Dichiarazione di Conflitto di Interessi

Honorarium as a speaker in Scientific Events

Sigma-Tau	Lilly/Boheringer Ingelheim	Abbott
AstraZeneca BMS	Takeda	Janssen
Eli-Lilly	Sanofi-Aventis	Menarini Diag
MSD	Novo Nordisk	Roche Diag
Novartis	Servier	Bayer

Grant support

Novo Nordisk (Investigator-Initiated-Study Grant)
Kellogg (Investigator-Initiated-Study Grant)

AstraZeneca, Lilly, Sanofi, Novo Nordisk, Sigma-Tau, Menarini (Travel grants)

Scientific advisory boards

AstraZeneca, Lilly, Sanofi, Takeda, NovoNordisk



Glicemia, insulina, acidi grassi e funzionalità cardiaca; quale connessione metabolica

Gianluca Perseghin

Policlinico di Monza
1821

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Qual’è la connessione metabolica ?

Il metabolismo energetico

Quale connessione metabolica ?

Miocardio sano e meccanismi di adattamento

Miocardio insulino resistente (diabete tipo 2 e obesità)

Miocardio malato (scompenso cardiaco)

Potenziali strategie di intervento metabolico

Energy metabolism in the normal and diseased human heart

Cardiac energy metabolism

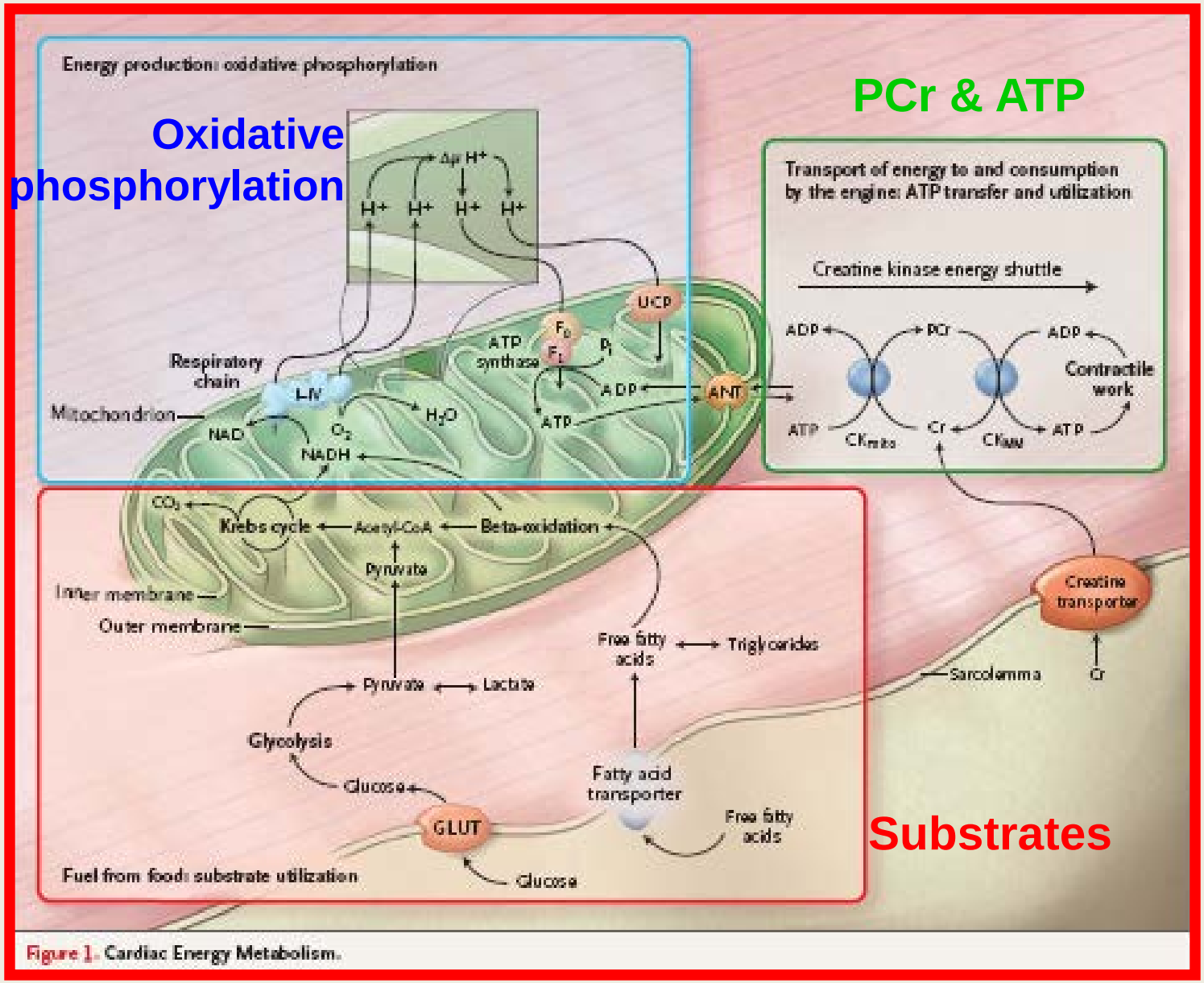


Figure 1. Cardiac Energy Metabolism.

Neubauer S. *N Engl J Med*, 2007

Metabolic flexibility

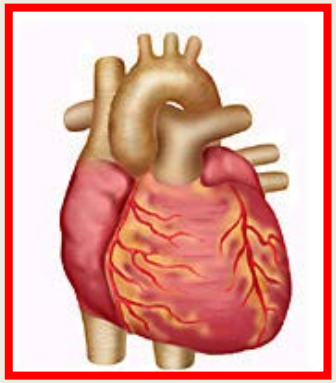
5 kg of ATP every day

Perfusion
Oxygen supply

Mechanical work

Fatty acids

Fatty acids



Glucose

Glucose

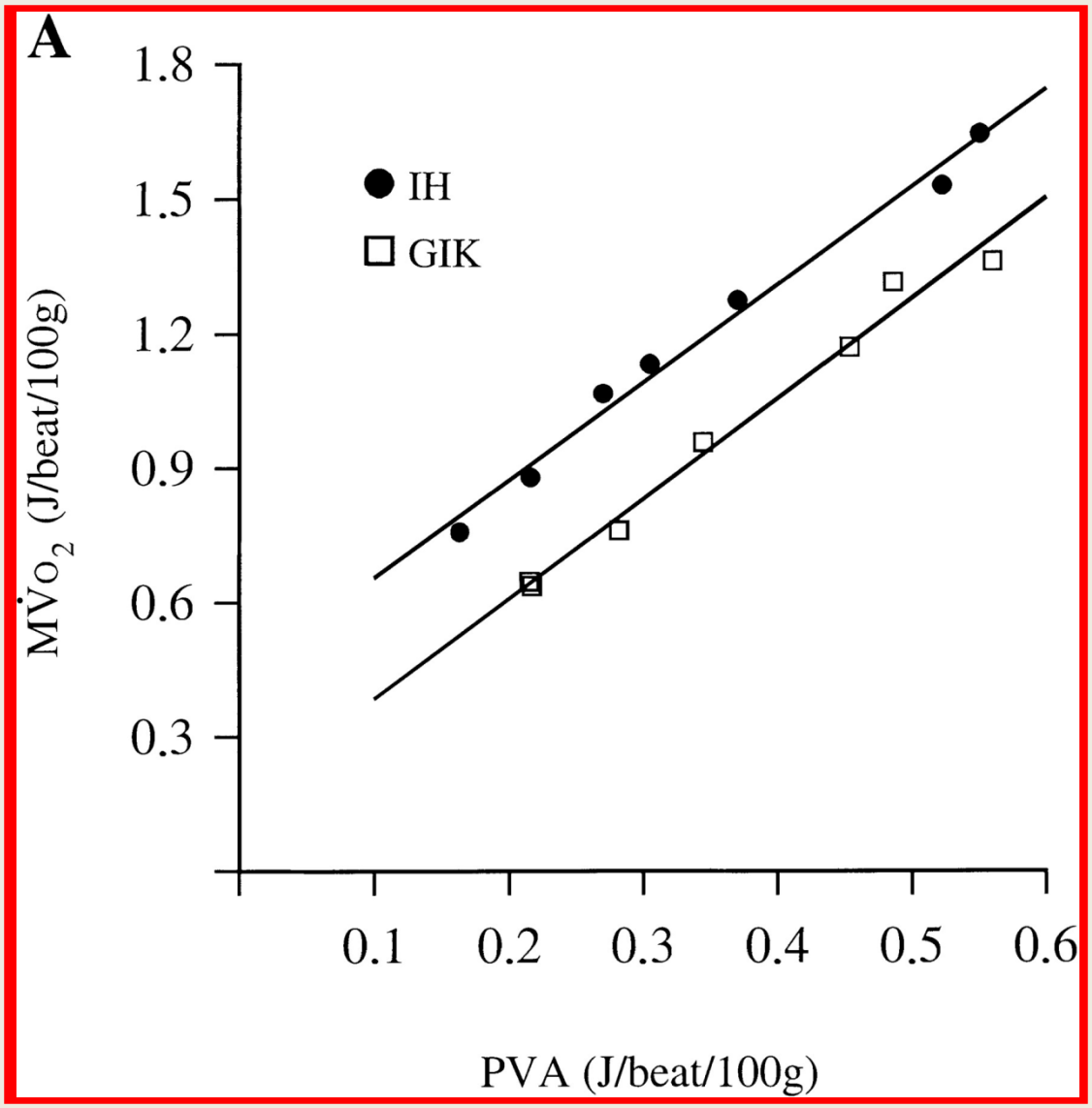
Low Perfusion
Low Oxygen supply

Why ?

Taegtmeyer H et al *Circulation*, 2002

Neubauer S. *N Engl J Med*, 2007

Metabolic switch: why ?



