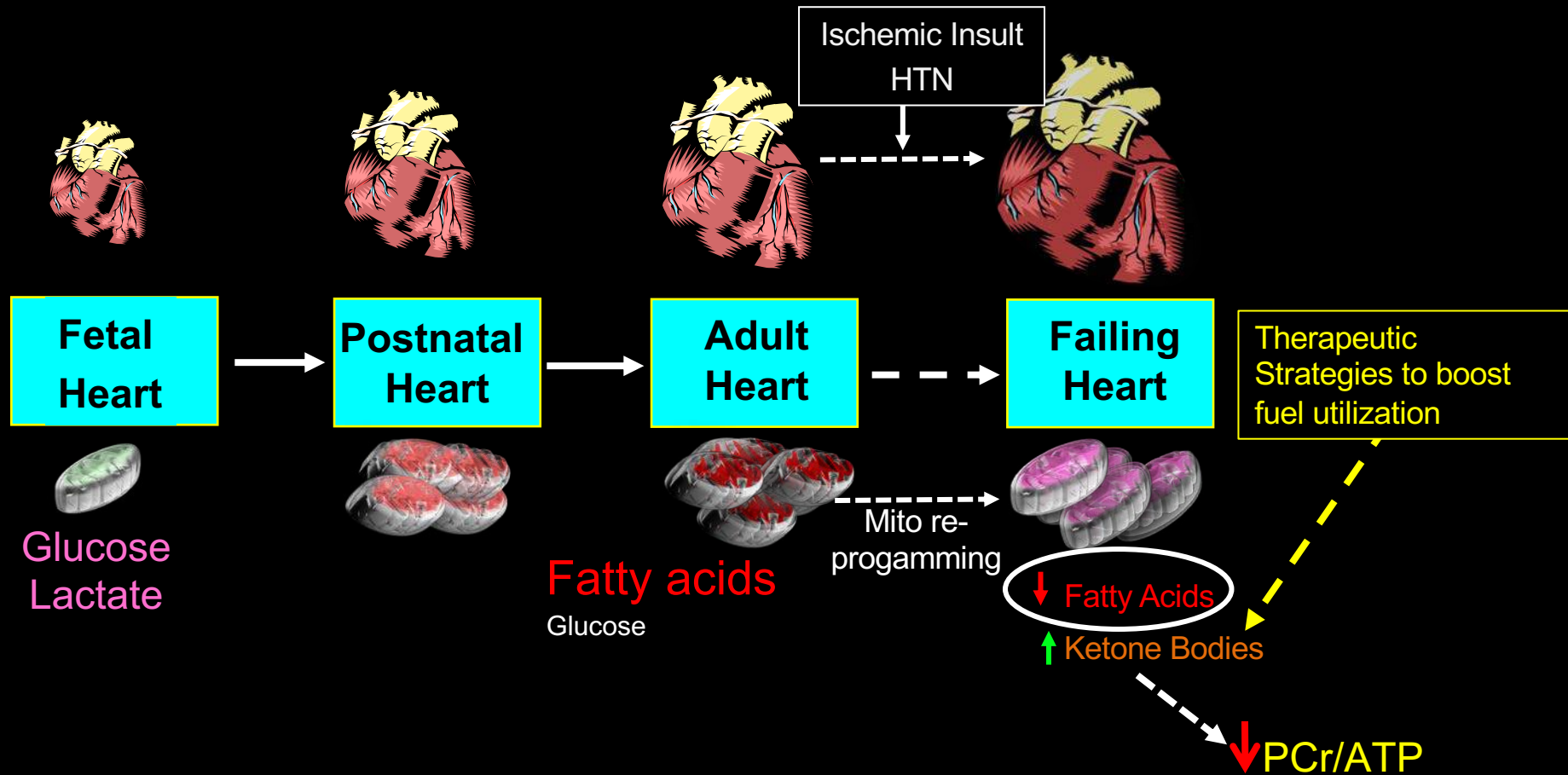
Burton Sobel

Clinical Manifestations of Inborn Errors in Mitochondrial Fatty Acid Oxidation (FAO)

