Molecular Mechanisms Leading to Diabetic Cardiomyopathy

Gary D. Lopaschuk

Department of Pediatrics
Mazankowski Alberta Heart Institute
University of Alberta

ADA 2023
San Diego
June 26th, 2023

Disclosures

Affiliations I have had with pharmaceutical companies are listed below:

Unrestricted educational grants	Industry sponsored professional presentations	Investigator initiated research	Contract research	Share holdings
Amgen	Boehringer Ingelheim, Amgen, Takeda, Novartis, Servier, REMD, Astra Zeneca Jansen Ultragenyx	MMRL	Sanofi, Amgen, Boehringer Ingelheim, Applied Therapeutics	MMRL

Diabetic Cardiomyopathy

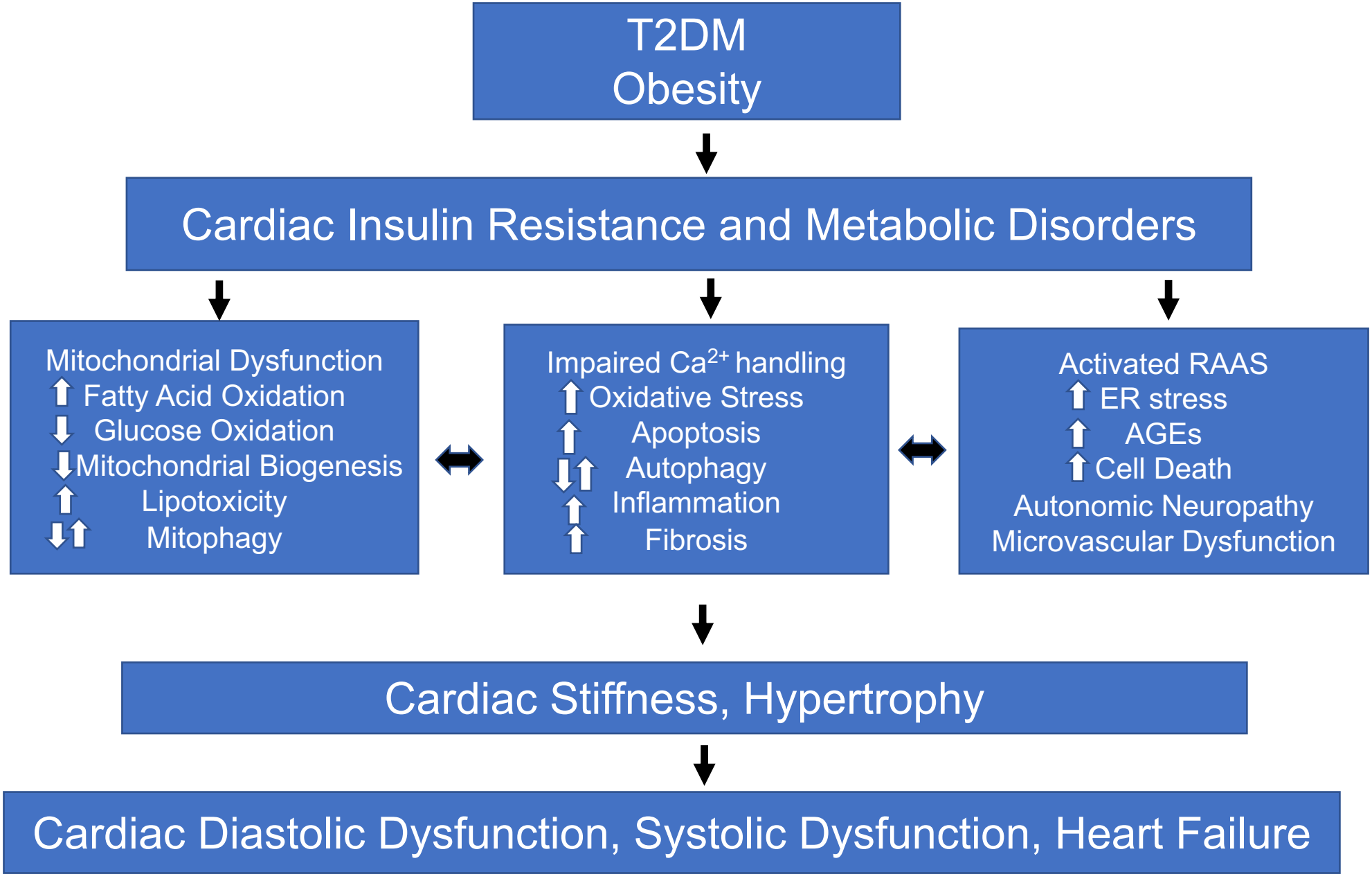
- **Diabetic Cardiomyopathy is defined as the presence of abnormal heart function and structure that can occur independent of risk factors such as coronary artery disease and hypertension.**

- **Heart failure is prevalent in diabetics, ranging from 19-26%.** ***(Ryden L et al, Eur Heart J 2000;21:1967-1978)***

- **The prevalence of diabetic cardiomyopathy is increasing in parallel with the increase in diabetes mellitus incidence.**

- **Diabetic cardiomyopathy is initially characterized by myocardial fibrosis, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical heart failure.**

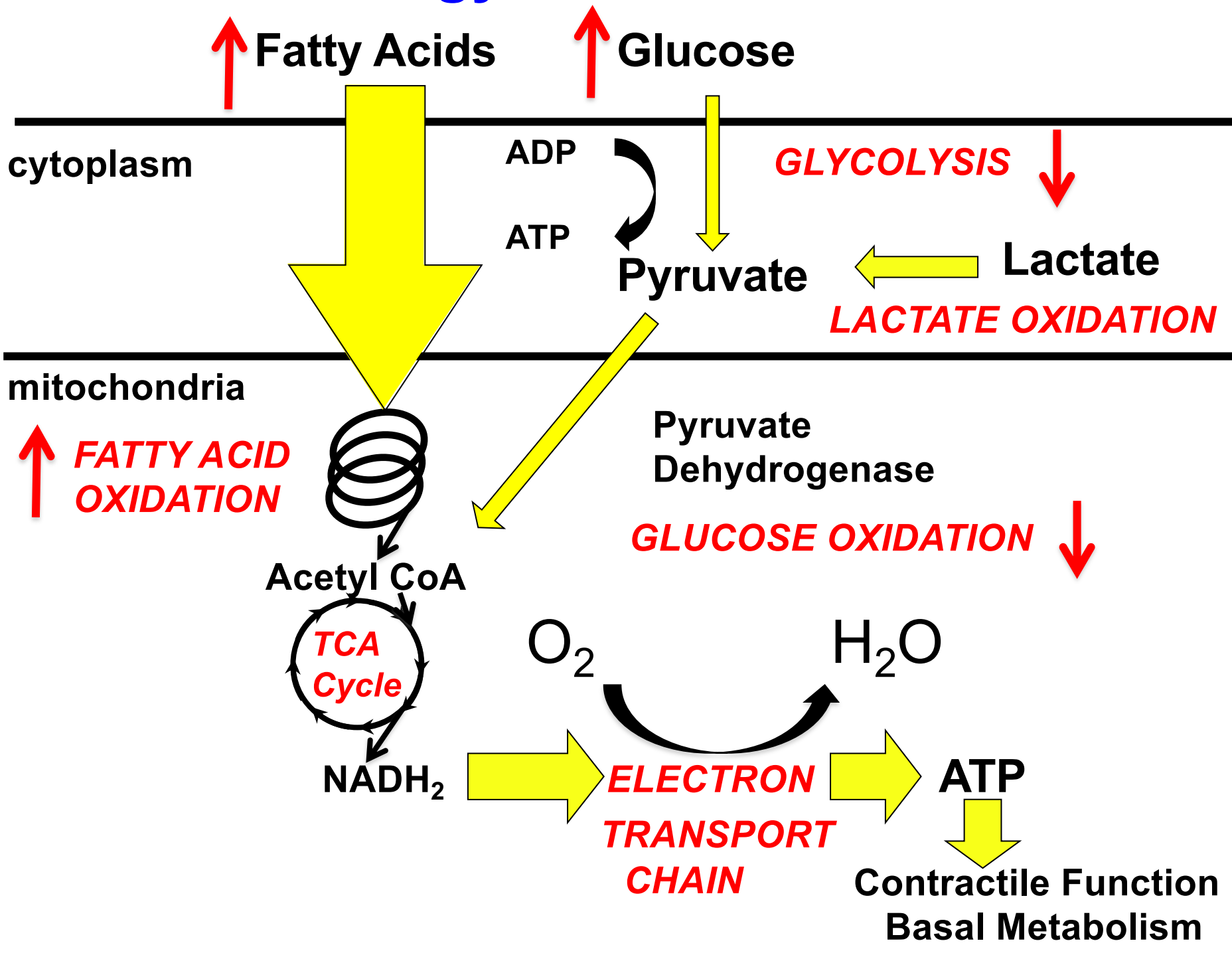
Pathological Mechanisms Involved in the Development of Diabetic Cardiomyopathy



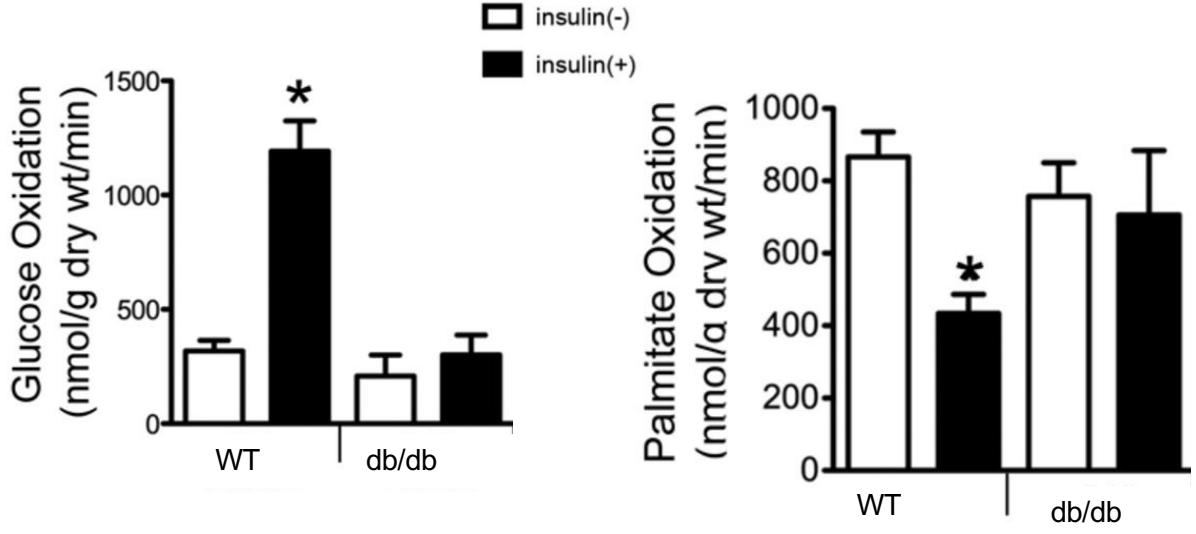
Cardiac Metabolic Changes That Occur In Diabetes and Obesity