GIK:
glucose+insulin+K

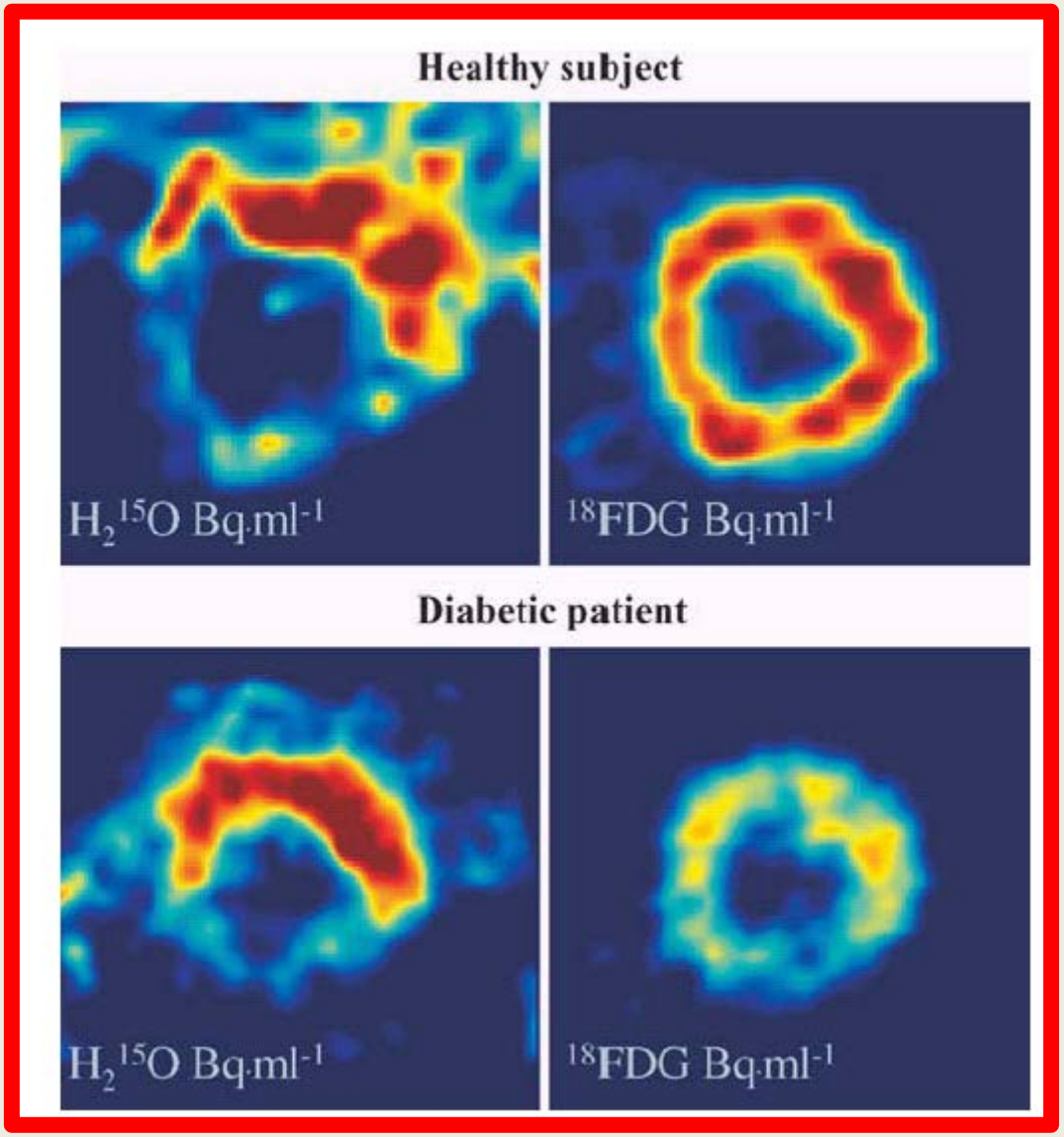
IH:
Intralipid+heparin

PVA:
pressure-volume area
(Pig model)

Korvald C et al,
Am J Physiol 2000

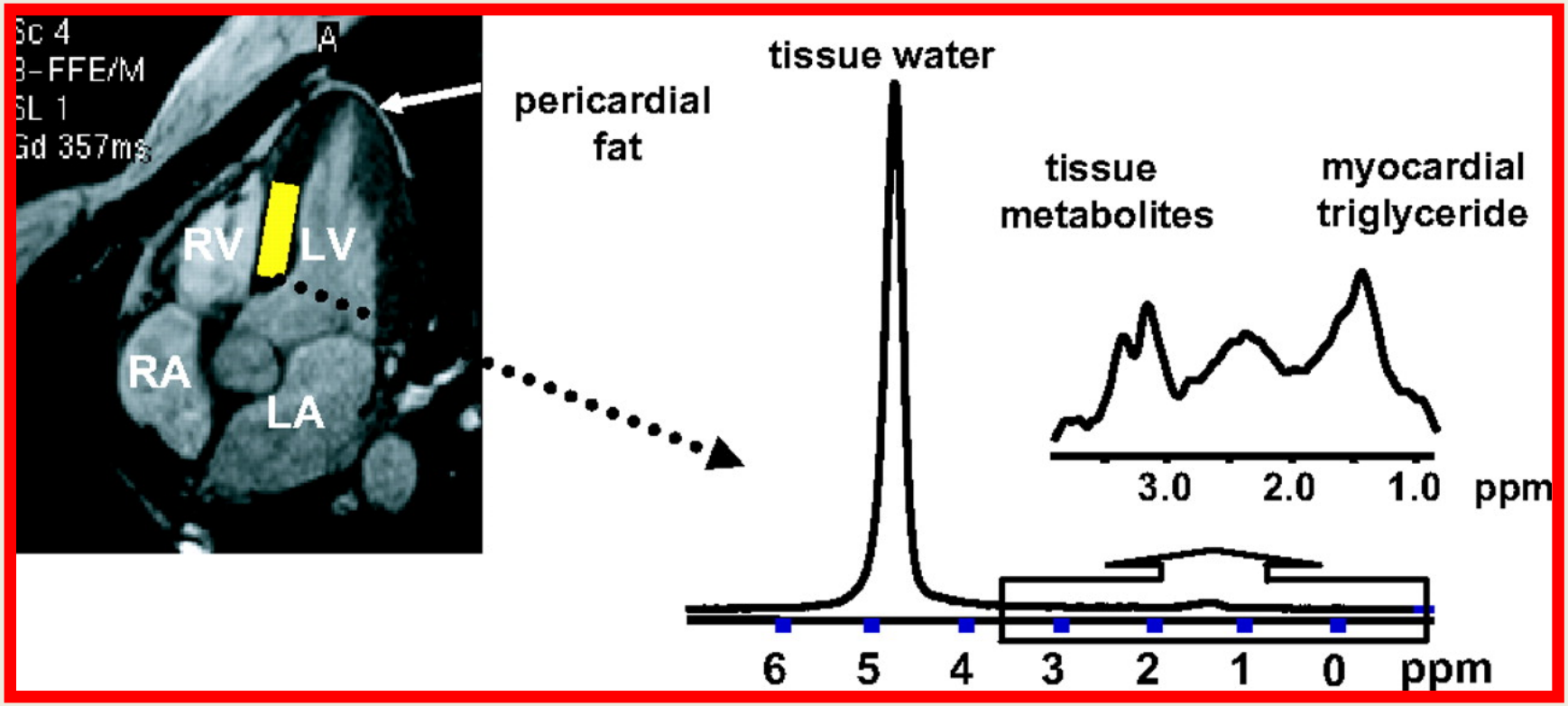
Cardiac insulin resistance; metabolic maladaptation or inflexibility