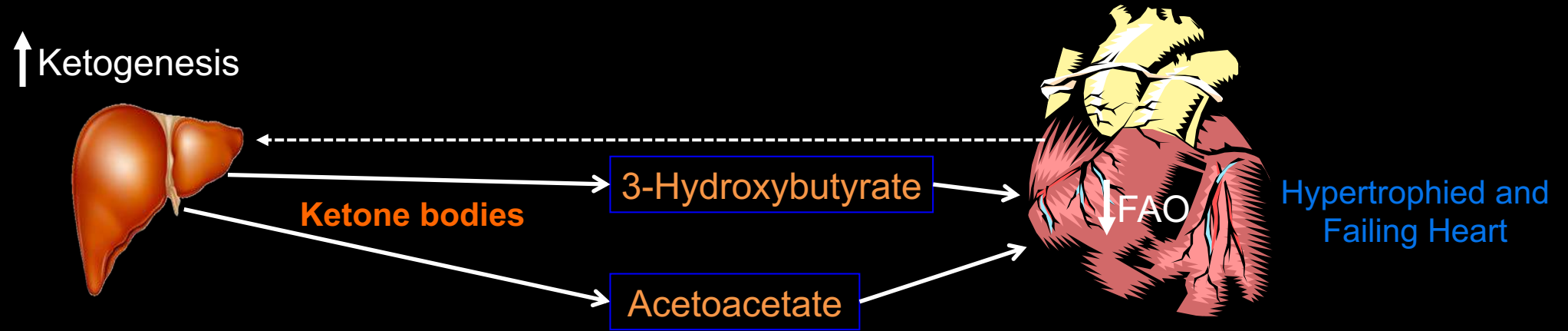
- Hypoketotic hypoglycemia
- Toddler sudden death
- **Cardiomyopathy**
- **Skeletal myopathy**
- Liver and heart lipid accumulation



Fuel Metabolic Re-programming in Acquired Forms of Heart Failure: Lessons from Genetic Cardiomyopathies

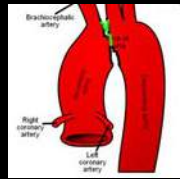


The Failing Heart Utilizes Ketone Bodies: Provision of an Ancillary Fuel in the Context of Reduced Fatty Acid Oxidation

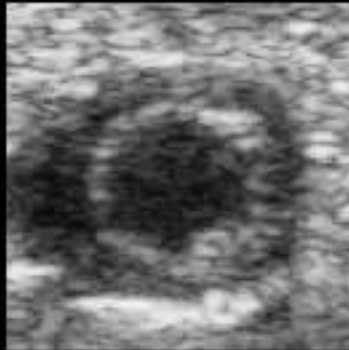


- The failing heart increases utilization of ketone bodies (Aubert et al; Bedi et al, *Circulation*. 2016; *Nature Rev. Cardiol*. 2016).
- Disabling cardiac ketone oxidation in mice worsens HFrEF (Horton et al, *JCI Insight*, 2019).
- Infusion of 3OHB reverses cardiac dysfunction and remodeling in canine tachypacing model of HFrEF (Horton et al, *JCI Insight*, 2019).
- Oral ketone esters are effective as both preventive and treatment strategies in mouse and rat models of HFrEF (Yurista et al, *Circ. HF*, 2021).

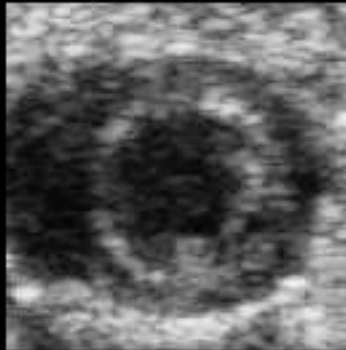
Ketone ester Supplementation Protects Against Pressure Overload-induced Heart Failure in Mice