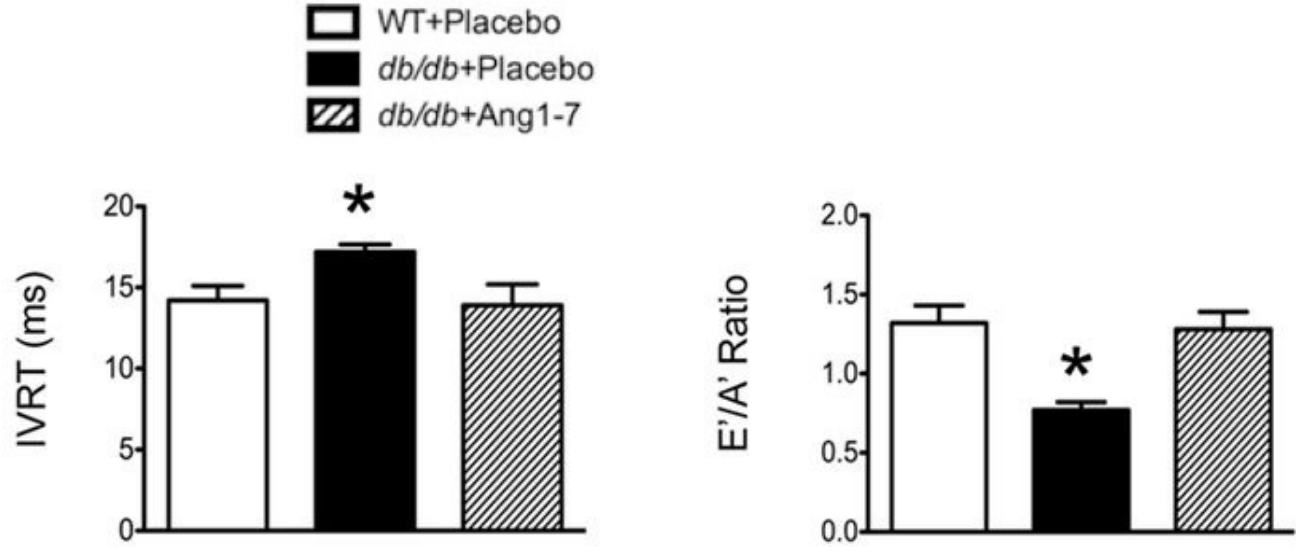
- **The heart becomes more reliant on fatty acid oxidation as a source of energy in diabetes and obesity, with a decrease in myocardial glucose uptake and oxidation.**
- **A marked cardiac insulin resistance can occur in diabetes and obesity.**
- **This switch in cardiac energy metabolism can decrease cardiac efficiency and contribute to the onset and severity of diabetic cardiomyopathies.**

Cardiac Energy Metabolism in Diabetes



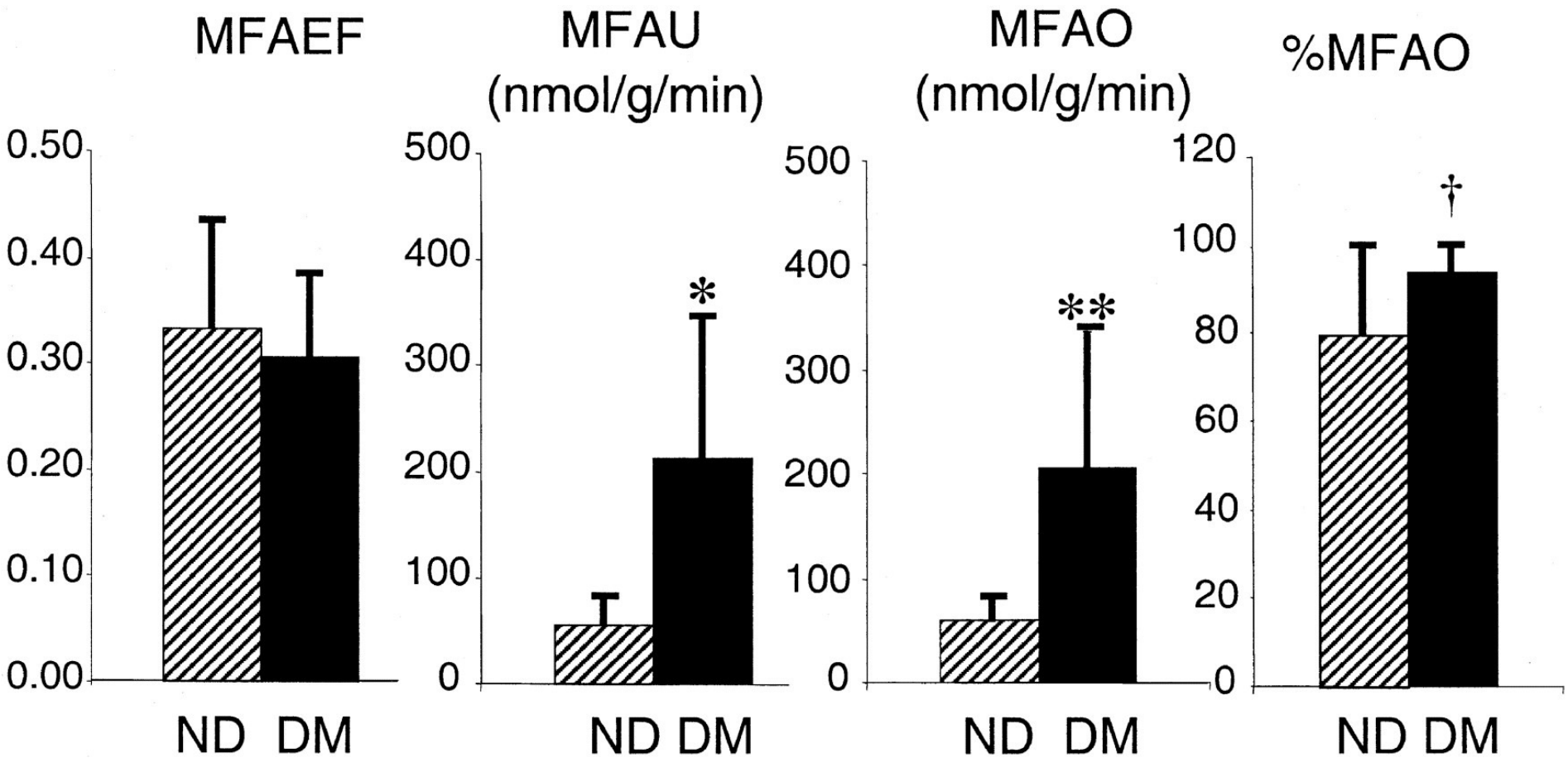
Cardiac Insulin Resistance Occurs in Diabetes and is Associated with Diastolic Dysfunction





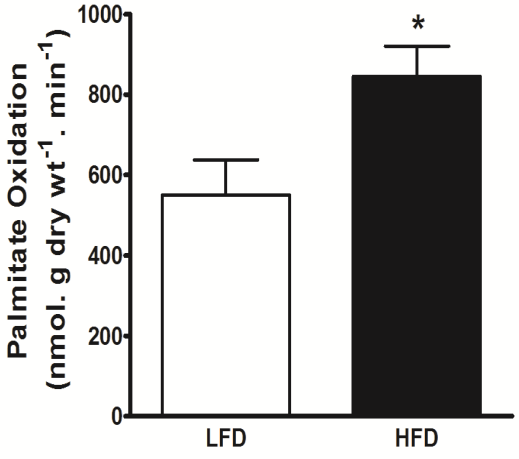
Mori J et al: Circ Heart Fail 2014;7:327-39

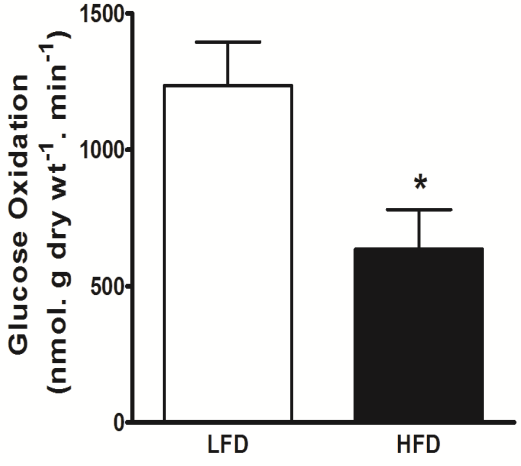
Myocardial Fatty Acid Oxidation in Non-Diabetic (ND) and Diabetes Mellitus (DM) patients

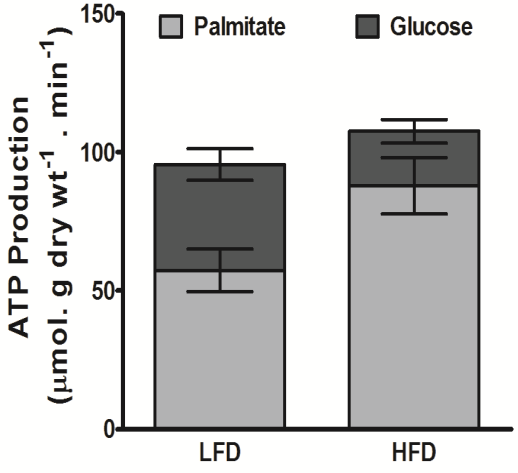


Herrero P et al: JACC 2006;47:598–604

The Contribution of Fatty Acid Oxidation to Cardiac ATP Production Increases in Obese Mice