Myocardial insulin resistance in T2DM



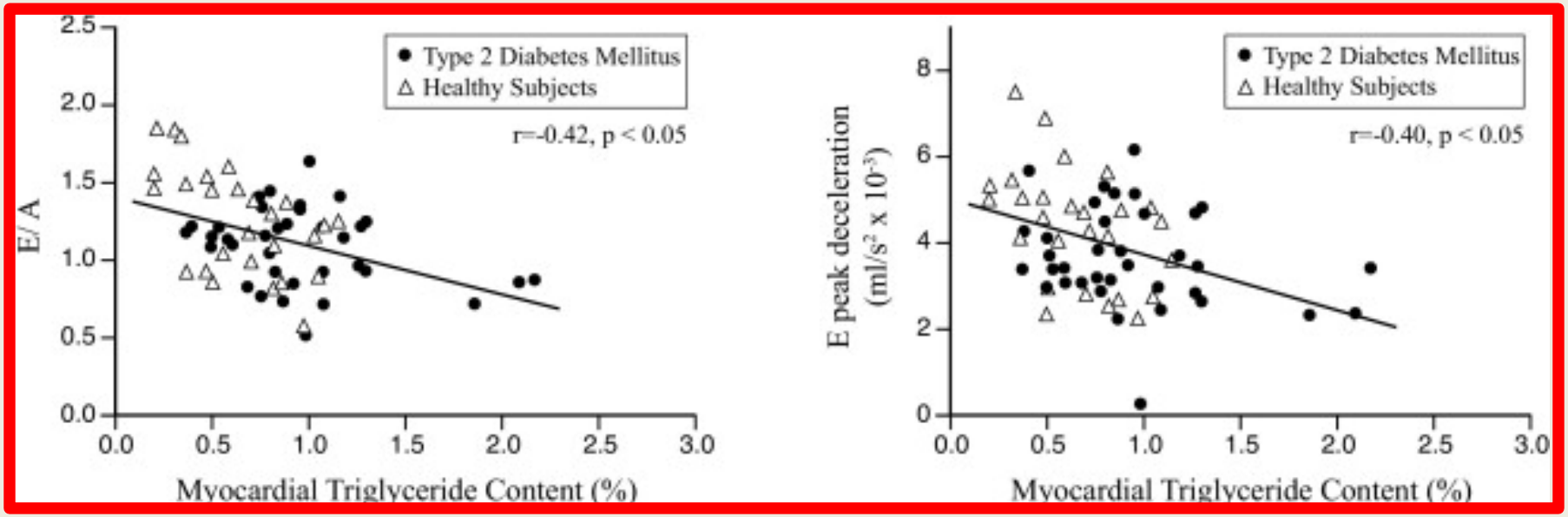
Iozzo et al. Diabetologia 2002

Ectopic fat in the heart



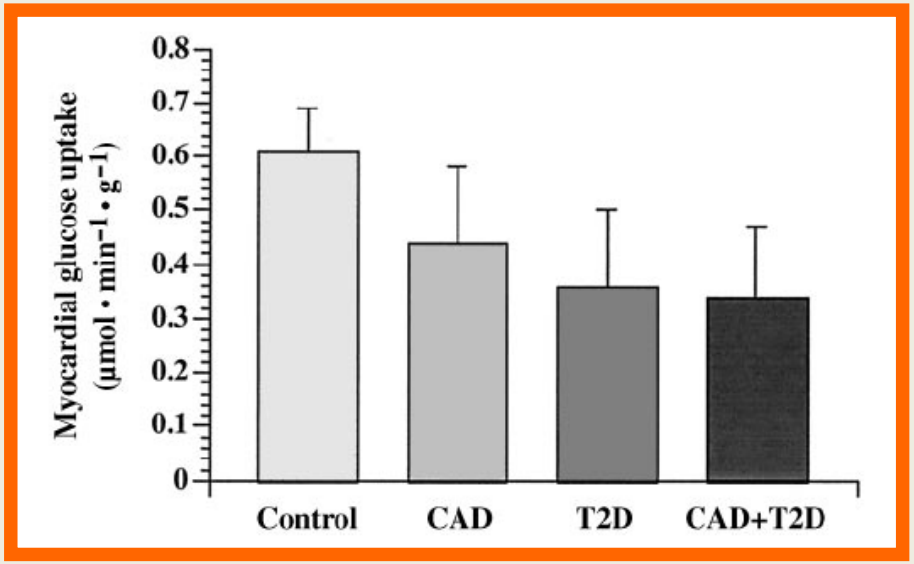
McGavock JM et al Circulation 2007

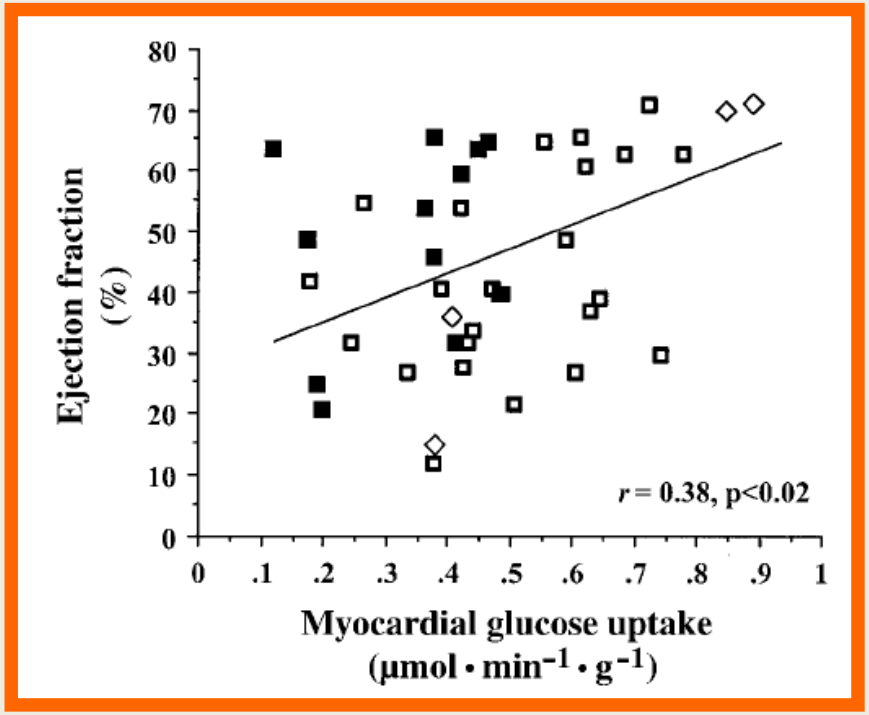
Ectopic cardiac fat and LV function



Iozzo et al, J Clin Endocrinol Metab 2009
Rijzewijk et al, J Am Coll Cardiol 2008 and 2009

Myocardial insulin resistance in T2DM





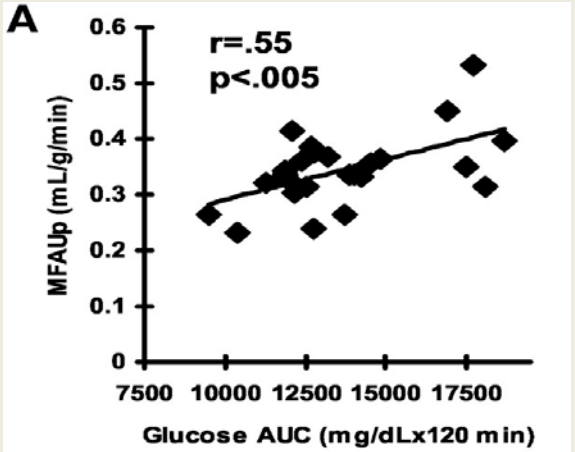
Baseline blood flow (^{15}O-water) and insulin-stimulated glucose uptake (18fluoro-deoxyglucose) during clamps combined with PET

Iozzo P et al Diabetes, 2002

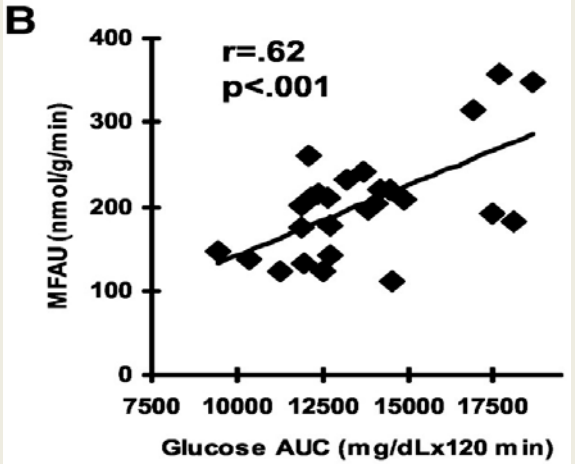
American Heart Association
Learn and Live
Circulation

Effect of Obesity and Insulin Resistance on Myocardial Substrate Metabolism and Efficiency in Young Women

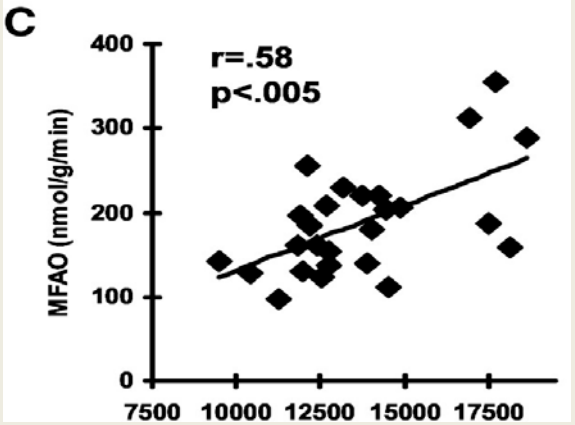
Fatty Acids Uptake



Fatty Acids Utilization



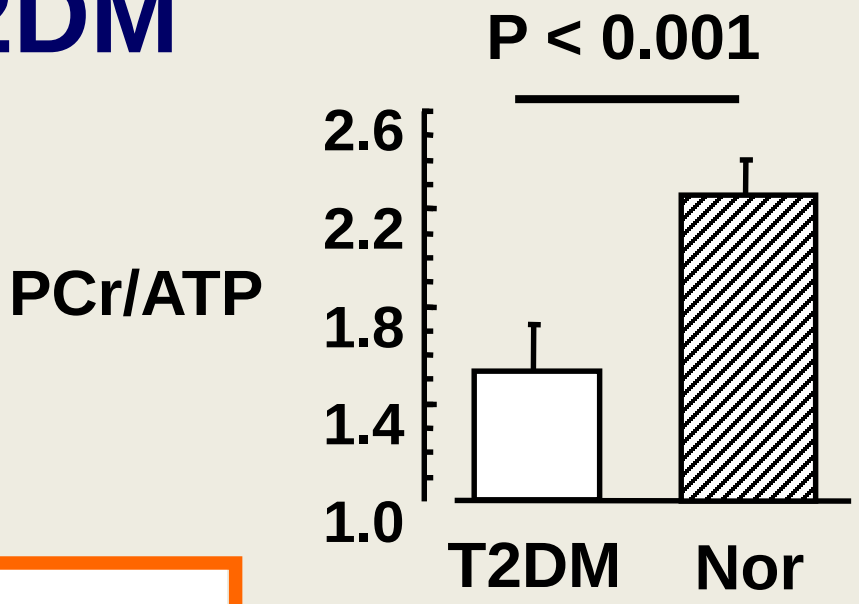
Fatty Acids Oxidation

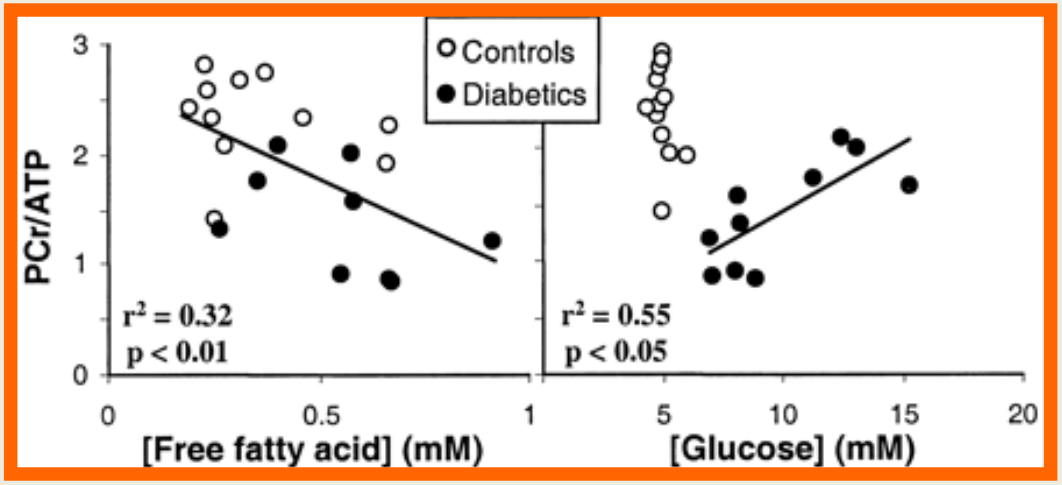


Peterson L R et al Circulation, 2004 (slightly modified)