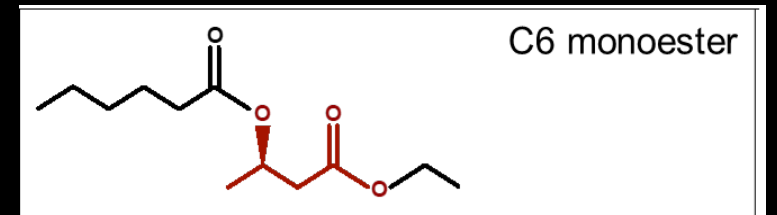
Trans-aortic constriction
(TAC) + MI



Pre-OP



Ketone Ester



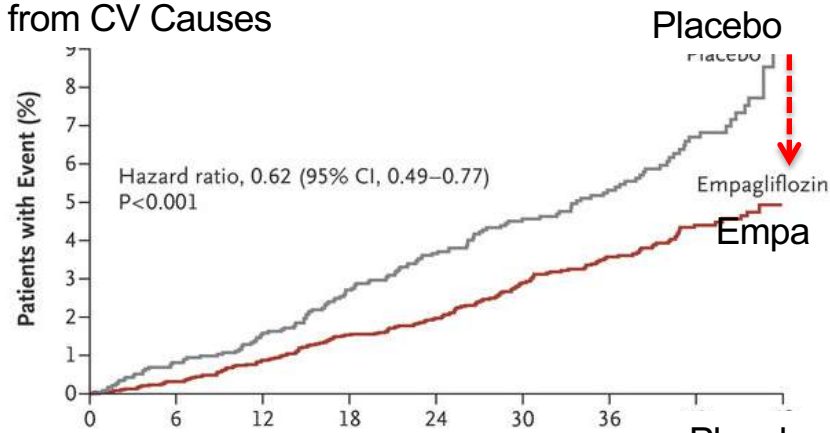
Ketones and Heart Failure -

Relevance to Humans?