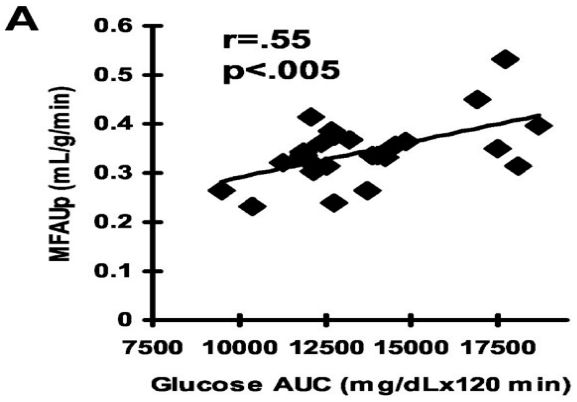


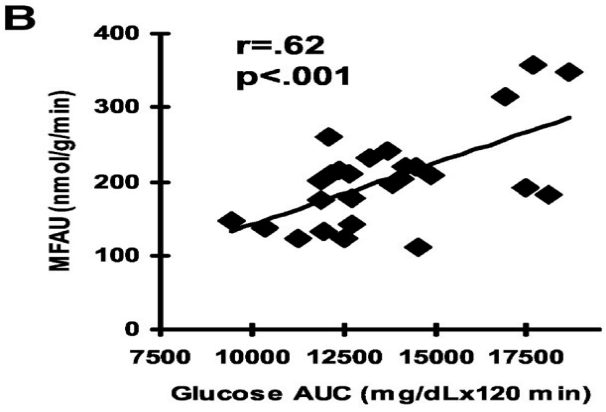


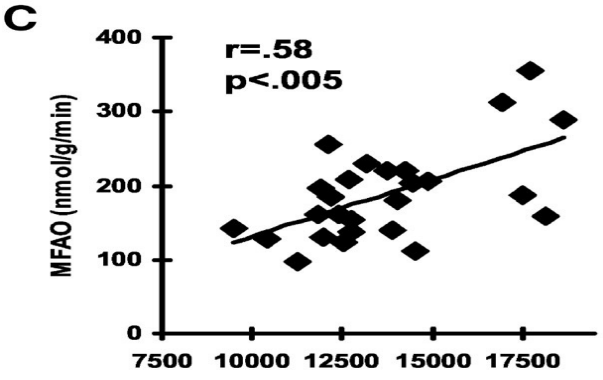


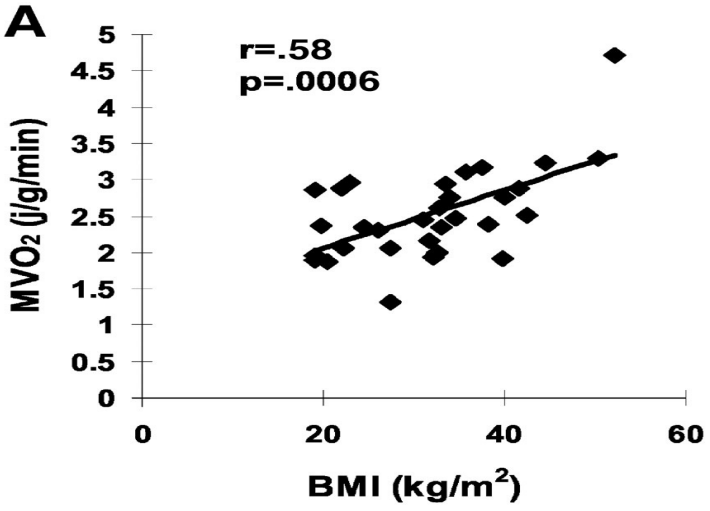
Zhang L, Ussher JR, Oka T, Cadete VJ, Wagg C, Lopaschuk GD. Cardiovasc Res. 2011;89(1):148-56

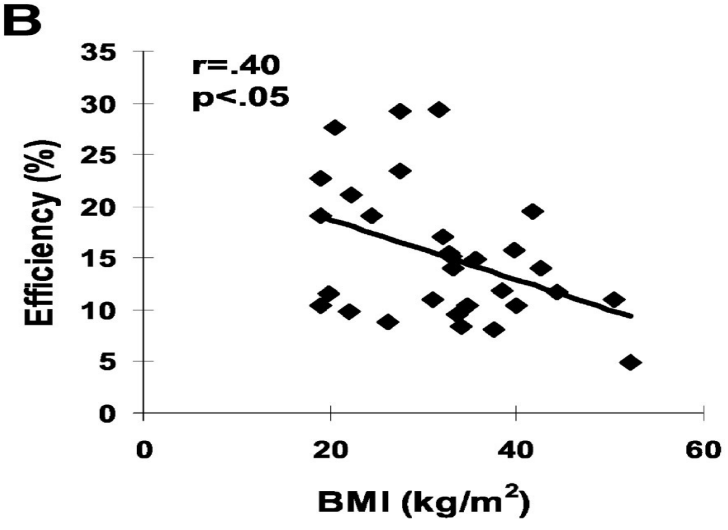
Relationship between myocardial fatty acid uptake and cardiac efficiency in obese humans











Peterson L R et al. Circulation 2004;109:2191-2196

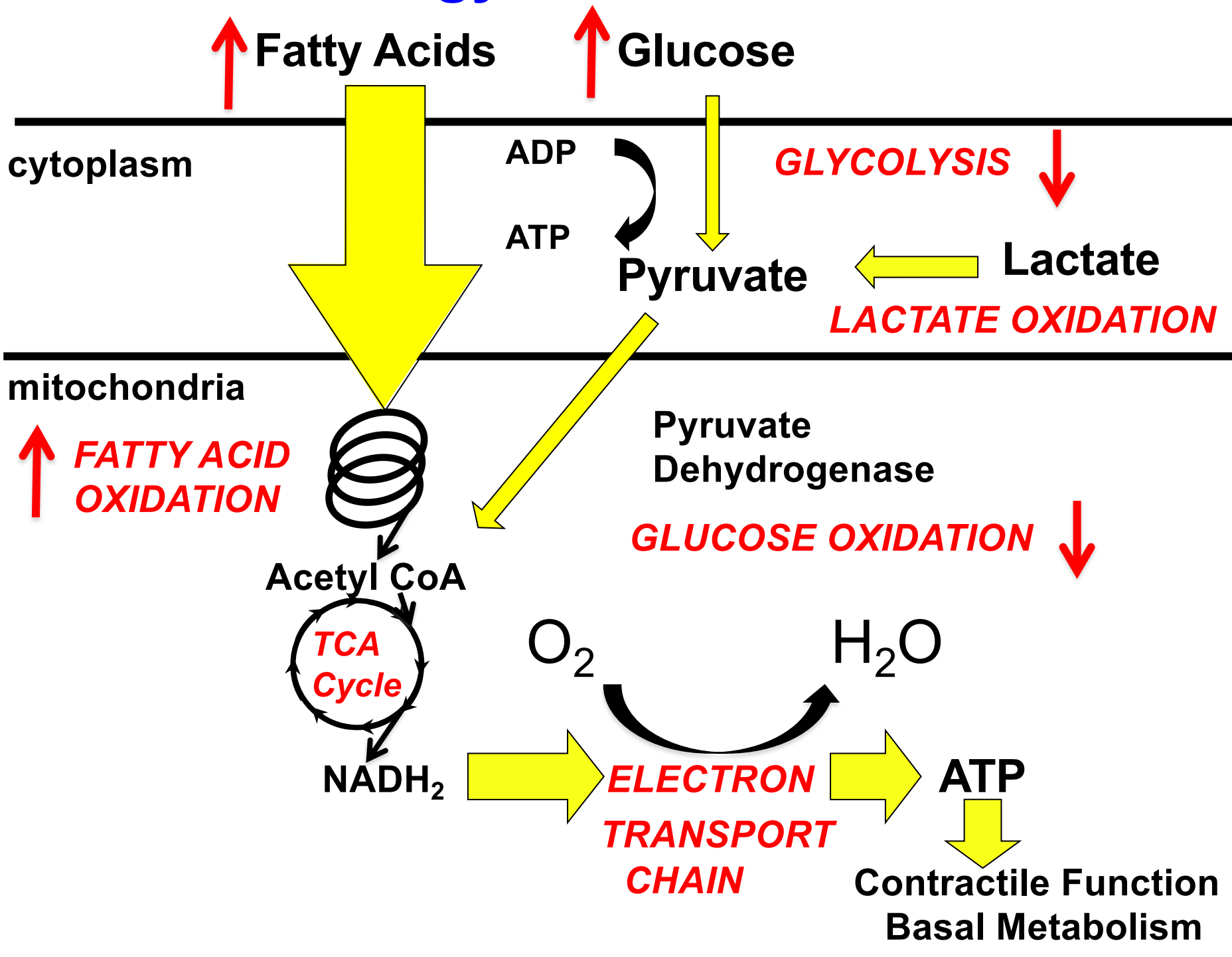
Implications of Increased Cardiac Fatty Acid Use in Diabetes and Obesity

- An excessive reliance on fatty acid oxidation as a source of energy decreases cardiac efficiency (cardiac work/O_2 consumed)
- Fatty acid intermediates accumulate in the heart (lipotoxicity)
- Increased oxidative stress
- Increased mitophagy
- Increases apoptosis
- Increased fibrosis
- Increased inflammation