Copyright ©2004 American Heart Association

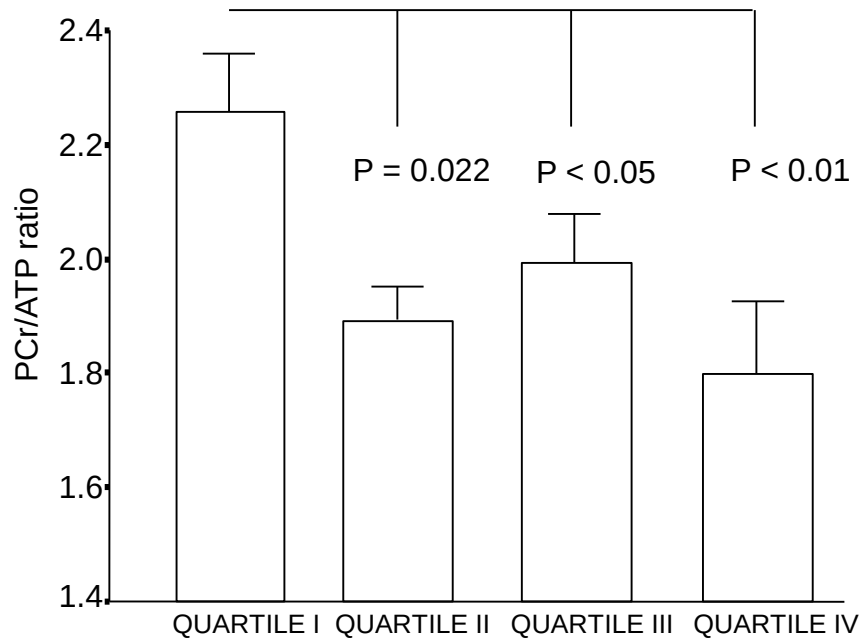
Cardiac energy metabolism in T2DM



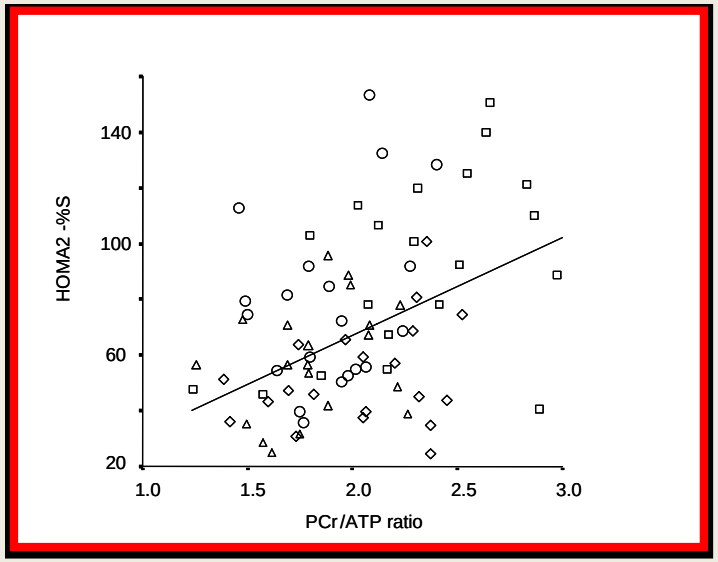


Scheuermann-Freestone M et al, *Circulation* 2003

Cardiac energy metabolism in non diabetic obese individuals



One-way ANOVA and Bonferroni post hoc

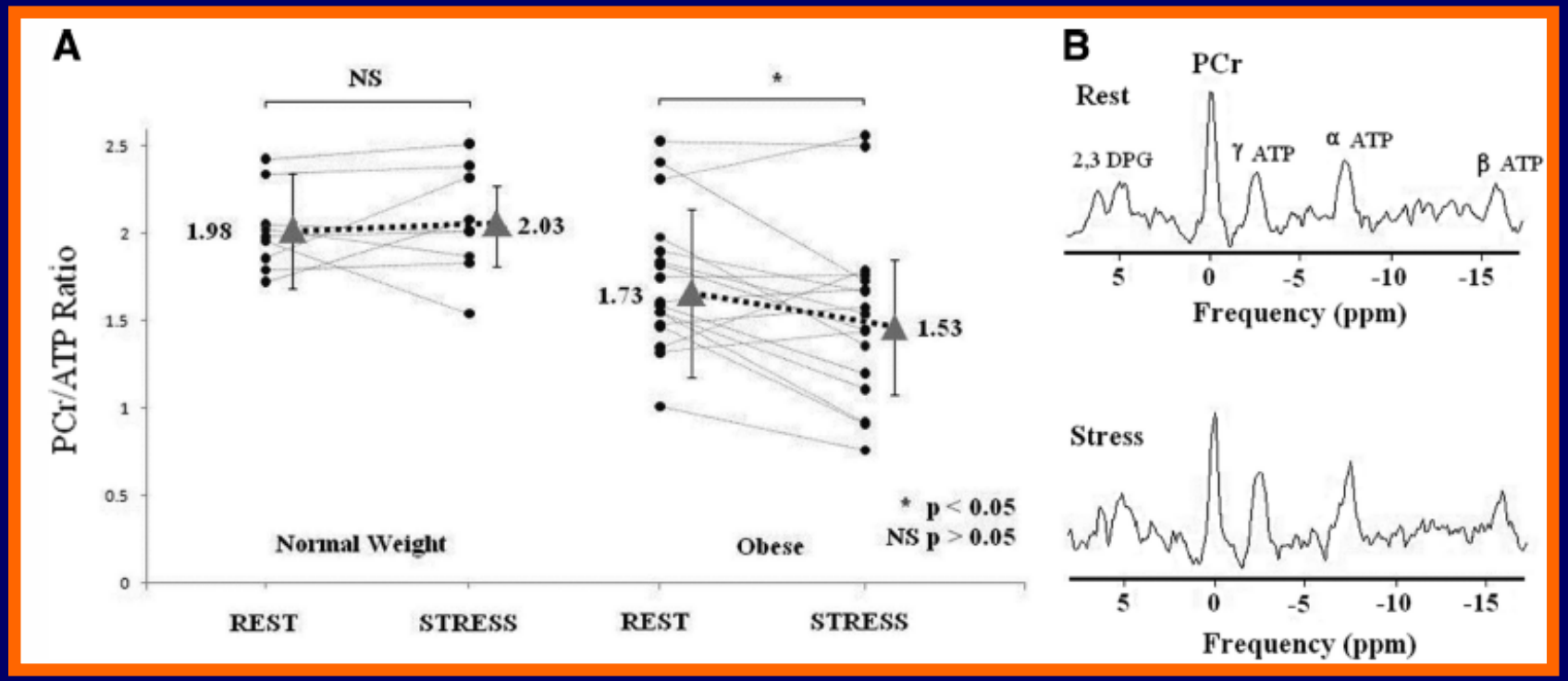


r = 0.43; P < 0.001

Quartile I: 18.5-23.2 kg/m^2
II: 23.3-25.5 “
III: 25.5-29.0 “
IV: 30.0-35.3 “

Perseghin G et al, *Diabetes Care* 2007

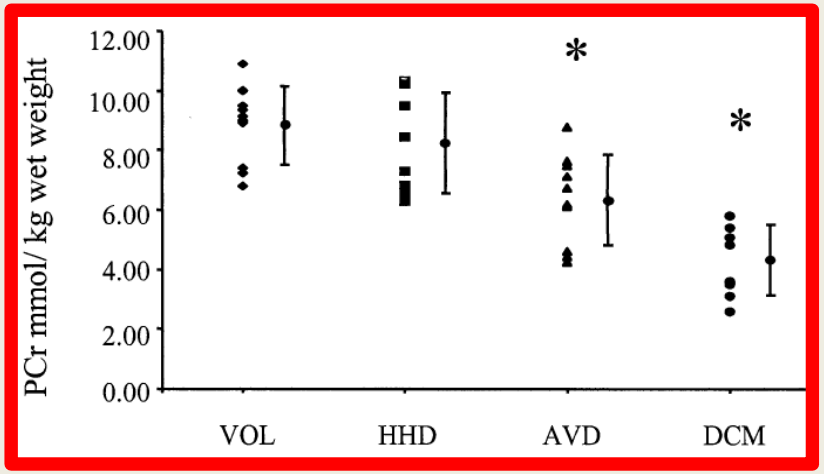
Obesity: metabolic abnormalities and functional alterations during catecholamine stress test