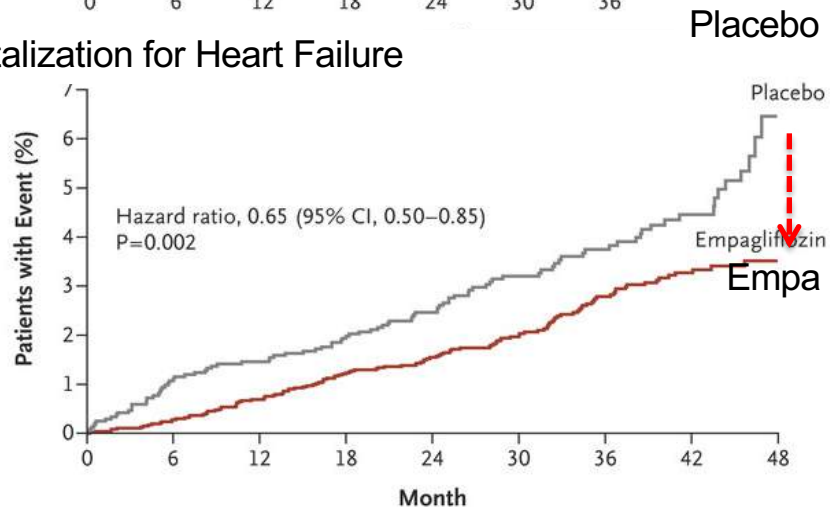
SGLT2 inhibitors are Ketogenic

EMPA-REG TRIAL

Death from CV Causes

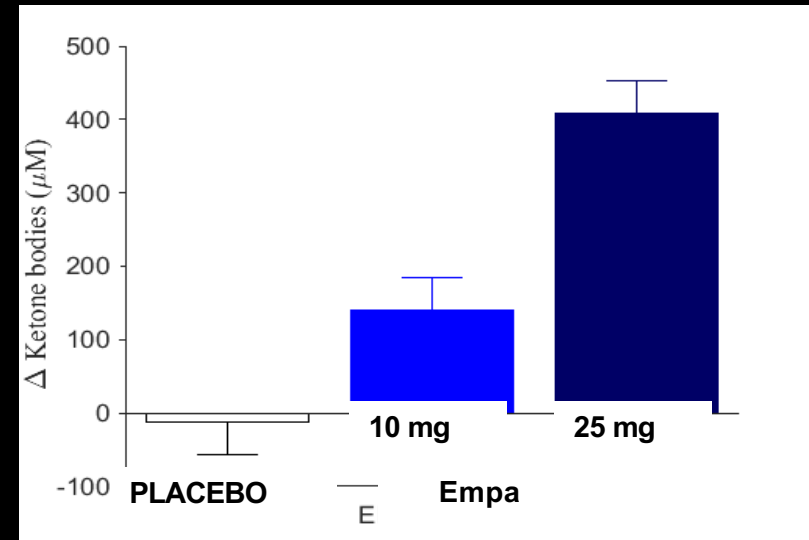


Hospitalization for Heart Failure



N Engl J Med 2015;
373:2117-2128

Serum Ketone Bodies



Dramatic Efficacy of 3OHB Infusion for Acute Heart Failure in Humans

Circulation

ORIGINAL RESEARCH ARTICLE



Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients

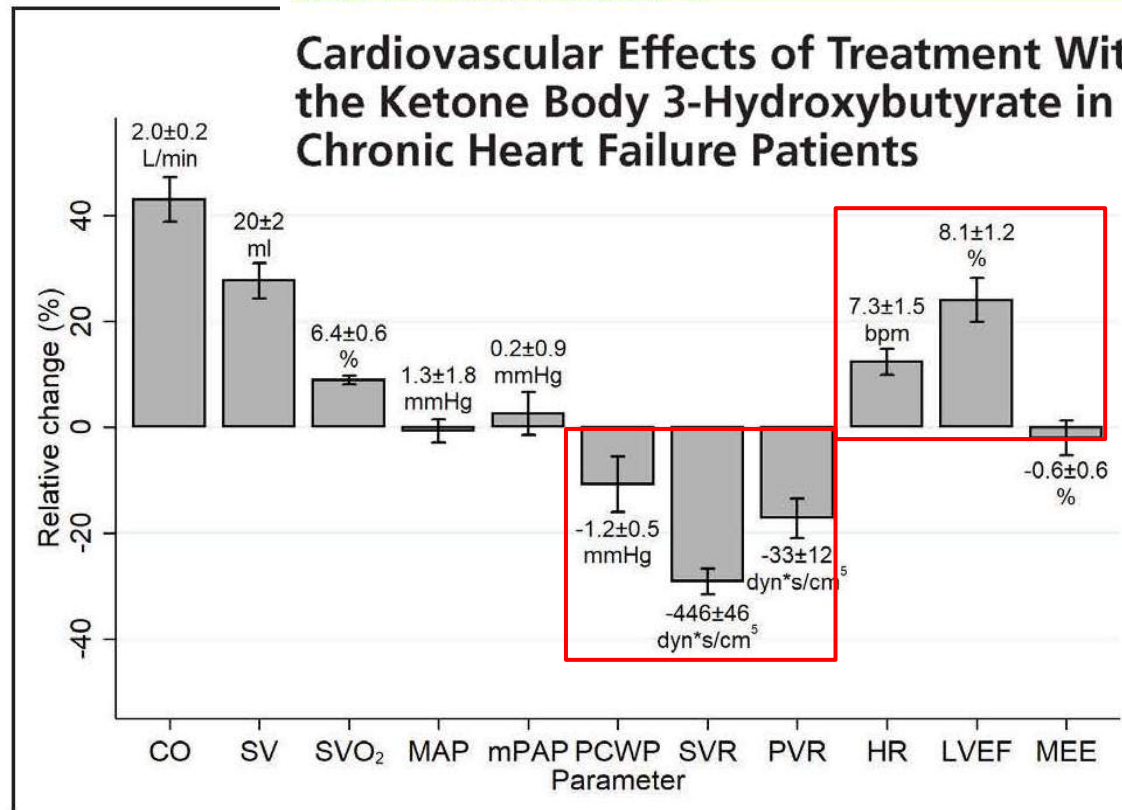
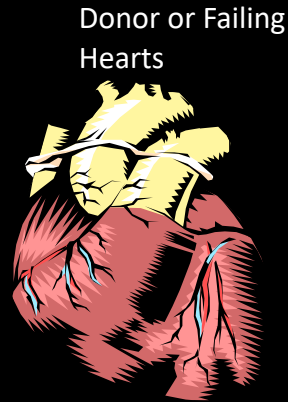


Figure 4. Changes in end point parameters from placebo to 3-OHB infusion.

Mean relative change with SEM and the corresponding mean absolute change ± SEM listed above or below each bar, respectively. Bpm indicates beats per minute; CO, cardiac output; HR, heart rate; LVEF, left ventricular ejection fraction (Study 1, n=16); MAP, mean arterial pressure; MEE, myocardial external efficiency (Studies 3 and 4, n=20); mPAP, mean pulmonary pressure; PVR, pulmonary vascular resistance; SV, stroke volume; SVO₂, mixed venous saturation measured in the pulmonary artery; and SVR, systemic vascular resistance.

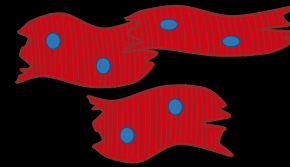
Nielsen, R et al, 2019 *Circulation*

Ketone Bodies Directly Improve Contractility of Cardiomyocytes Isolated from Failing Human Hearts