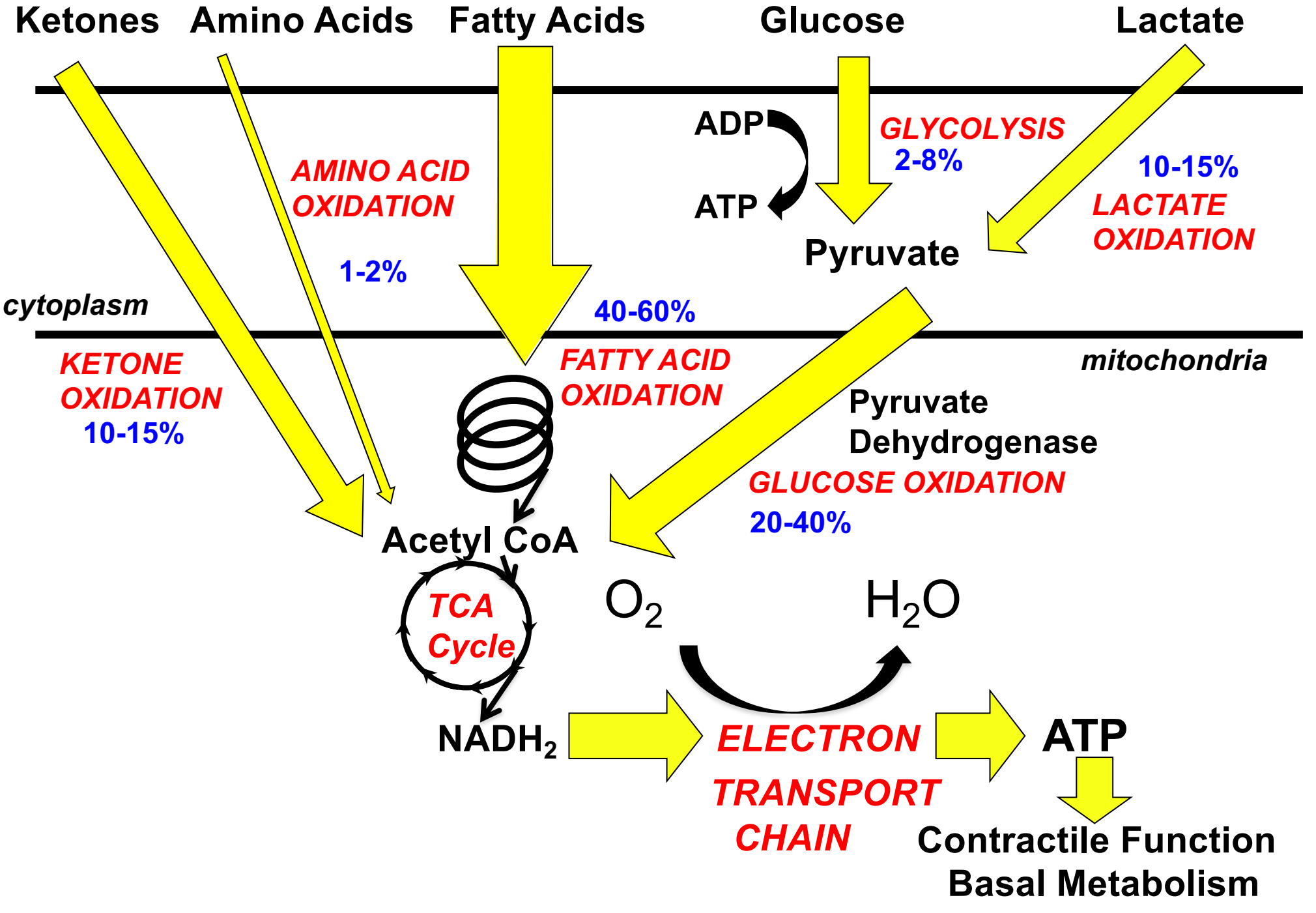
What Causes the Increase in Cardiac Fatty Acid Oxidation and Decrease in Glucose Oxidation in Diabetes and Obesity?

- Increased circulating fatty acids
- Cardiac insulin resistance
- Alterations in transcriptional control of fatty acid and glucose oxidative enzymes (E2F1α, PGC-1α/PPARα, ERRα, and HIF-1α)
- Acute changes in the allosteric control of fatty acid oxidation
- Post-translational modification of fatty acid oxidative enzymes, particularly via acetylation and deacetylation pathways

Cardiac Energy Metabolism in Diabetes



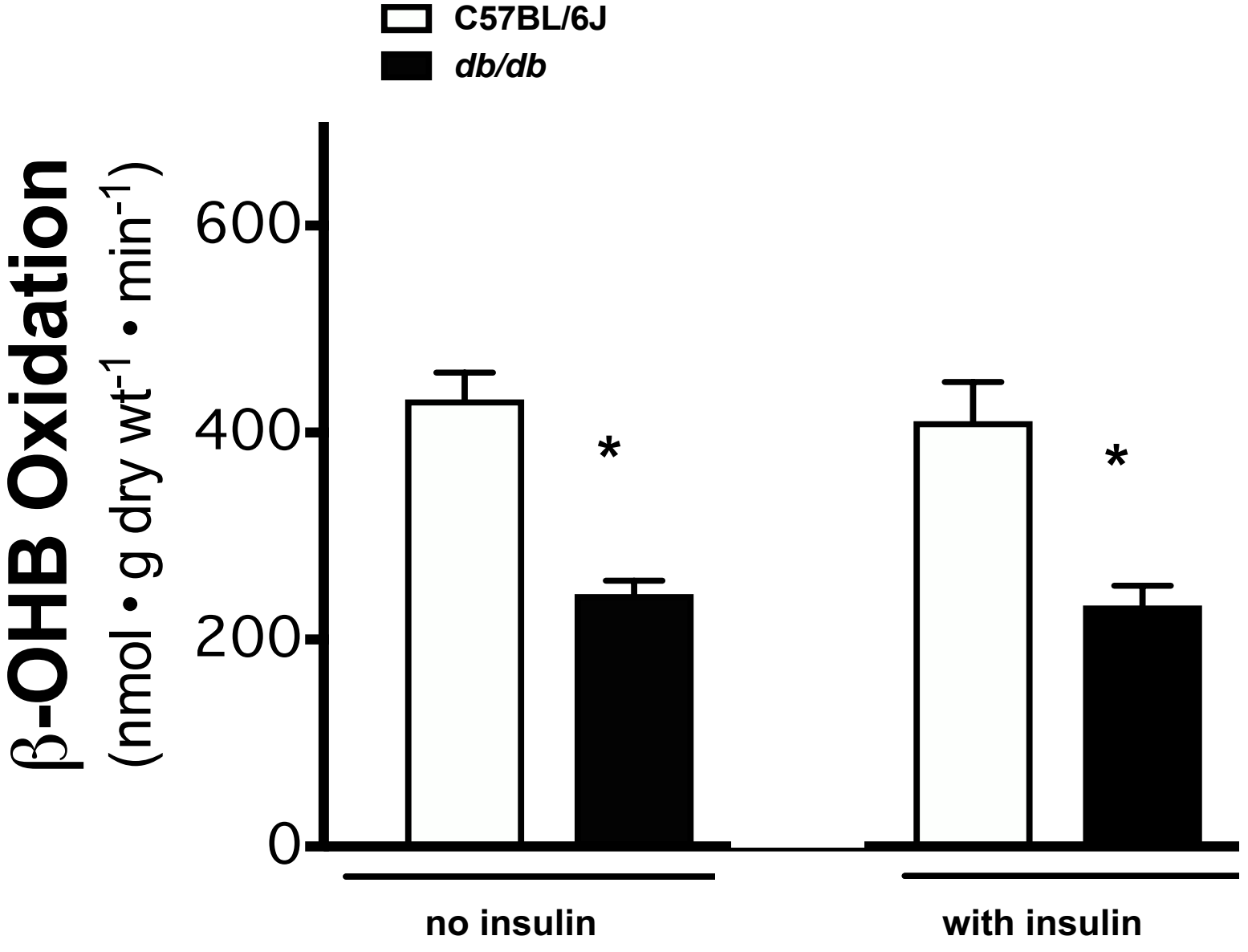
Energy Metabolism in the Normal Heart



Ketones as a Source of Energy for the Heart

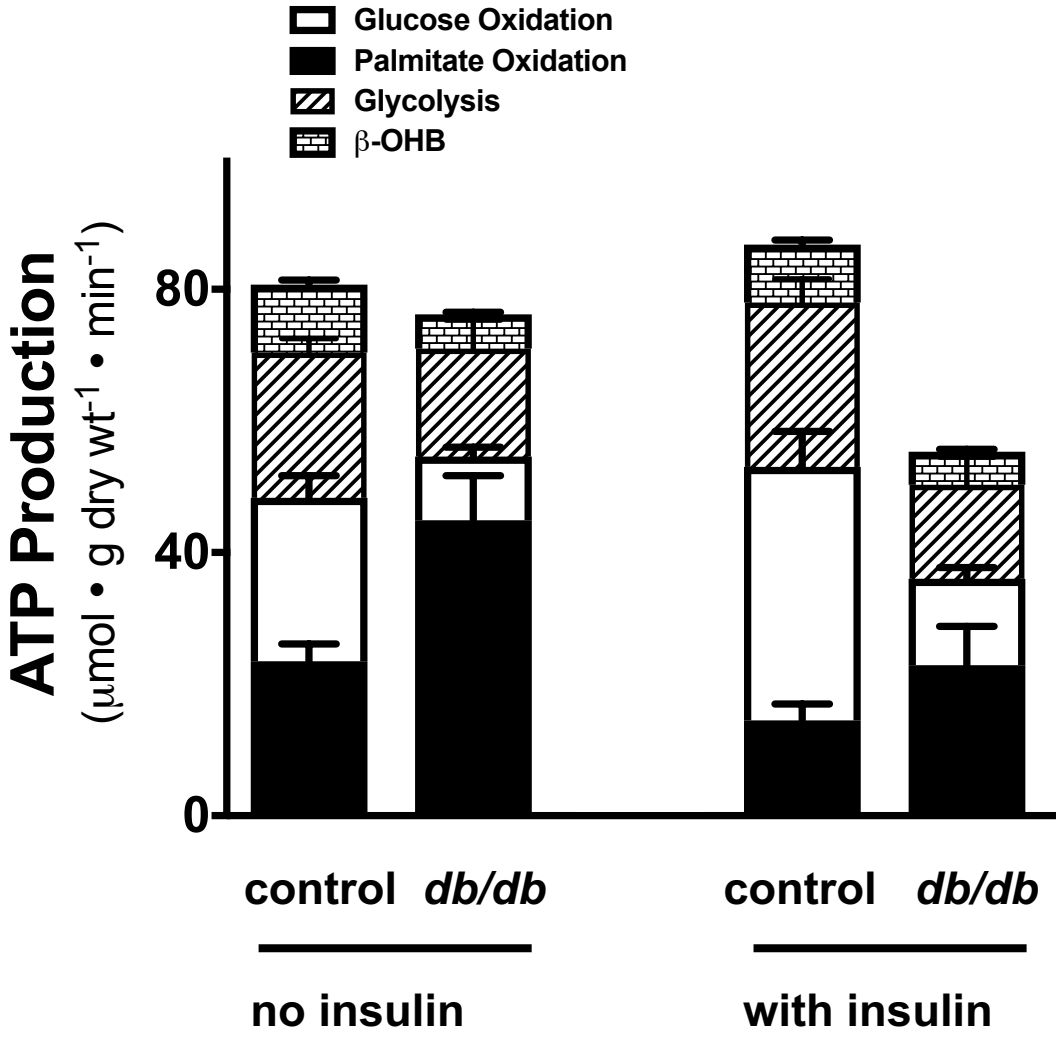
- Ketone bodies are a potential source of energy for the heart
- It has been proposed that ketones are a “super fuel” or a “thrifty” fuel” that may increase cardiac efficiency and benefit the failing heart
- It has also been suggested that ketone oxidation is increased in the failing heart
- However, it is not known to what extent ketone oxidation contributes to cardiac energy production in diabetes or obesity.