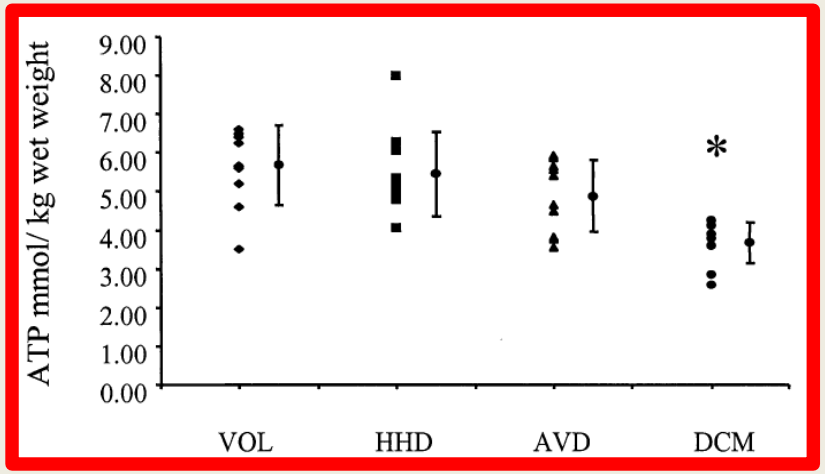


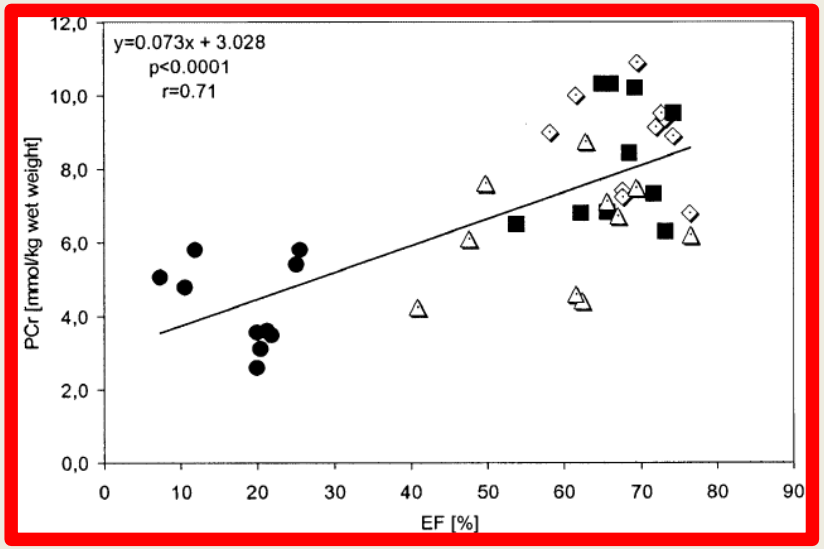
Rider OJ et al, *Circulation* 2012

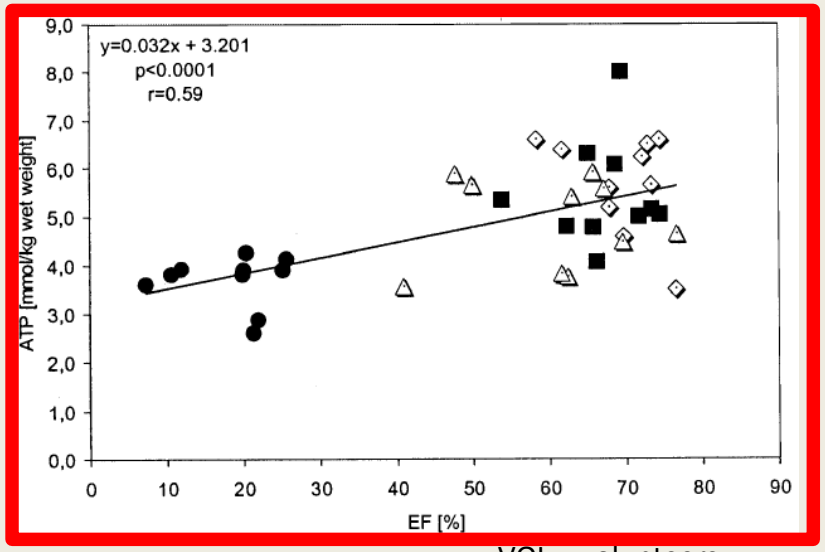
Heart failure; metabolic failure

Cardiac PCr/ATP ratio in heart failure
The starved heart







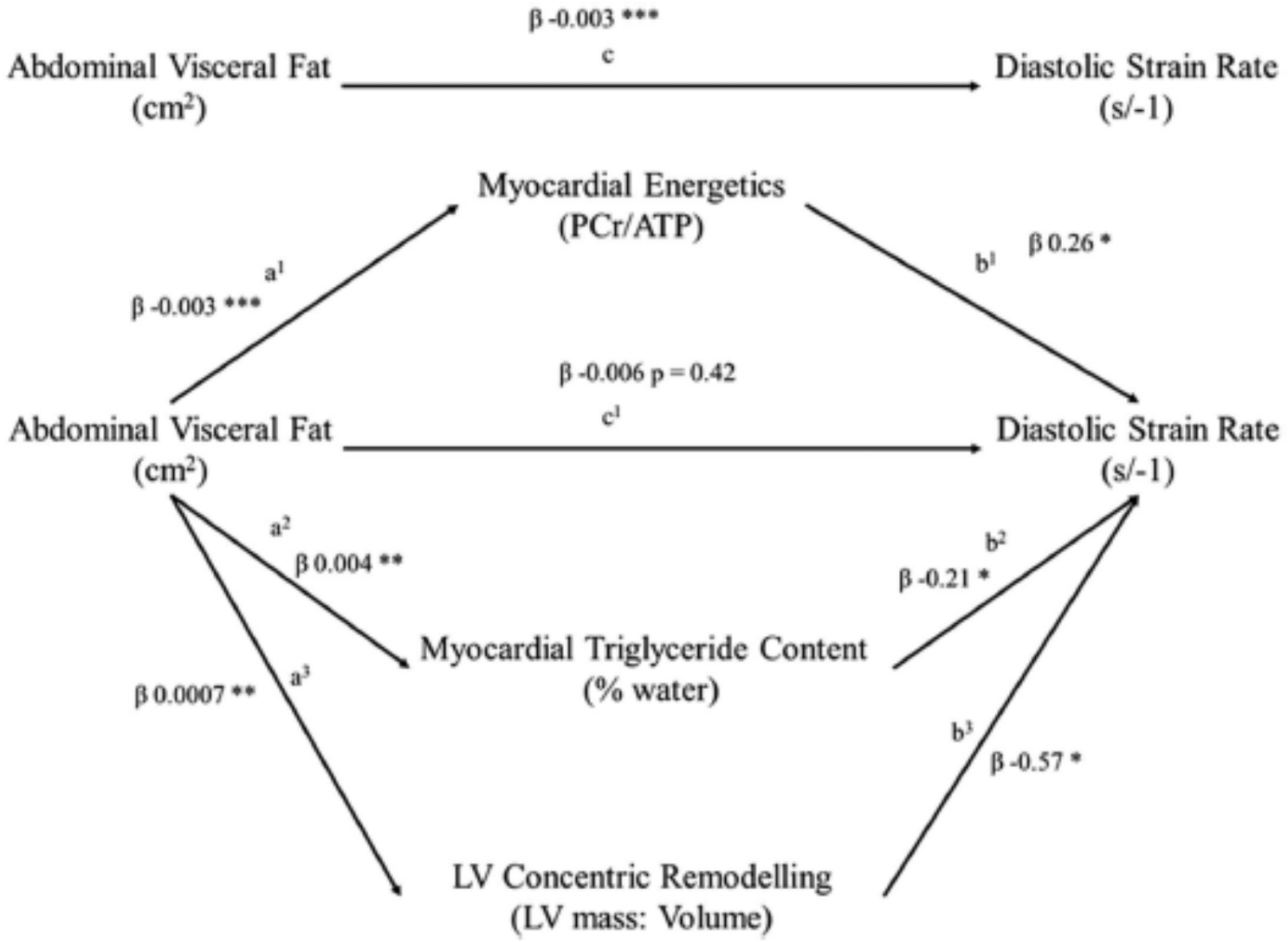


Beer et al J Am Coll Cardiol 2002

VOL = volunteers
HHD = hypertensive heart disease
AVD = aortic valve disease
DCM = dilated cardiomyopathy

Interventional Strategies

Rationale



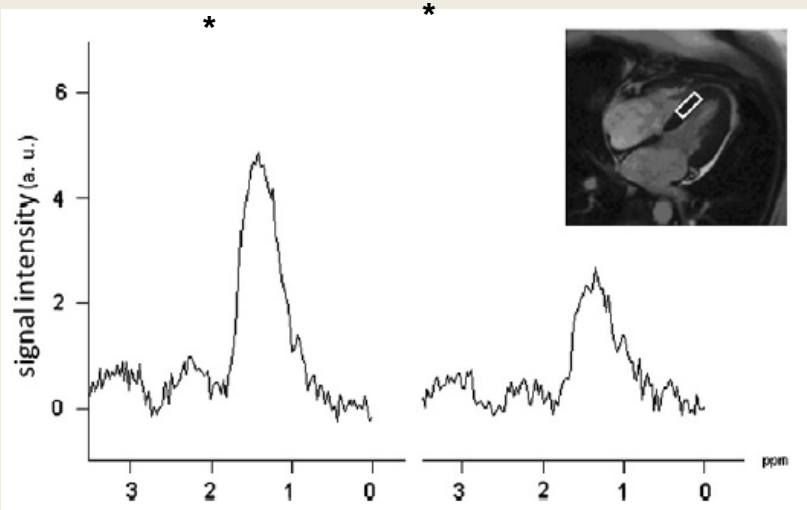
Riden L et al Int J Obesity, 2017

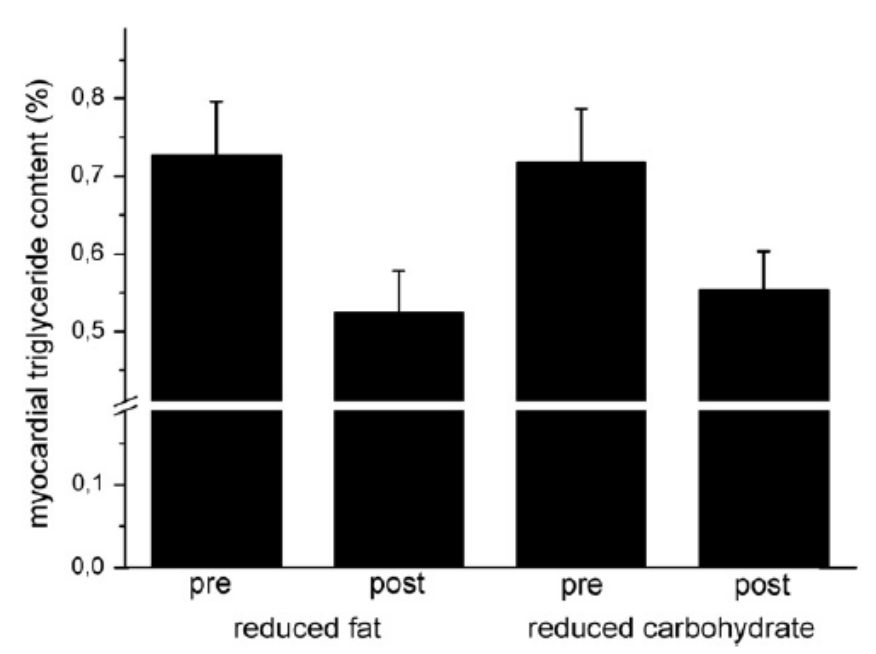
Interventional Strategies

Nutritional/Surgical

Nutritional intervention on cardiac fat and function

6 mo, n=38 (overwt/ob)
↓ carb, ↓ fat
-5.4 kg





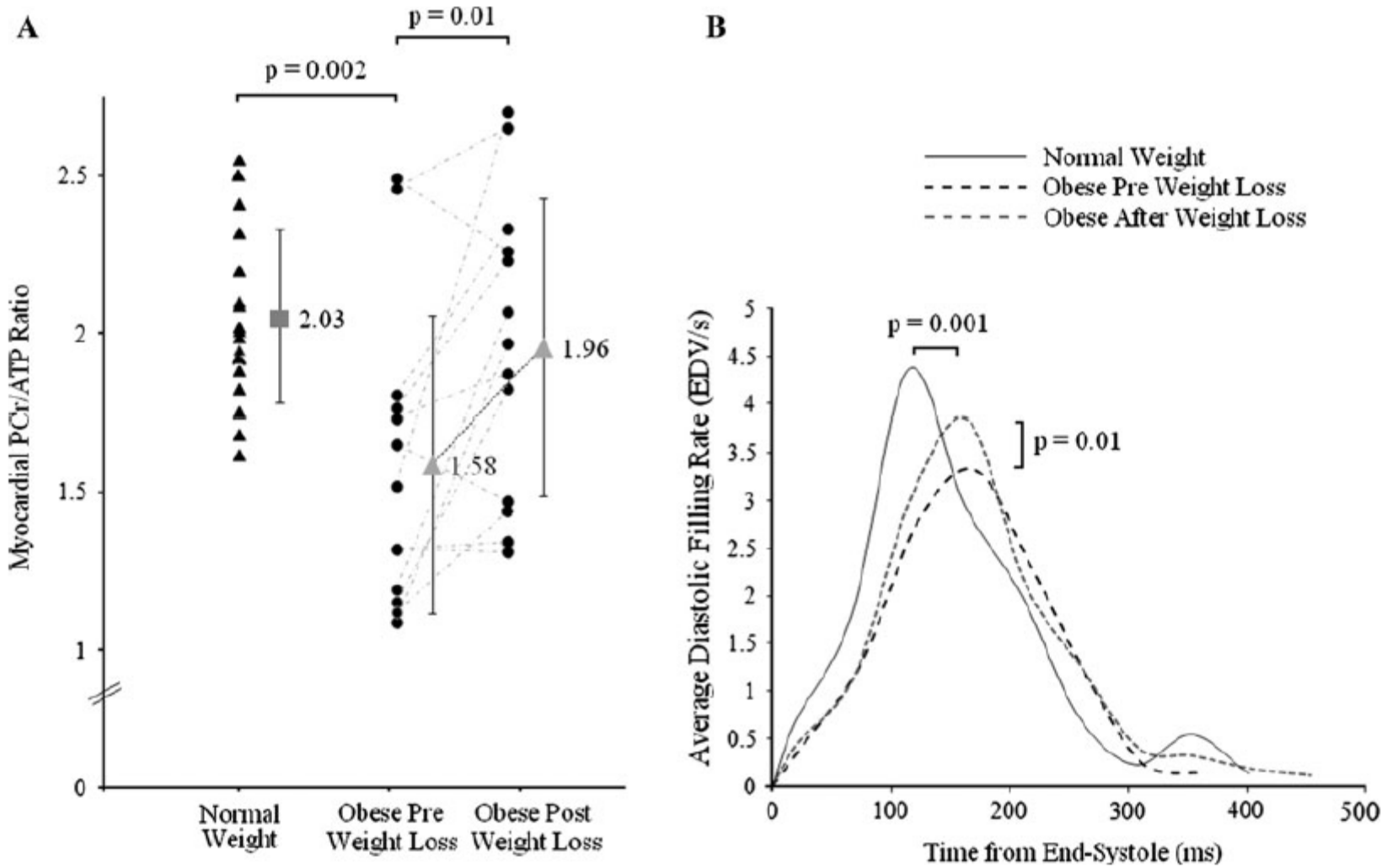
- ↓ LV mass, cardiac output, heart rate
- ↑ Diastolic function

Changes in cardiac fat & parameters did not correlate

Utz et al Int J Cardiol 2012

Effects of bariatric surgery on cardiac fat and function

Int J Cardiovasc Imaging (2013) 29:1043–1050



Interventional Strategies drugs

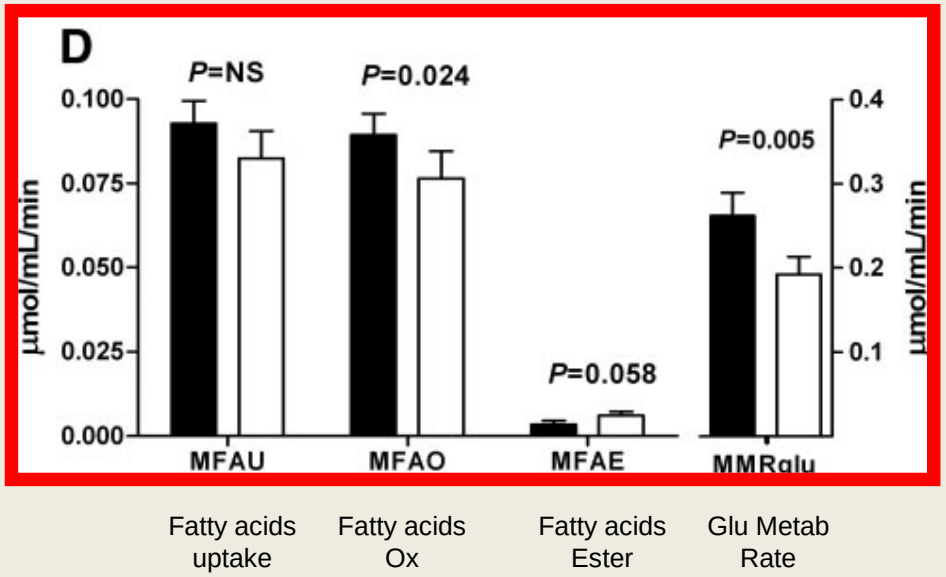
Effects of Met and Pio in T2DM without heart failure