Myocyte
Isolation

Glucose $\pm$ FFA and BHB



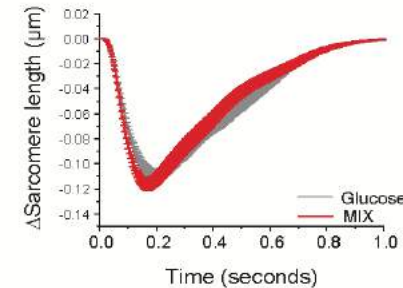
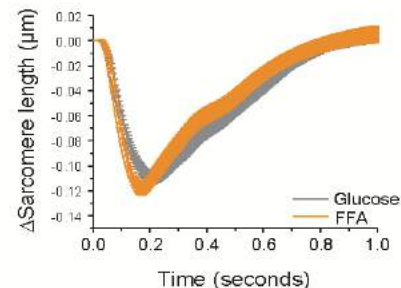
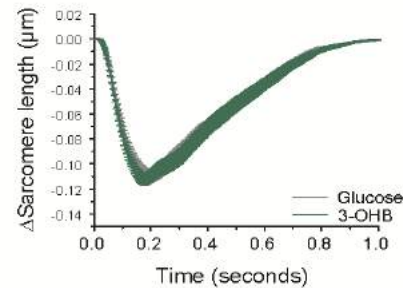
Ken Margulies Lab
(Penn CVI):
Alexia Vite, Ken Bedi

+BHB

+FFA

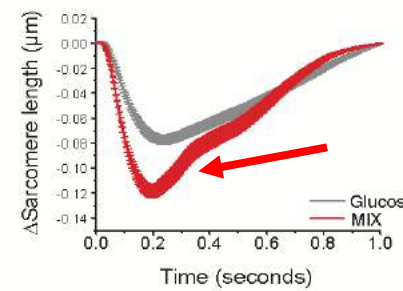
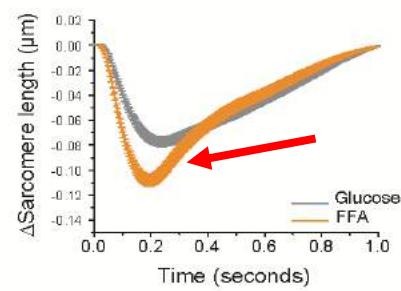
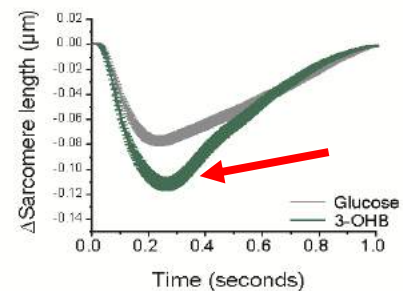
+BHB & FFA