Cardiac Ketone Oxidation Decreases in *db/db* Mice



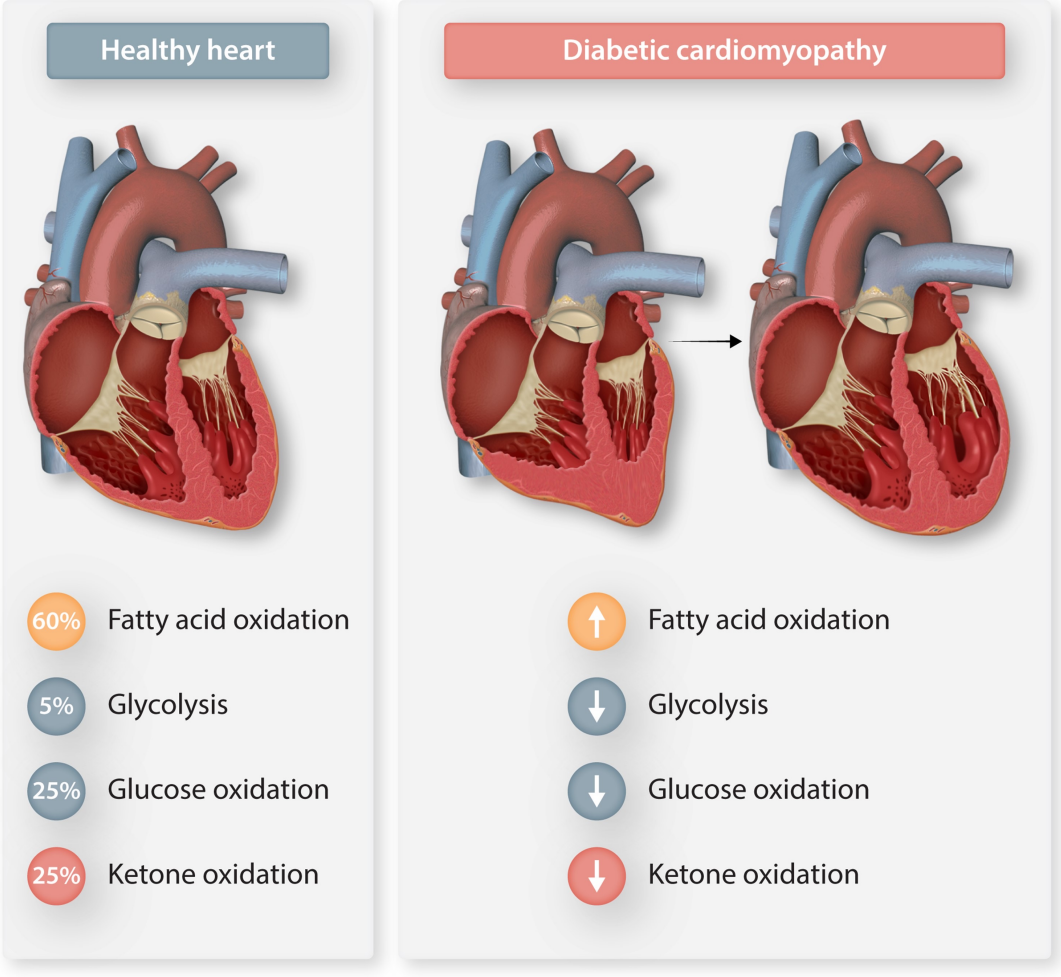
Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587

Cardiac Energy Production is Decreased in *db/db* Mice



Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587

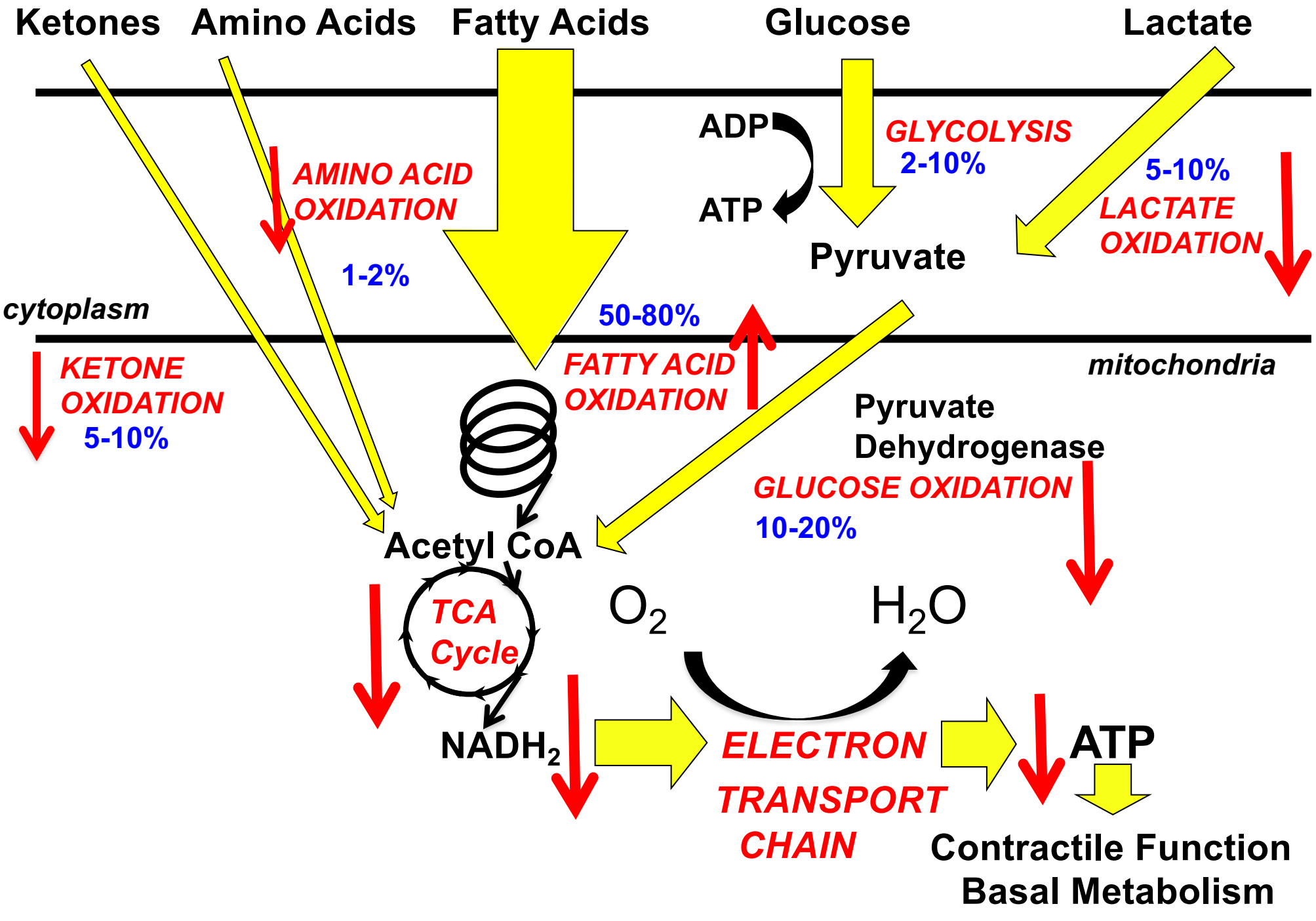
Cardiac Energy Metabolic Changes in Diabetic Cardiomyopathy



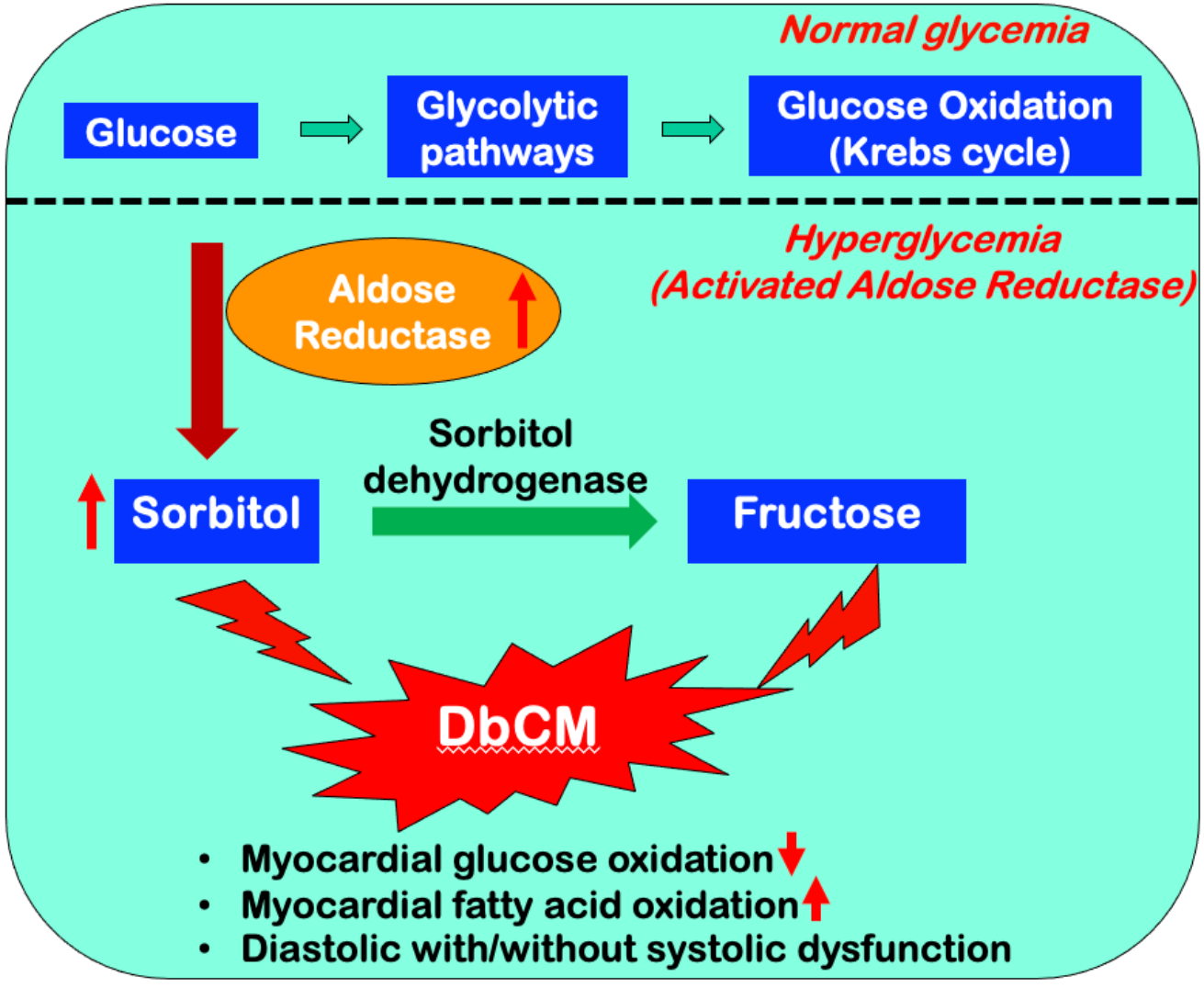
Karwi Q et al, Cardiovasc Res, cvab120, https://doi.org/10.1093/cvr/cvab120