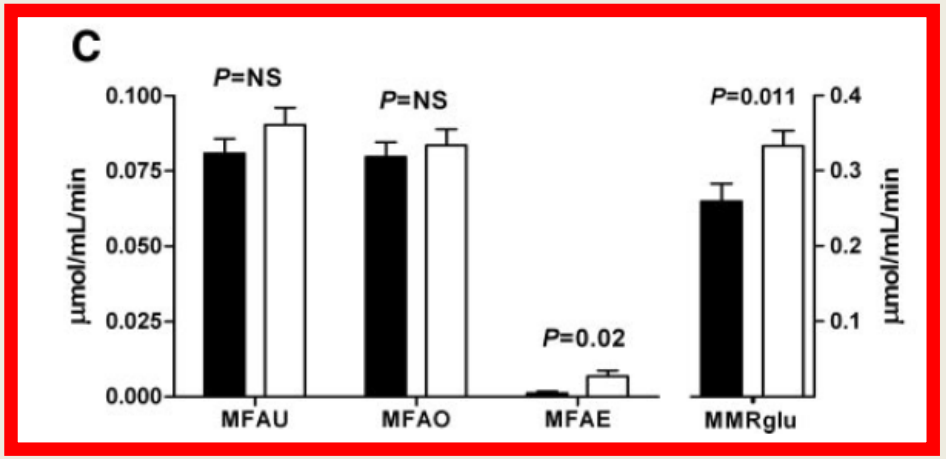
Metformin
2 g/die

78 T2DM

24 weeks

Pio
30 mg/die





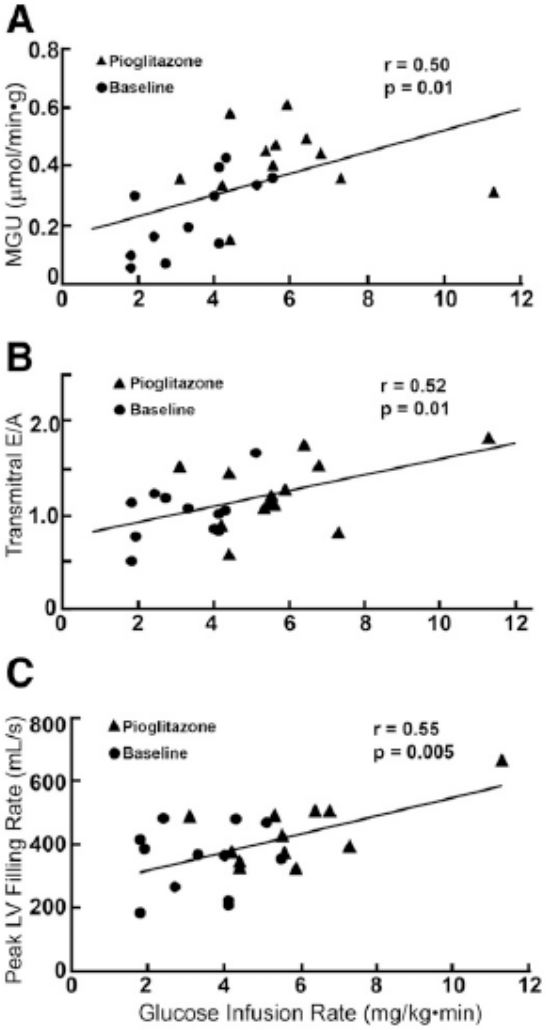
PET techniques
Fatty acids 11C palmitate
fasting
Glucose: (18FDG)
clamp

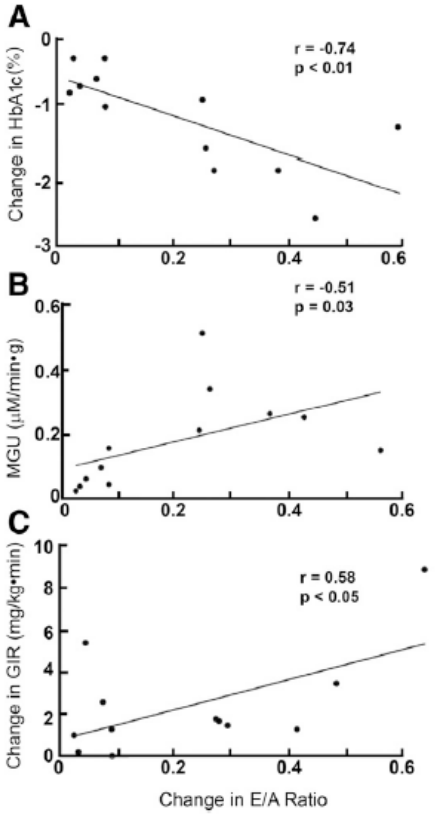
van den Meer RW et al. Circulation, 2009

Pioglitazone Improves Left Ventricular Diastolic Function in Subjects With Diabetes

https://doi.org/10.2337/dc17-0078

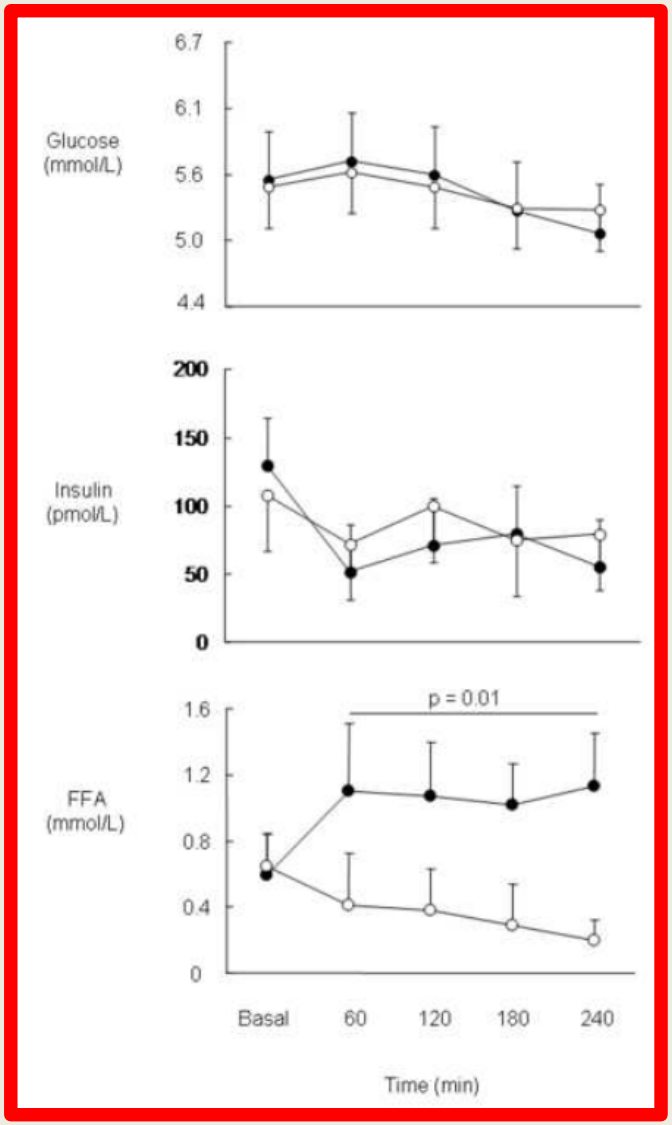
Geoffrey D. Clarke,[1,2]
Carolina Solis-Herrera,[1]
Marjorie Molina-Wilkins,[1]
Sandra Martinez,[1] Aurora Merovci,[1]
Eugenio Cersosimo,[1] Robert J. Chilton,[3,4]
Patricia Iozzo,[5] Amalia Gastaldelli,[1,5]
Muhammad Abdul-Ghani,[1] and
Ralph A. DeFronzo[1,4]