Non-Failing



Non-failing hearts
perform well with
all fuels

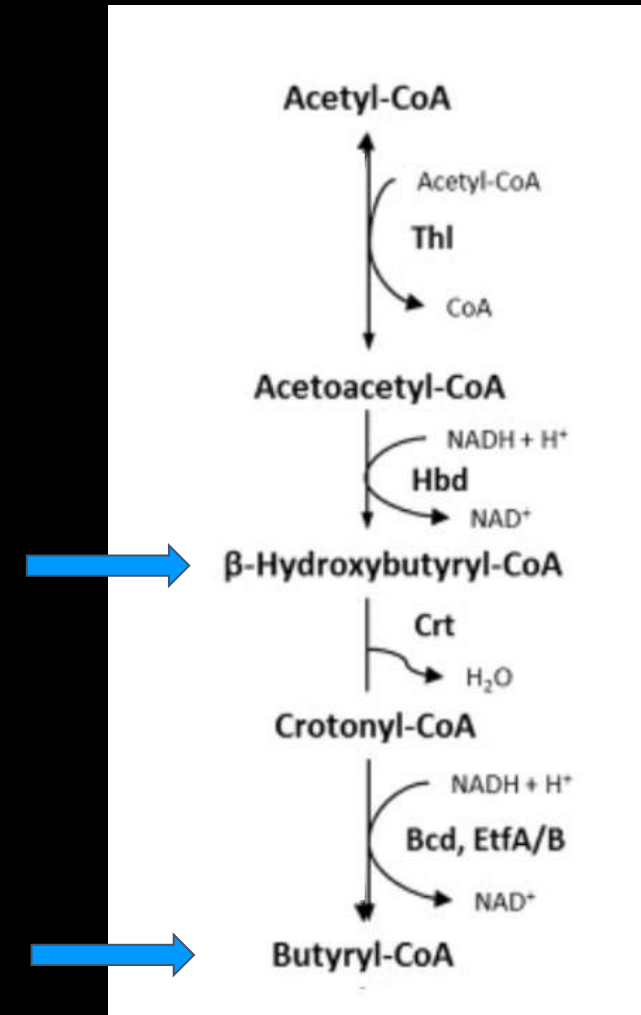
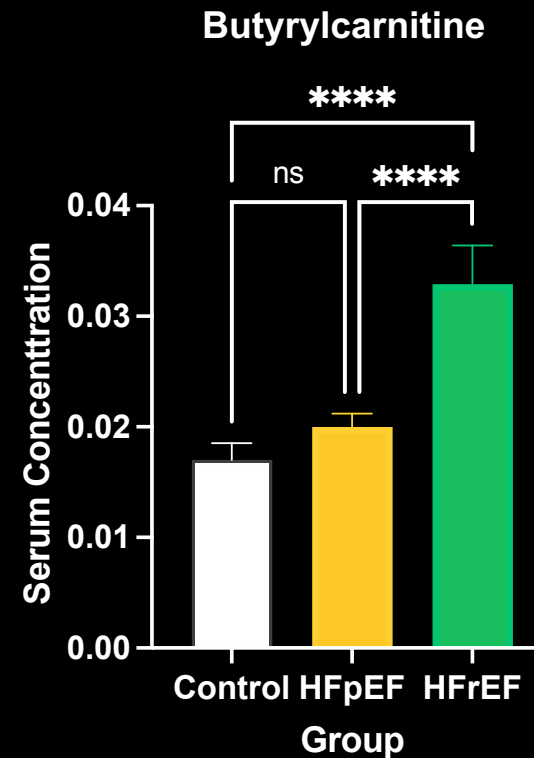
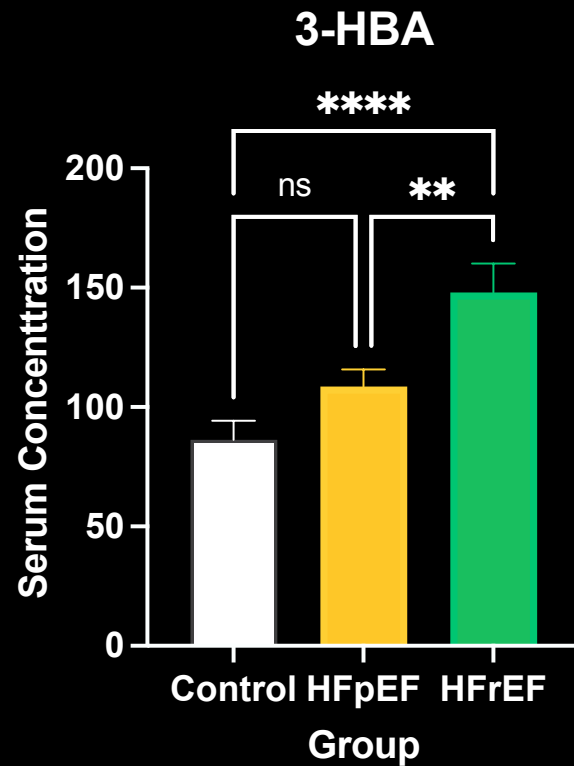
Heart Failure



Ketone bodies or FAs
improve sarcomere
shortening in HF
myocytes

Plasma Ketones as a Heart Failure Biomarker

Penn Medicine Biobank



Re-balancing Cardiac Mitochondrial Fuel Metabolism as an Emerging Therapy for Heart Failure and Muscle Diseases

Ketone Supplementation



First in human ketone ester studies are being launched

Kelly Lab

Greg Aubert

Rick Vega

Teresa Leone

Ling Lai

Fawaz Naeem

Tomoya Sakamoto

Tsunehisa Yamamoto

Richard Madnick

Peihong Ma

Julie Horton

Tim Matsuura

Bee Pruzinsky

Justin Berger

Kirill Batmanov

Mitja Karwowski

Russ Callaway

Renee Taing

Mouse Phenotyping and Metabolomics Cores

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Ingrid Marti-Pamies (Penn,CVI)

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Joe Baur (Penn, IDOM/DRC)

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Debbie Muoio (Duke)

John Newman/Eric Verdin (Buck Institute)

Gary Lopaschuk (U Alberta)

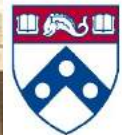
Peter Crawford (U Minn)

Doug Lewandowski (OSU)

Fabio Recchia (Temple)

Dan Rader (Penn)

Pfizer IMRU Group



Perelman
School of Medicine
UNIVERSITY of PENNSYLVANIA



National Institute of
Diabetes and Digestive
and Kidney Diseases



National Heart
Lung and Blood Institute



Children's Hospital
of Philadelphia[®]

RESEARCH INSTITUTE

Cardiovascular Institute



PennCVI
Cardiovascular Institute