ESC European Society of Cardiology

Energy Metabolism in Diabetic Cardiomyopathy

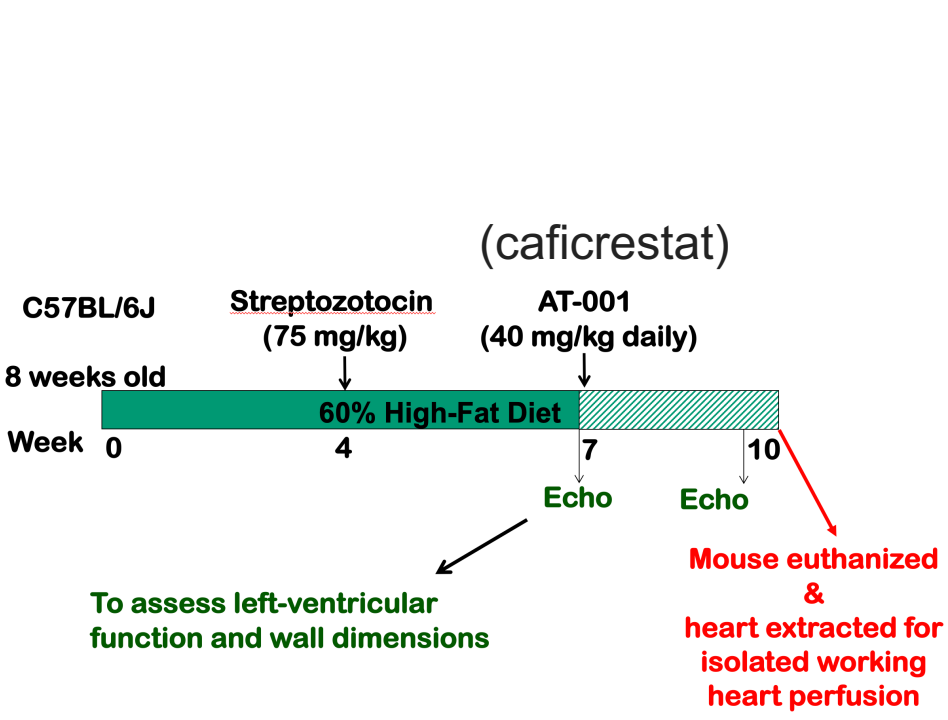


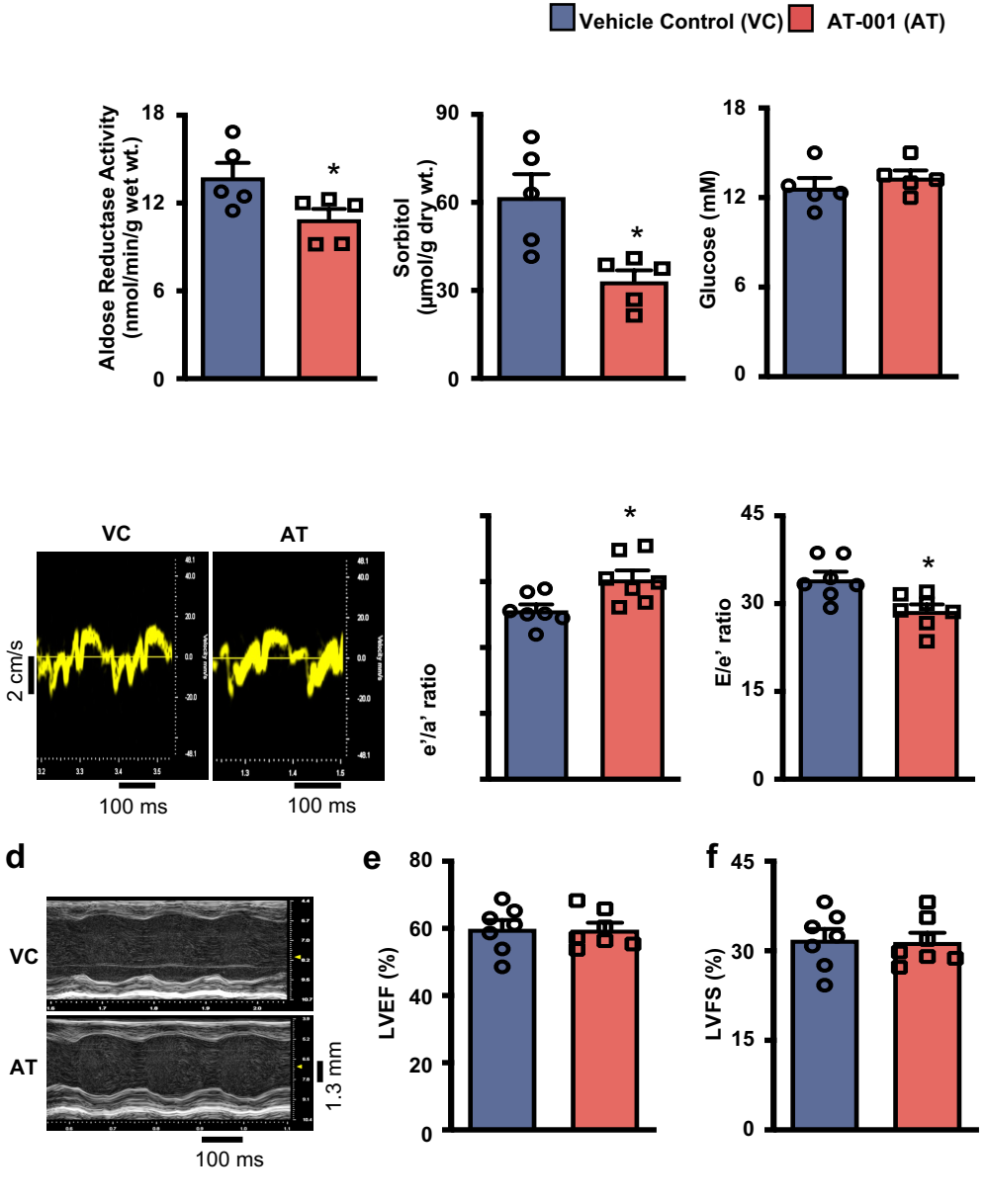
Cardiac Aldose Reductase Increases in Diabetes



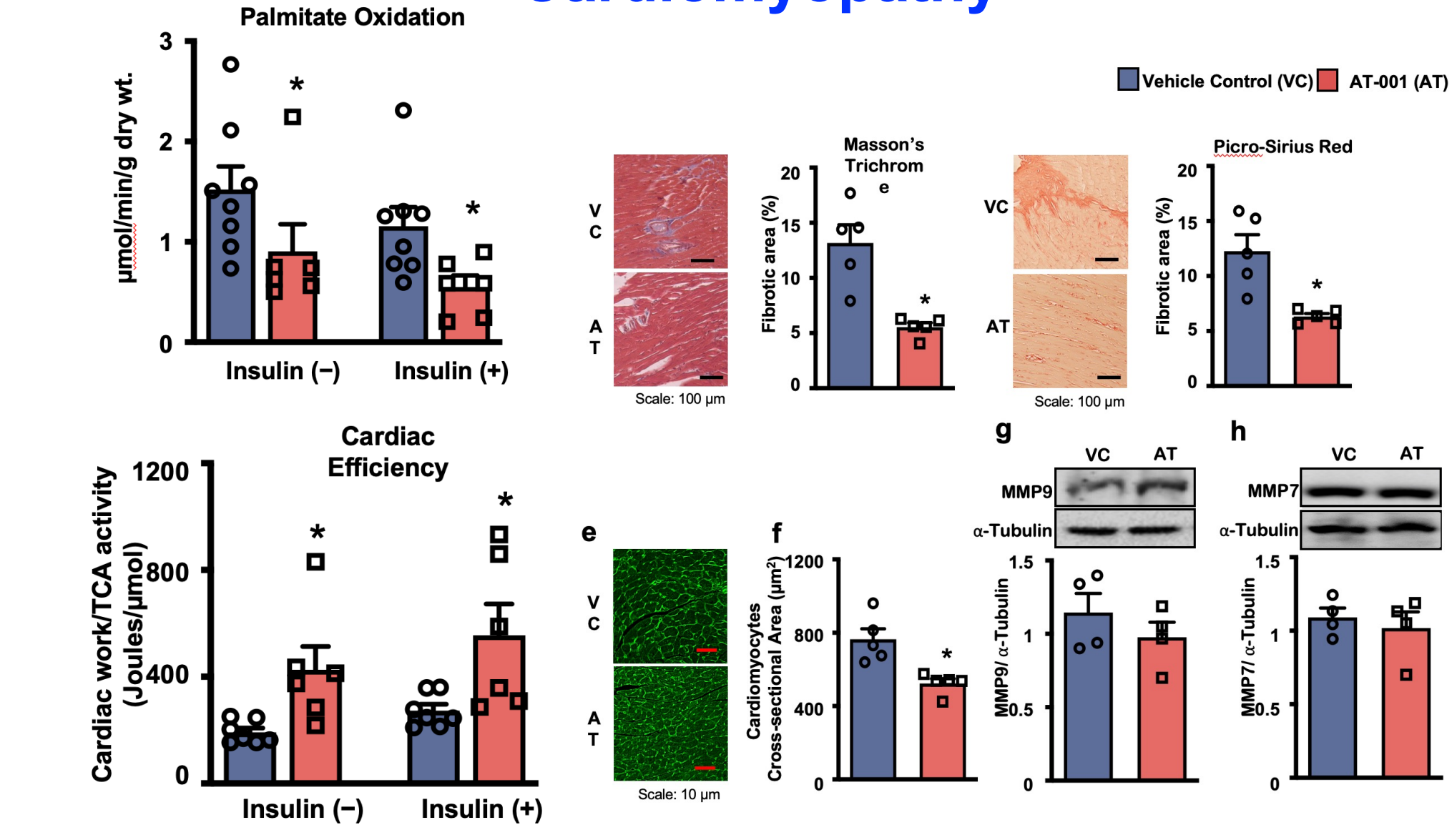
Brownlee M. Diabetes. 54(6):1615-1625 (2005)