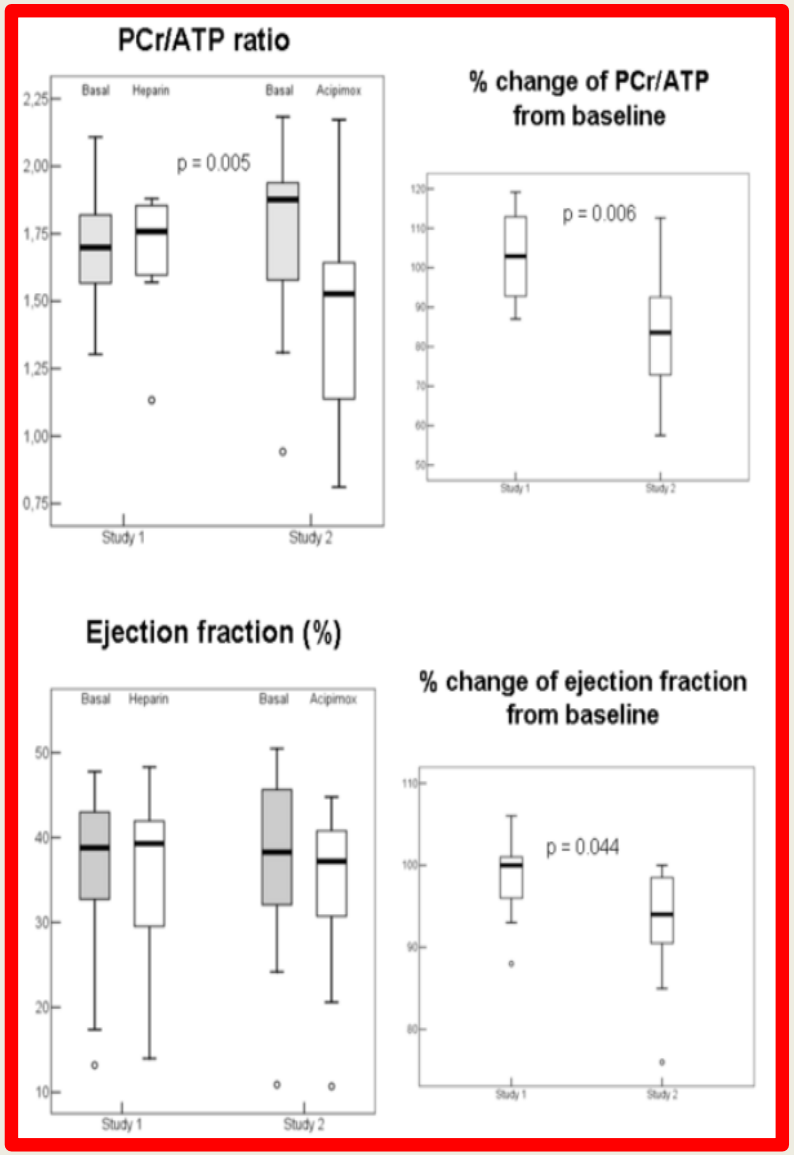




Clarke GD et al Diabetes Care, 2017

Suppression of NEFA availability

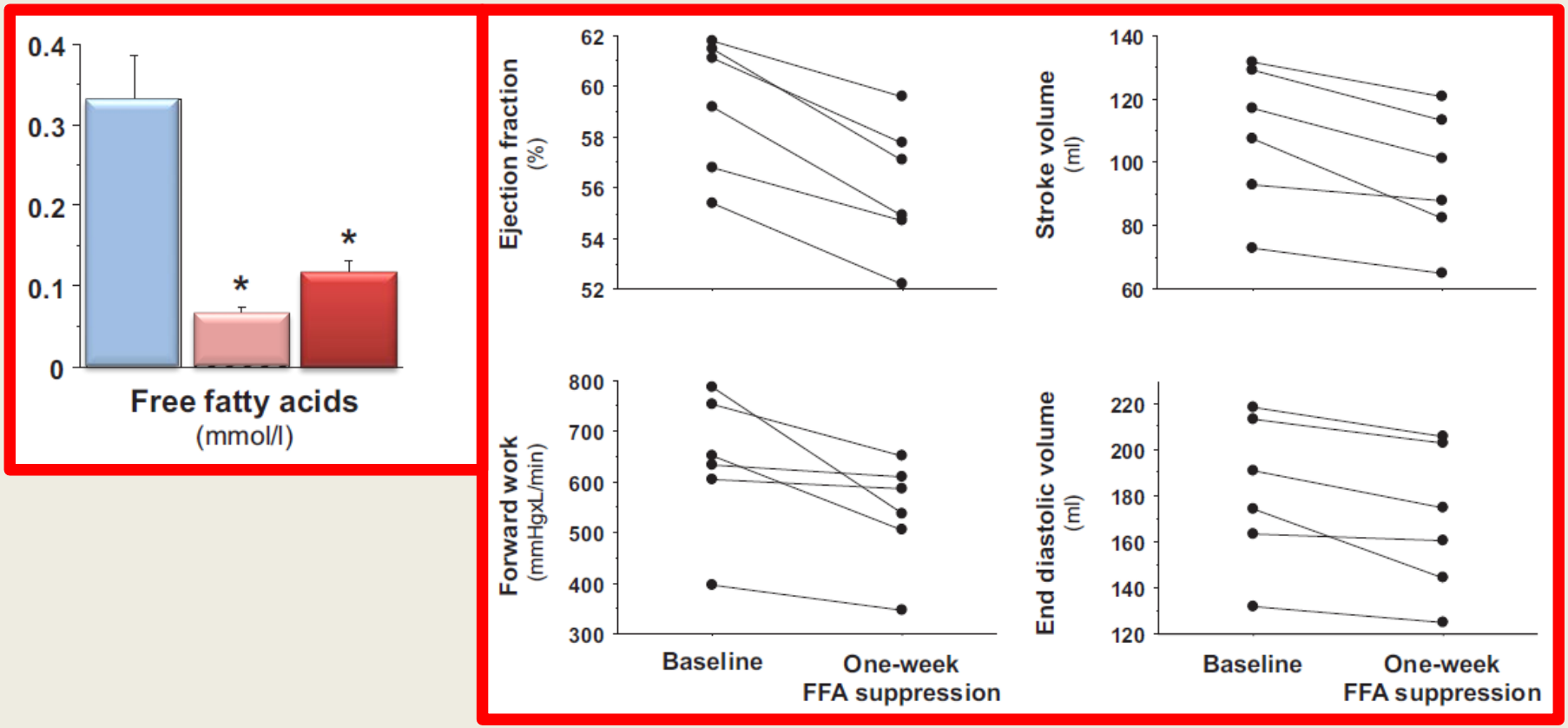




Salerno A et al Acta Diabetol 2015

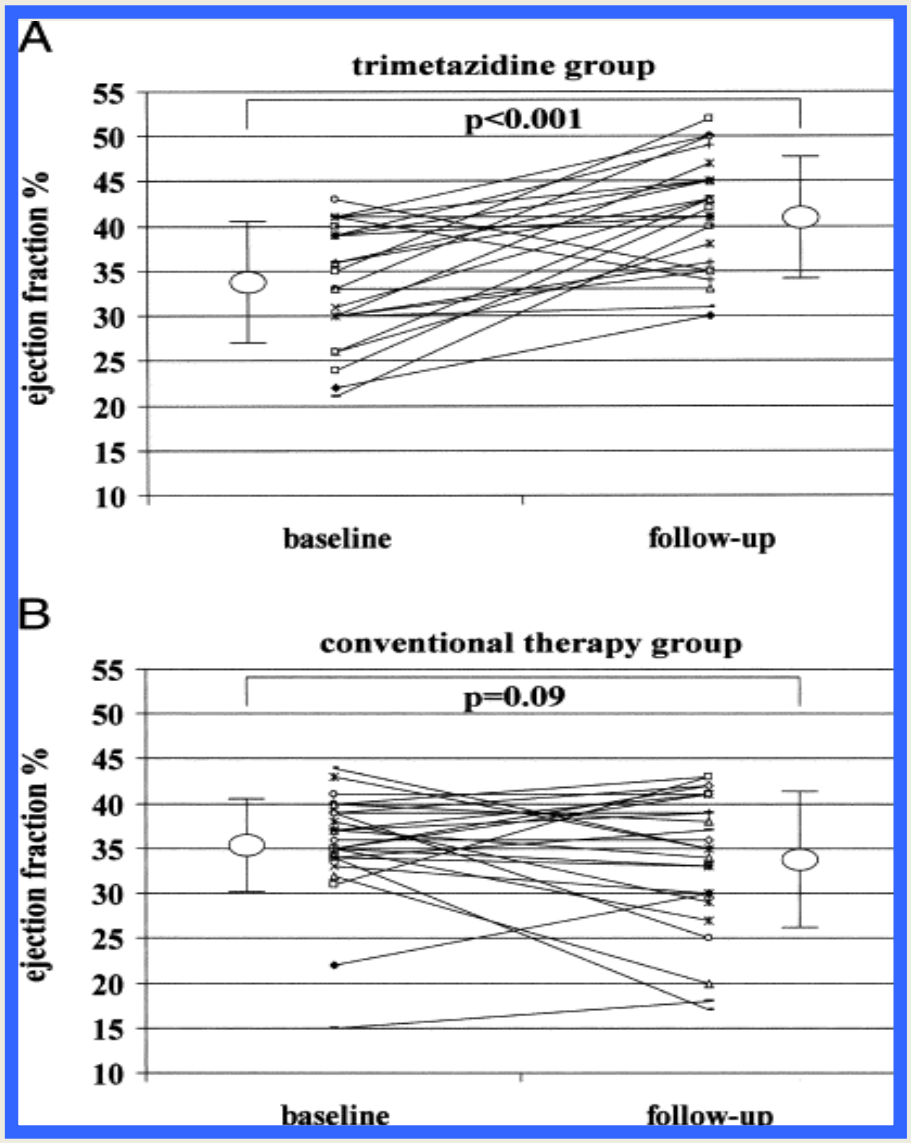
Suppression of NEFA availability

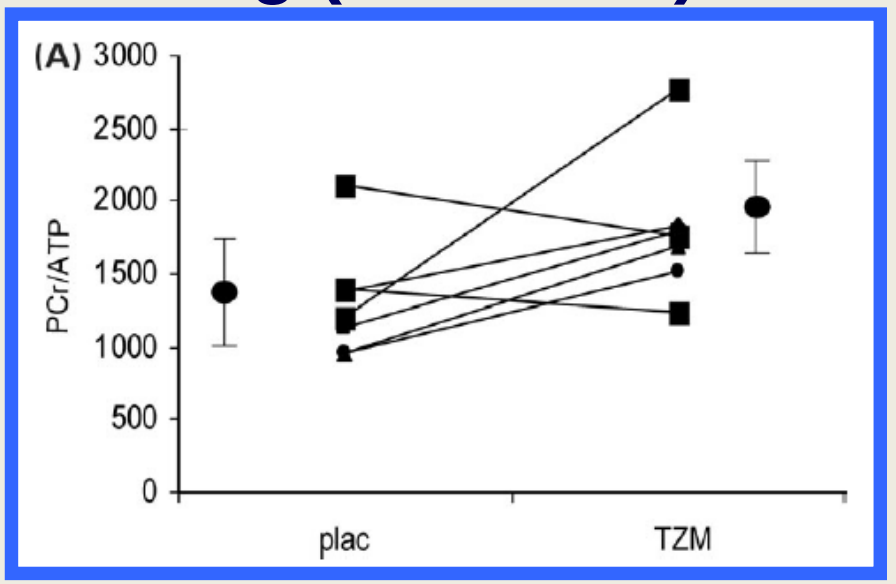
- Baseline
- Acute NEFA suppression
- One-week NEFA suppression

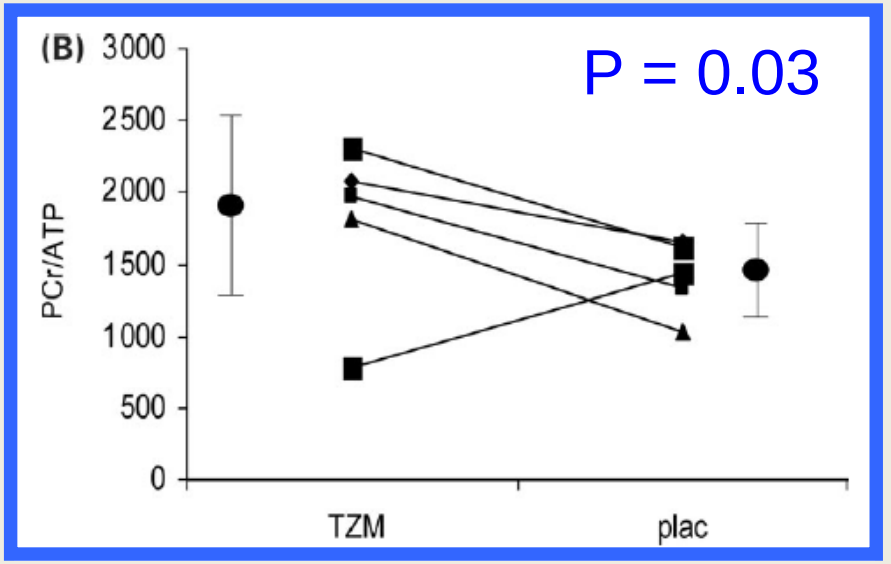


Lehto R et al J Clin Endocrinol Metab 2011

Metabolic therapy in cardiac failure: effects of Trimetazidine in the chronic setting (3 months)







Fragasso G et al, *Eur Heart J* 2006

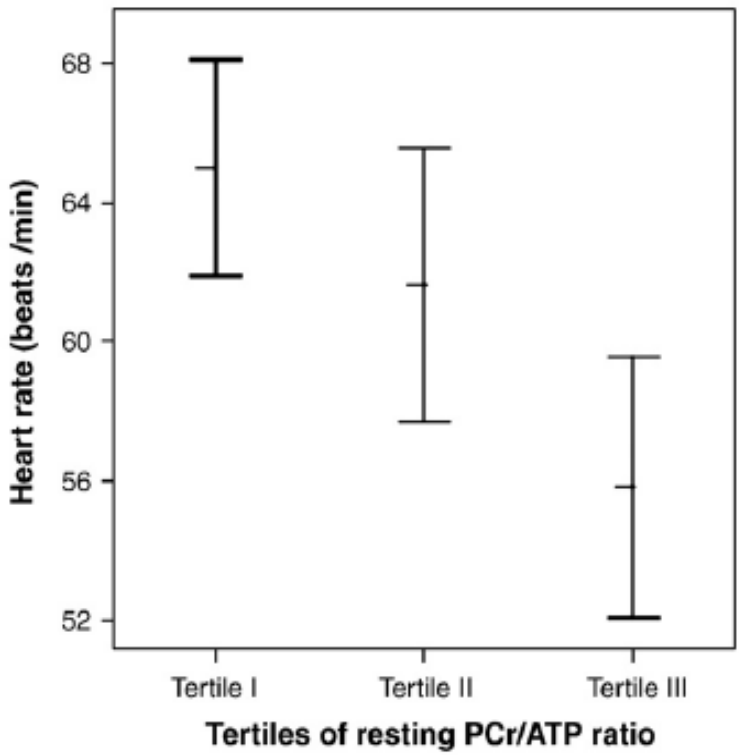
Cardiac energy metabolism & heart rate

Table I. Anthropometric, clinical and laboratory features of study subjects by tertiles of PCr to ATP ratio

	Tertile I	Tertile II	Tertile III
PCr/ATP	1.55 ± 0.18 range: 1.08-1.79	2.03 ± 0.13 range: 1.80-2.23	2.49 ± 0.24 range: 2.24-3.15
Age (years)	33 ± 7	34 ± 10	34 ± 12
Weight (kg)	82 ± 15*	78 ± 10	72 ± 9
Height (cm)	176 ± 7	178 ± 6	176 ± 7
BMI (kg/m^2)	26.3 ± 4.4*	24.8 ± 3.5	23.5 ± 2.8
PAI	7.9 ± 1.4	8.1 ± 1.7	8.5 ± 1.5
Systolic BP (mm Hg)	123 ± 10	124 ± 8	123 ± 9
Diastolic BP (mm Hg)	83 ± 7*	83 ± 8	77 ± 8
Total cholesterol (mg/dL)	186 ± 36	203 ± 48	182 ± 34
HDL-C (mg/dL)	50 ± 13	60 ± 15	56 ± 13
Triglycerides (mg/dL)	120 ± 115	100 ± 84	85 ± 40
Glucose (mmol/L)	5.1 ± 0.5*	5.1 ± 0.4*	4.8 ± 0.5
Insulin (μU/mL)	14.5 ± 5.9	13.7 ± 4.3	11.6 ± 6.7
HOMA-IR	3.3 ± 1.2*	3.2 ± 1.1	2.5 ± 1.3
FFA (mmol/L)	0.59 ± 0.21	0.58 ± 0.21	0.61 ± 0.22
Creatinine (mg/dL)	1.13 ± 0.78	0.97 ± 0.48	0.97 ± 0.23

Data are shown as mean ± 1SD.
BP, Blood pressure.
* $P < .05$ versus tertile III (one-way ANOVA and Bonferroni post hoc or Kruskal-Wallis non-parametric test).

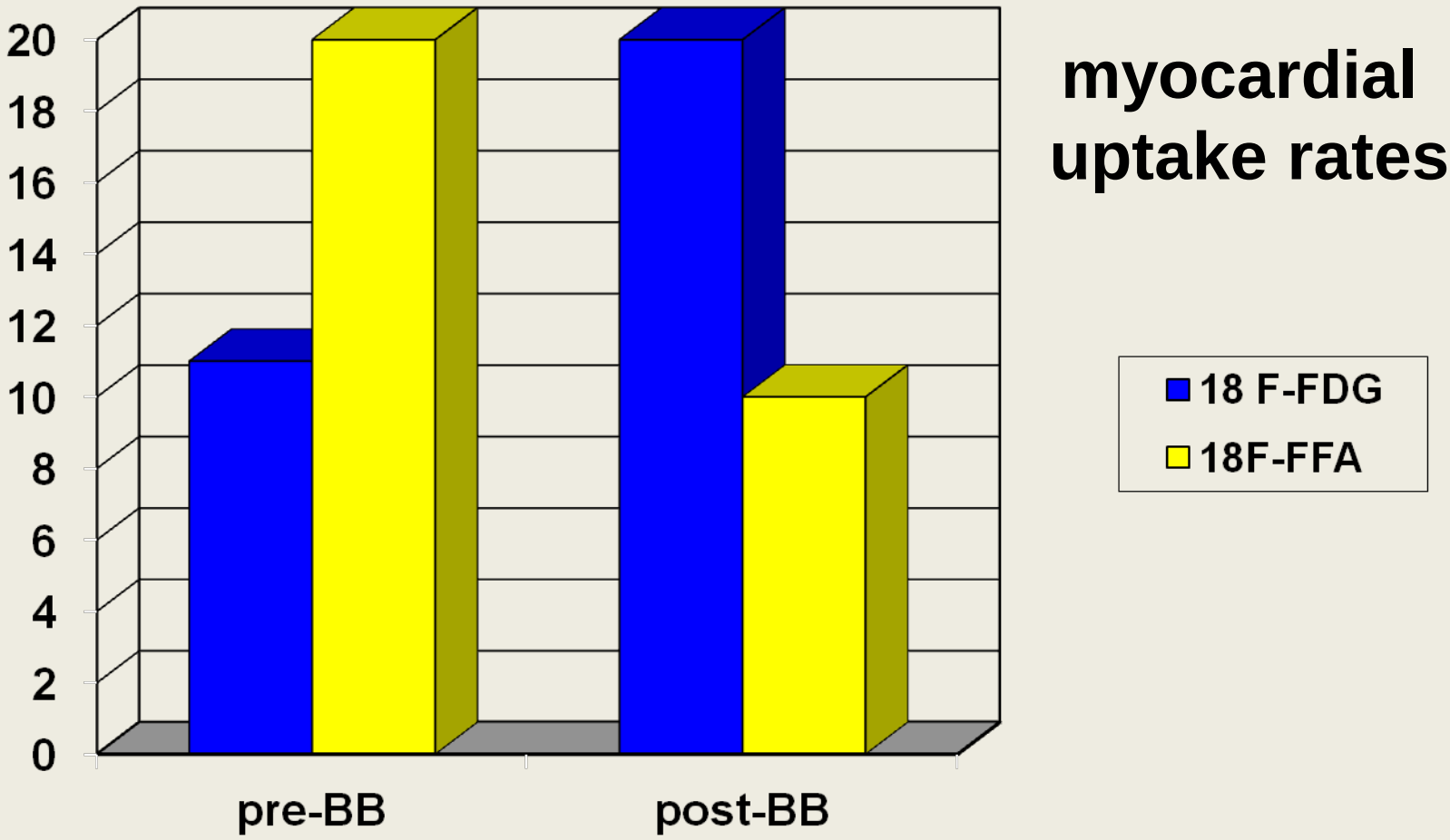
Figure 1



Tertiles of PCr/ATP ratio and heart rate. Spearman ρ –0.37; P = .0001. Data are means ± 95% CI.

Fragasso G et al Am Heart J, 2011

Myocardial FFA/Glucose Use After Carvedilol Treatment in Patients With Congestive Heart Failure

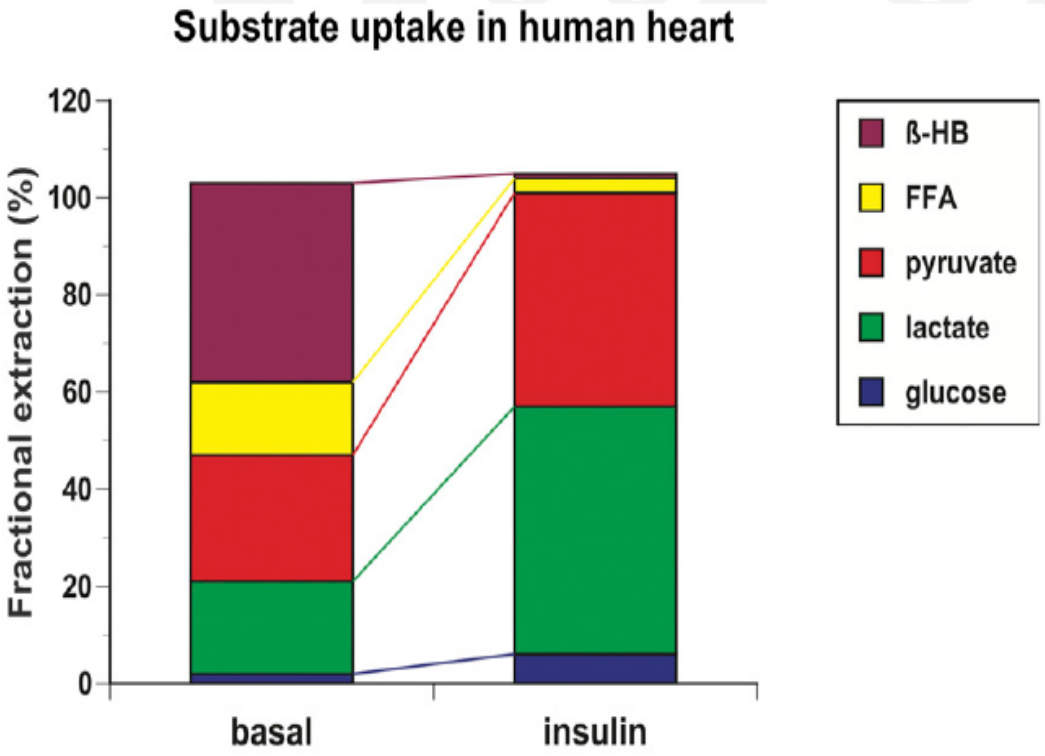


Wallhaus TR, et al, Circulation 2001

CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis

Ele Ferrannini,[1] Michael Mark,[2] and Eric Mayoux[2]

Diabetes Care 2016;39:1–7 | DOI: 10.2337/dc16-0330



SGLT2 in

Accelerated lypolisis
Reduced portal insulin/glucagon ratio
Higher hepatic lipid oxidation

Increased production of B-OH butyrate

Take home messages

Excessive cardiac fat accumulation appears to be a marker of insulin resistance and cardiac dysfunction rather than a pathogenic factor, even if – with few exceptions – it truly reflects metabolic derangements

Altered cardiac energy metabolism, related to abnormal substrates' disposal, is associated with altered cardiac function and may be pathogenically related

Modulation (up-regulation/down-regulation) of energy metabolism may represent a strategy to improve cardiac insulin sensitivity and function; patient's targeted approaches are likely to be preferable