Inhibition of Aldose Reductase Decreases the Severity of Diabetic Cardiomyopathy





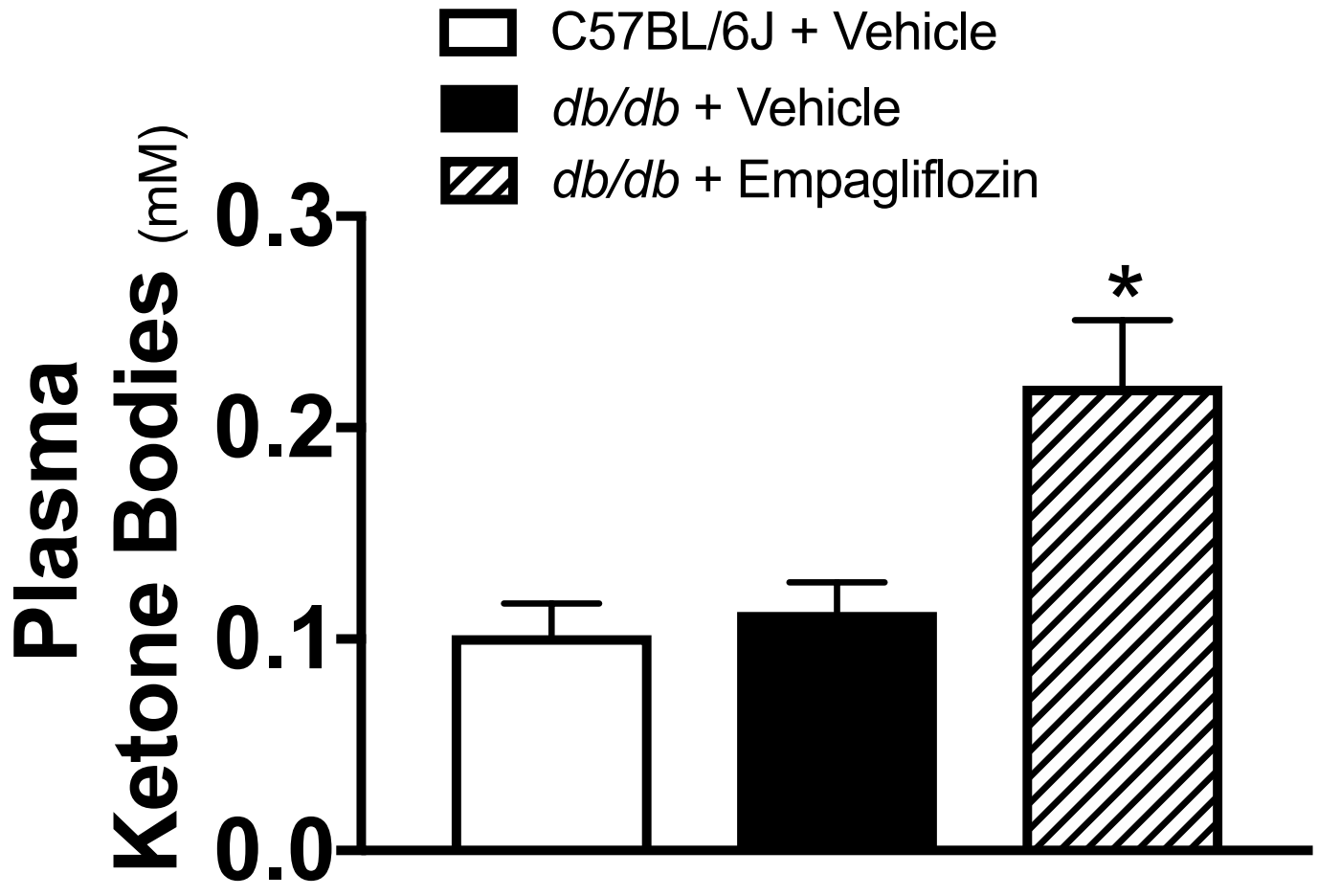
Inhibition of Aldose Reductase Decreases Fatty Acid Oxidation and Fibrosis in Diabetic Cardiomyopathy



SGLT 2 Inhibition and Heart Failure in the Diabetic

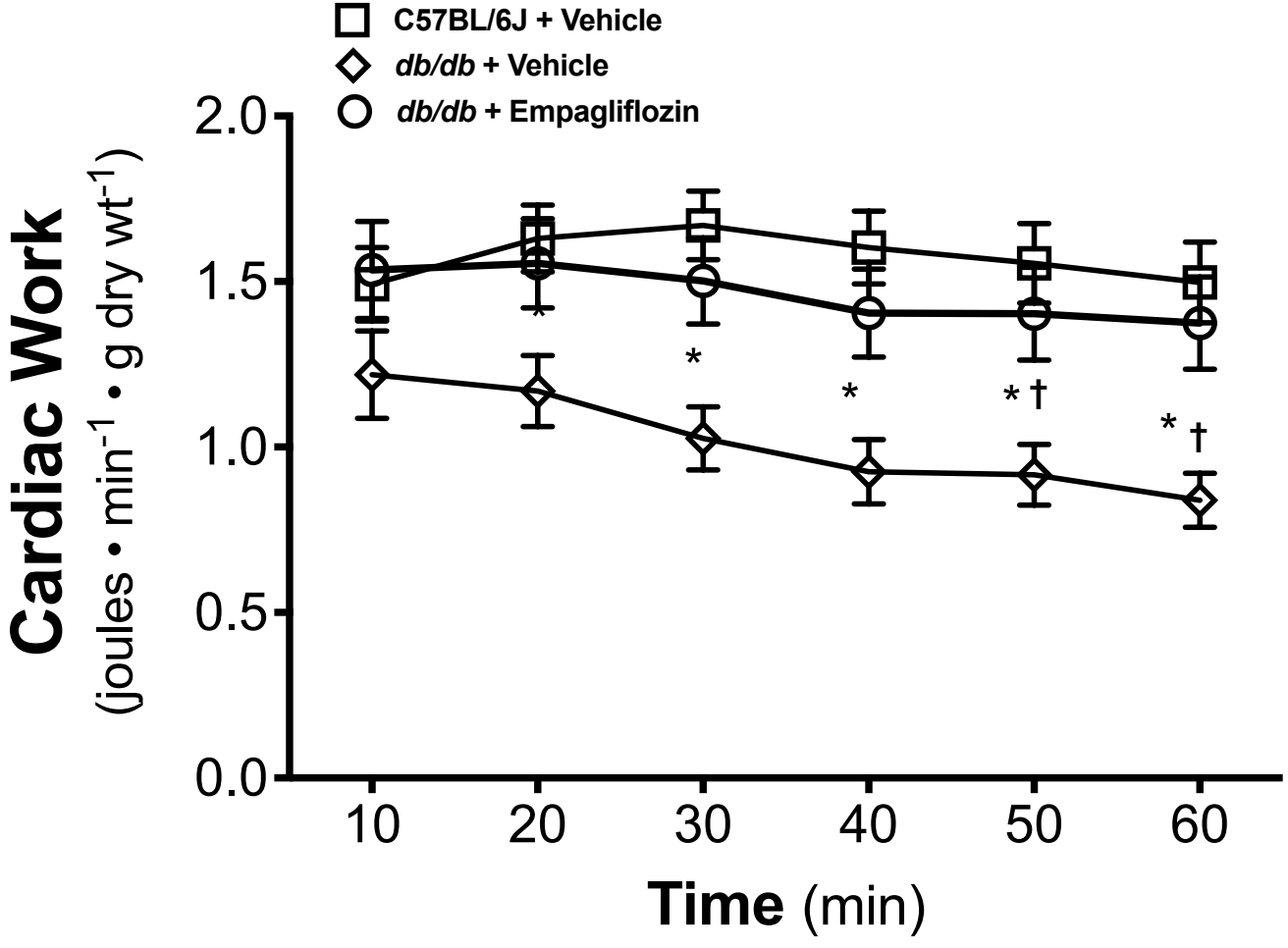
- A number of large outcomes trials have shown that SGLT2 inhibitors can decrease heart failure severity in diabetics at risk for cardiovascular disease
- The actual mechanism by which they do this is not clear
- It has been proposed that some of the benefit of SGLT2 inhibitors is related to an improvement in cardiac energy metabolism (i.e. an increase in ketone oxidation in the heart)

Empagliflozin Increases Plasma Ketone Levels in *db/db* Mice



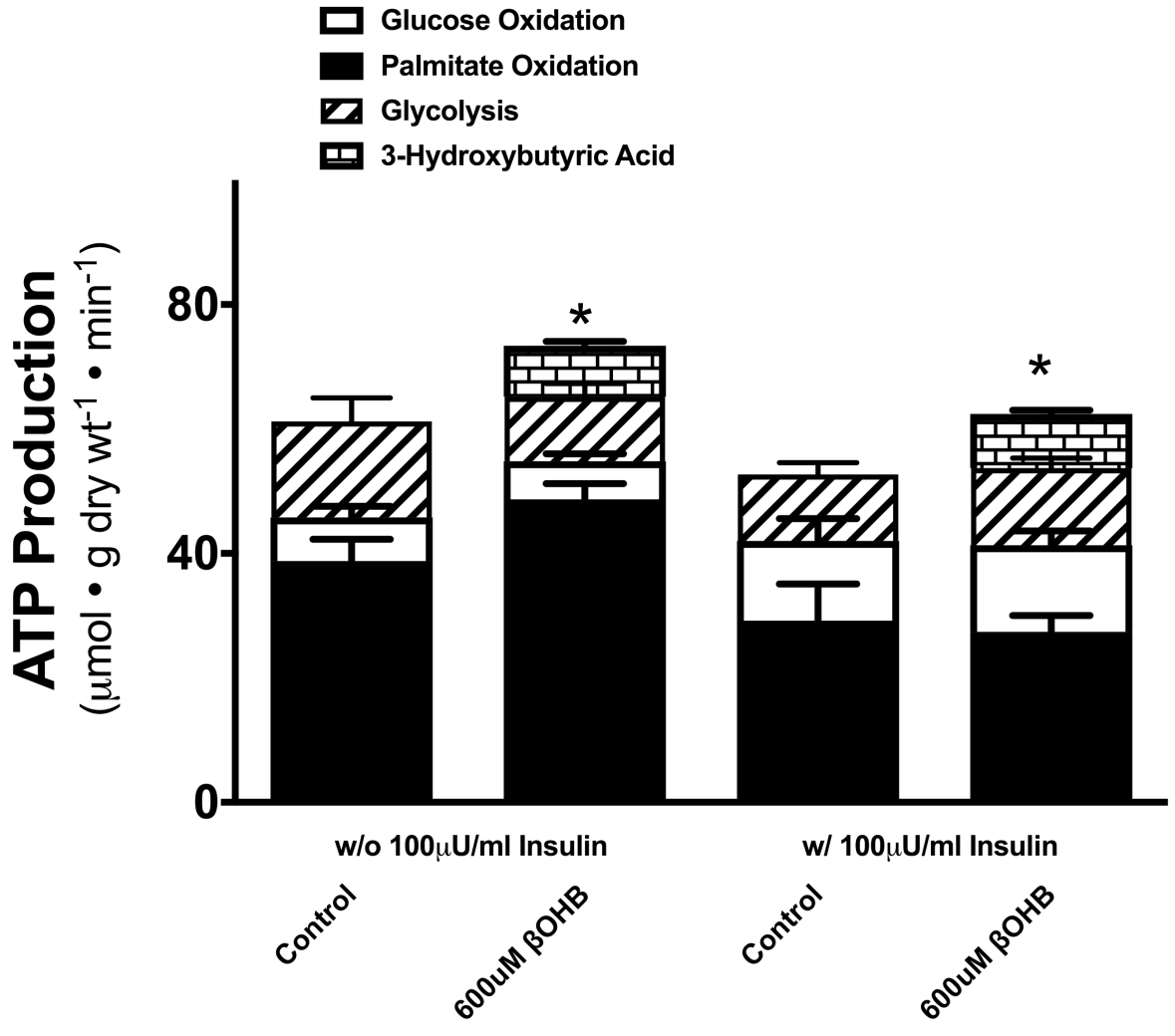
Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587

Empagliflozin Improves Cardiac Work in *db/db* Mice

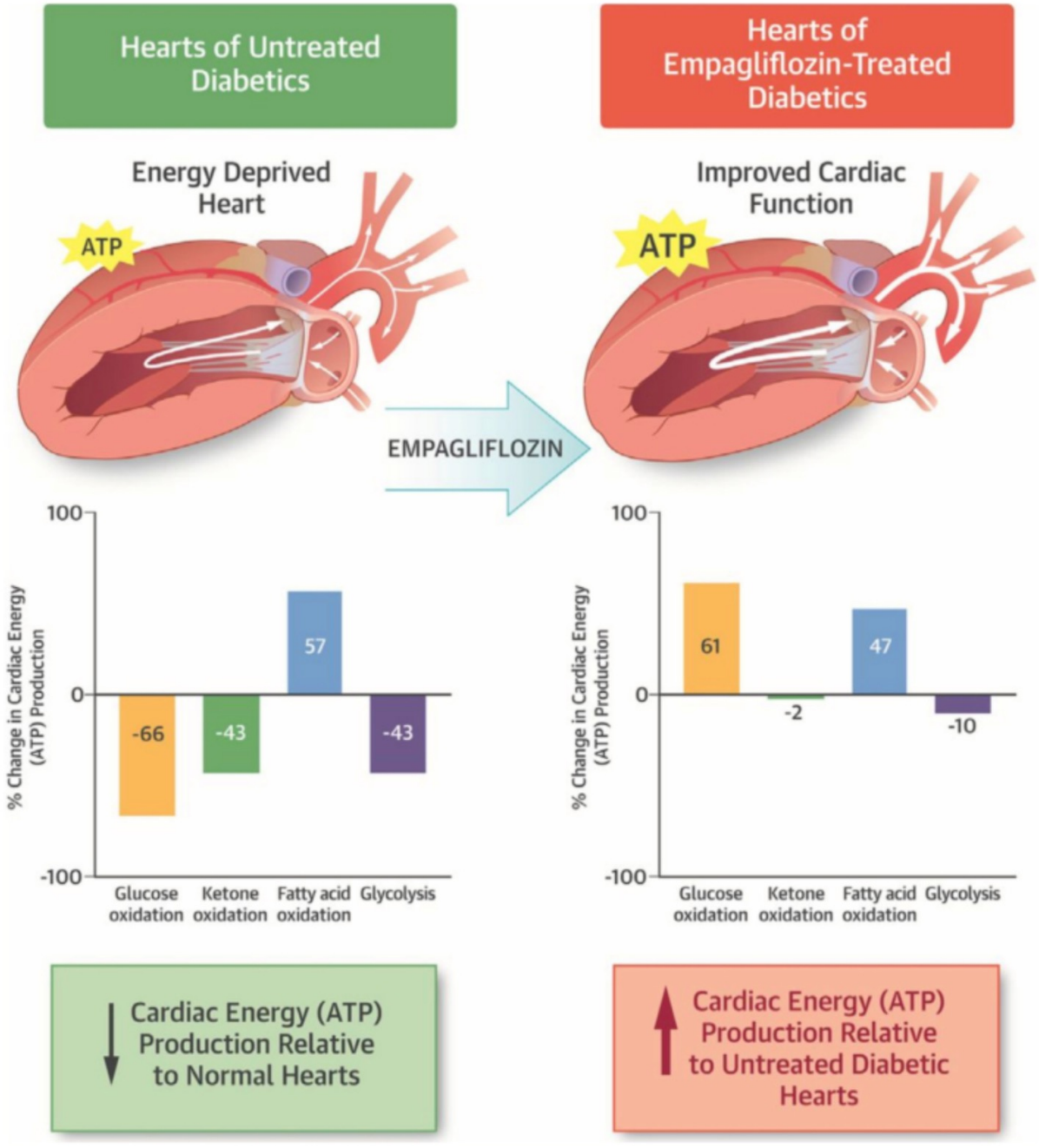


Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587

Ketones provide an extra source of energy for the heart and increase overall cardiac energy production in Diabetic Cardiomyopathy

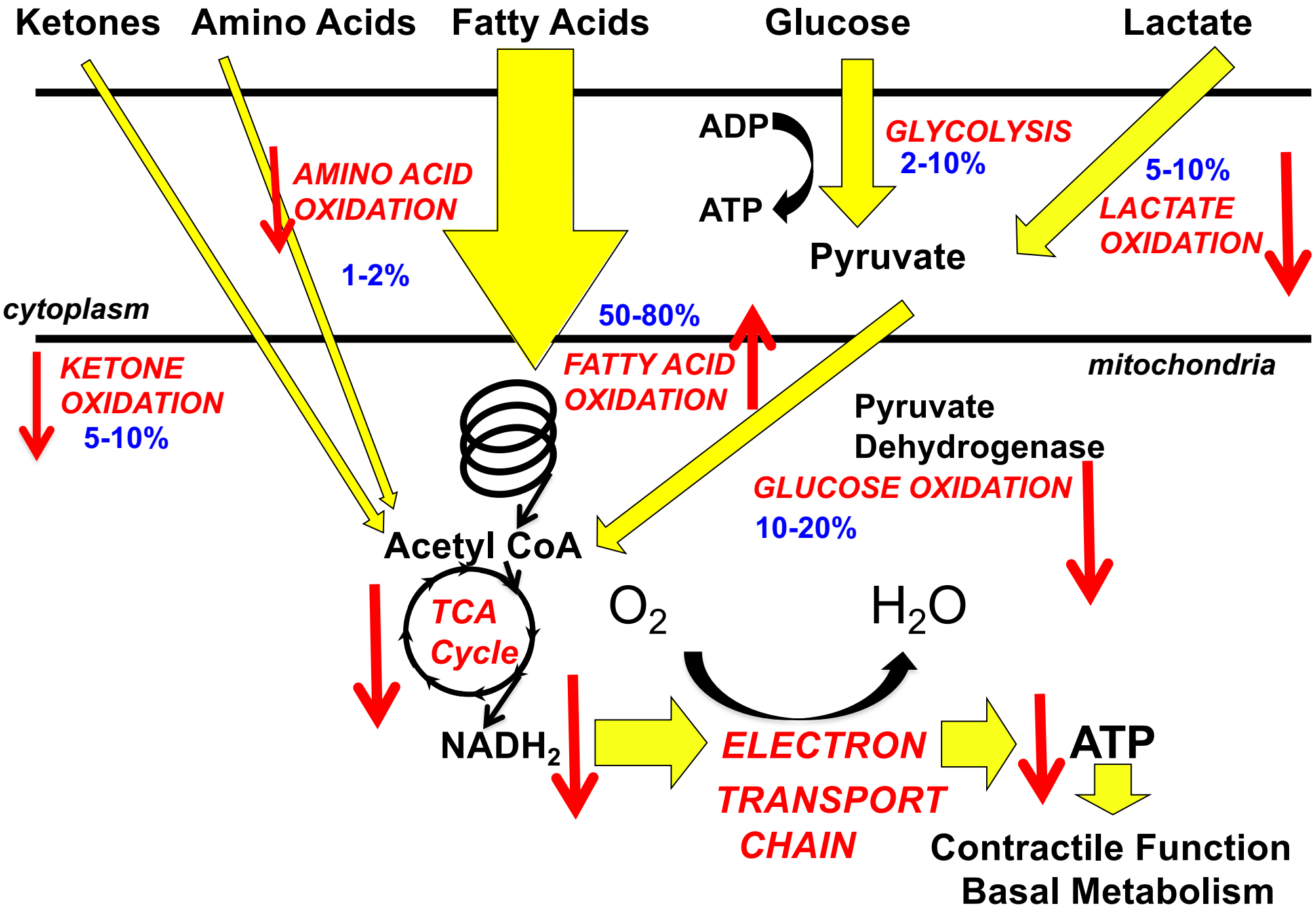


Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587



Verma S et al, JACC Basic Transl Sci. 2018;26;3(5):575-587

Energy Metabolism in Diabetic Cardiomyopathy



Conclusions

- Cardiac mitochondrial insulin resistance occurs in diabetic cardiomyopathy
- Myocardial glucose oxidation is markedly decreased in diabetic cardiomyopathy
- Myocardial fatty acid oxidation increases in diabetic cardiomyopathy
- Myocardial ketone oxidation is decreased in diabetic cardiomyopathy
- Stimulating glucose oxidation (by inhibiting pyruvate dehydrogenase kinase) can lessen the severity of heart failure
- Increasing ketone supply to the heart can increase cardiac energy cardiac production in diabetic cardiomyopathy

Acknowledgements

Lopaschuk Lab:

Qiuyu Sun
Berna Guven
Liyan Zhang
Donna Beker
John Ussher
Cory Wagg
Wei Wang
Qutaiba Karwi
Kim Ho
Tariq Altamimi
Osama Al Rob
Sonia Rawat
Jun Mori
Arata Fukushima
Ezra Ketema

Collaborators:

John Ussher (U. Alberta)

Gavin Oudit (U. Alberta)

Subodh Verma (Toronto)

CIHR IRSC

HEART AND STROKE FOUNDATION

AHFMR
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH