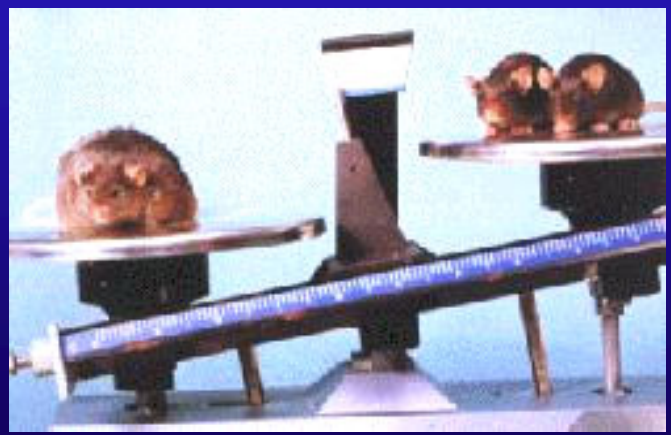
Animal Models of Type II Diabetes

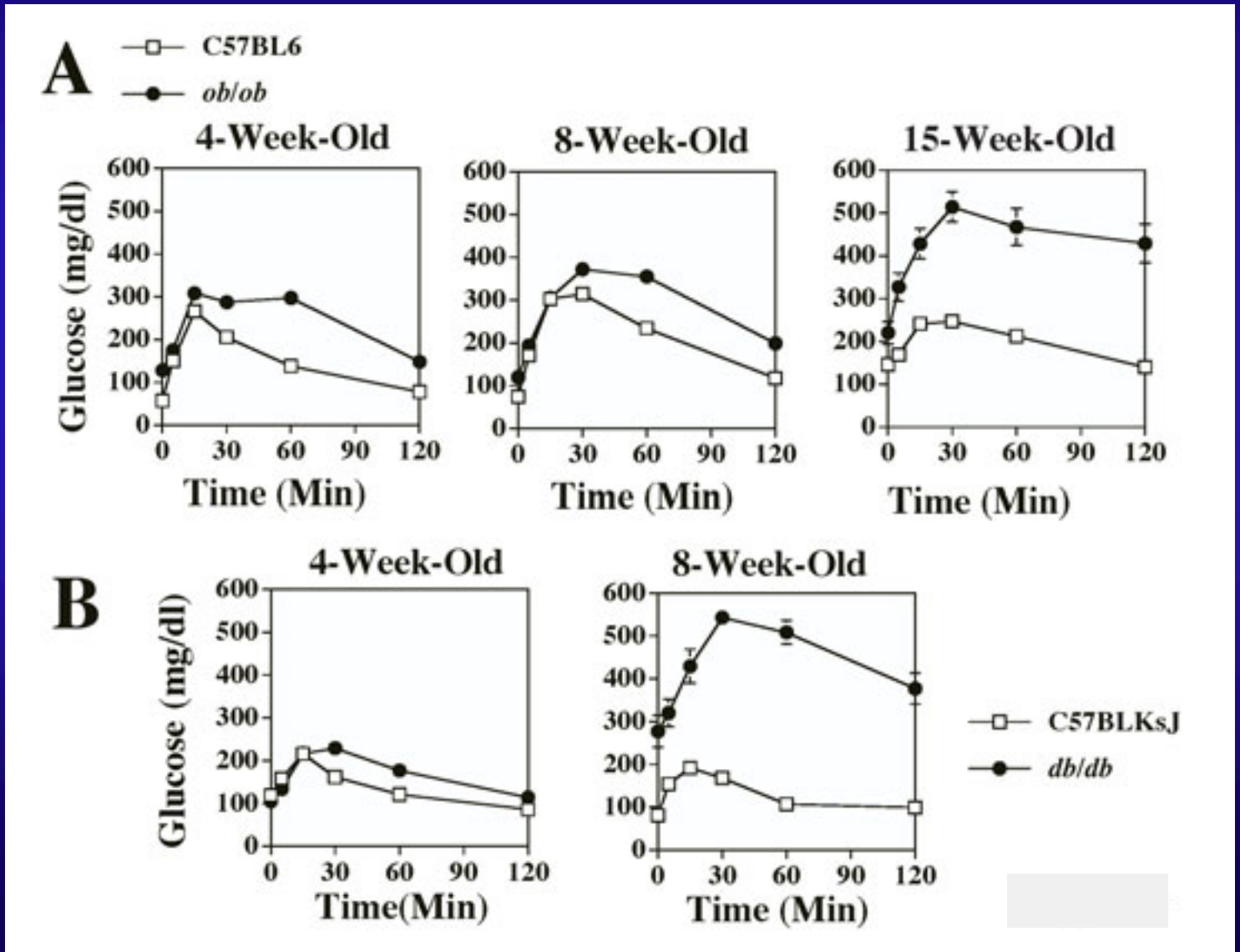
The Jackson Laboratory

9 week-old males ***db/db*** (C57BL/KsJ-*db/db*) mice & homozygous normal lean (C57BL/KsJ) litter mates



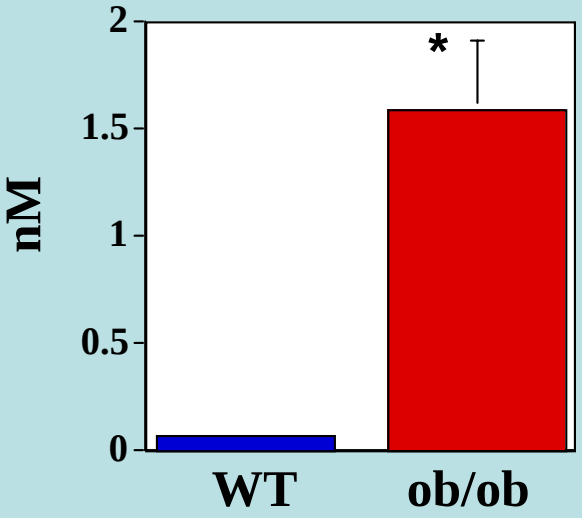
9 week-old males ***ob/ob*** (C57BL/J6-*ob/ob*) mice & homozygous normal lean (C57BL/J6) litter mates

Glucose Tolerance Tests in ob/ob and db/db Mice as a Function of Age

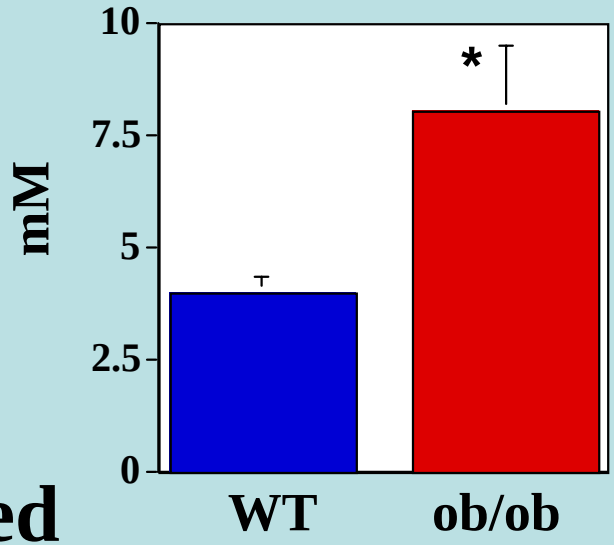


Metabolic Characteristics of ob/ob Mice

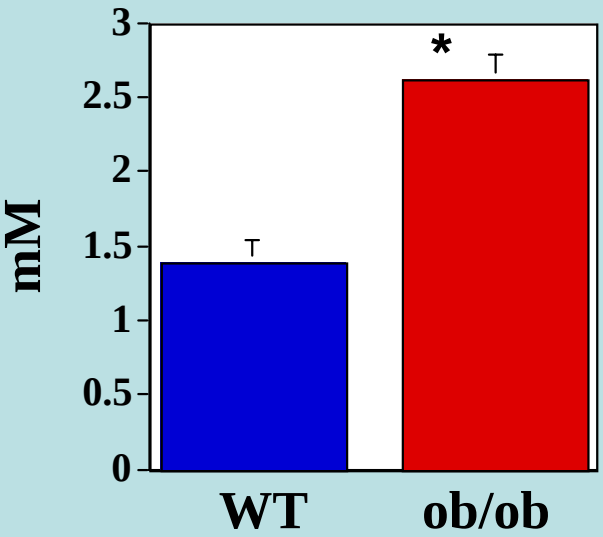
Serum Insulin



Serum Triglycerides



FFA -Fed



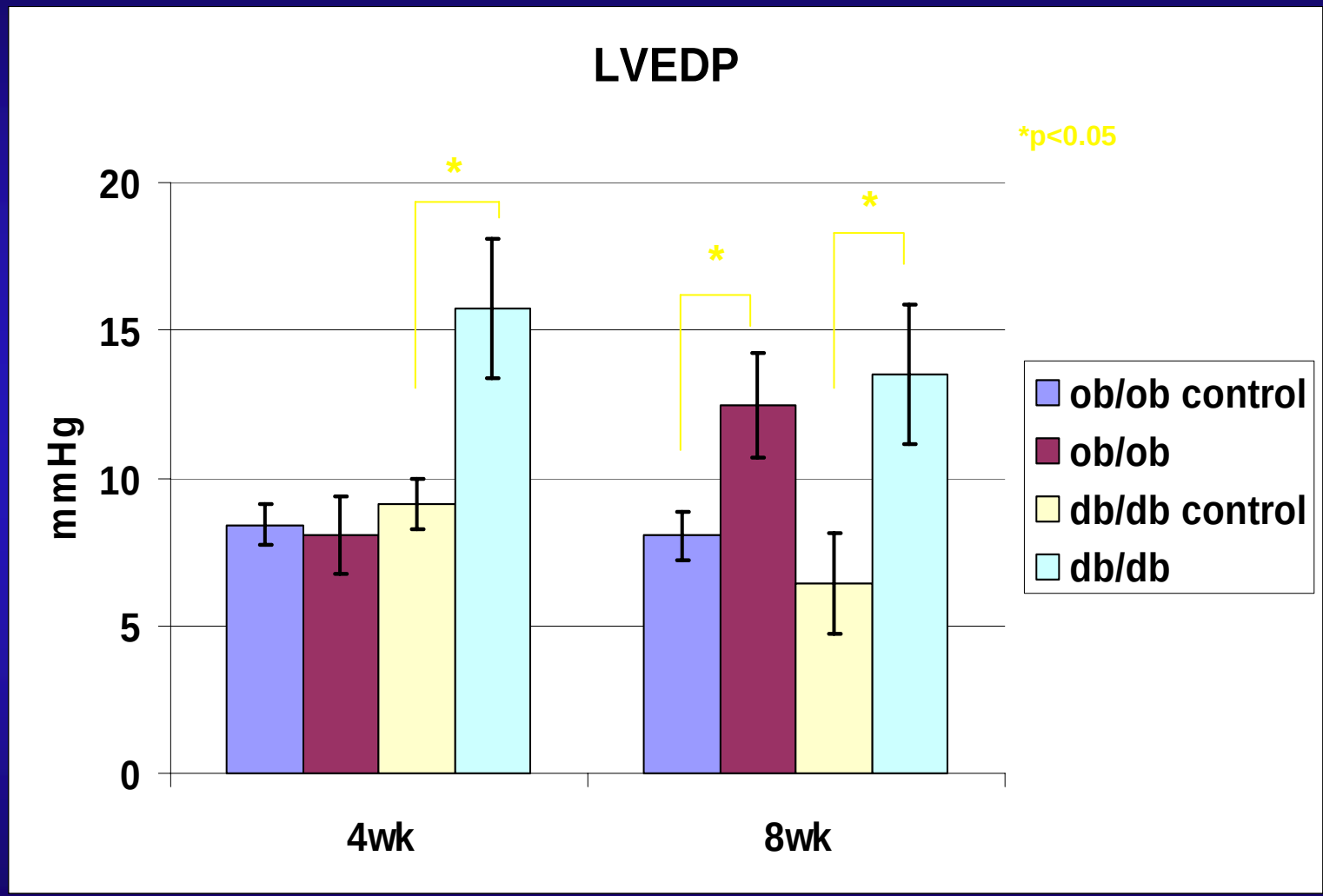
LV Dilatation in 8-week-old ob/ob Mice

Control

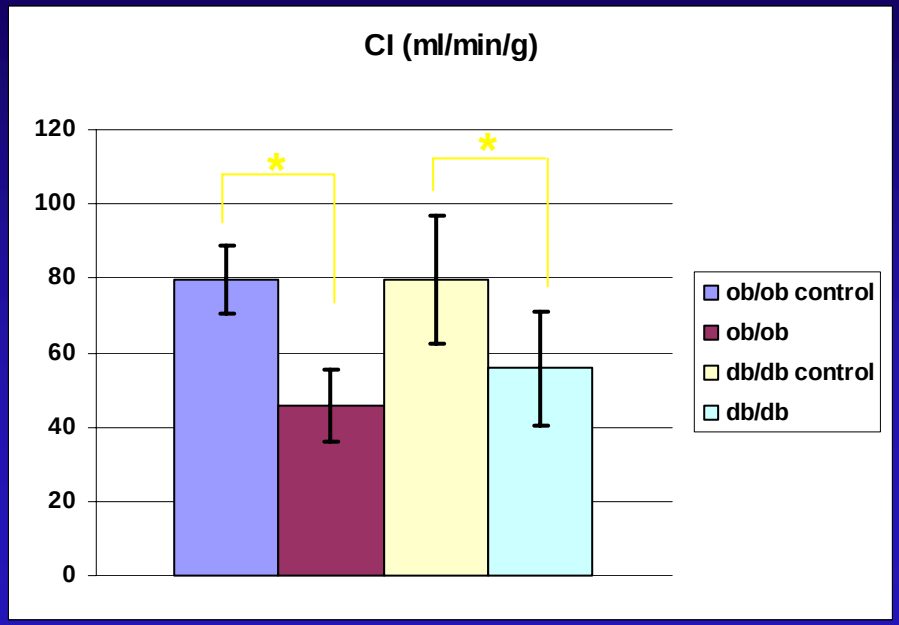
Ob/ob

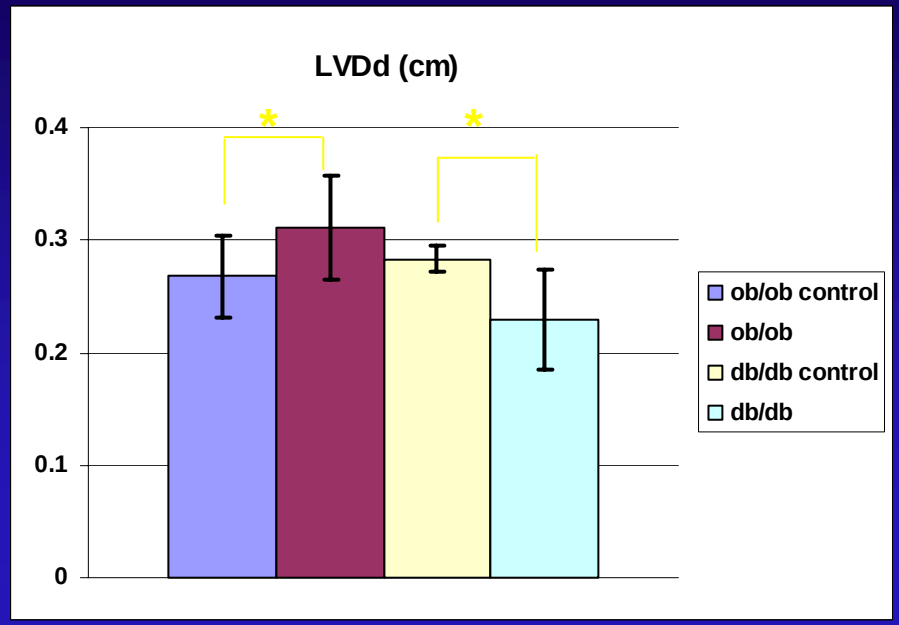
Ob/Ob Mice

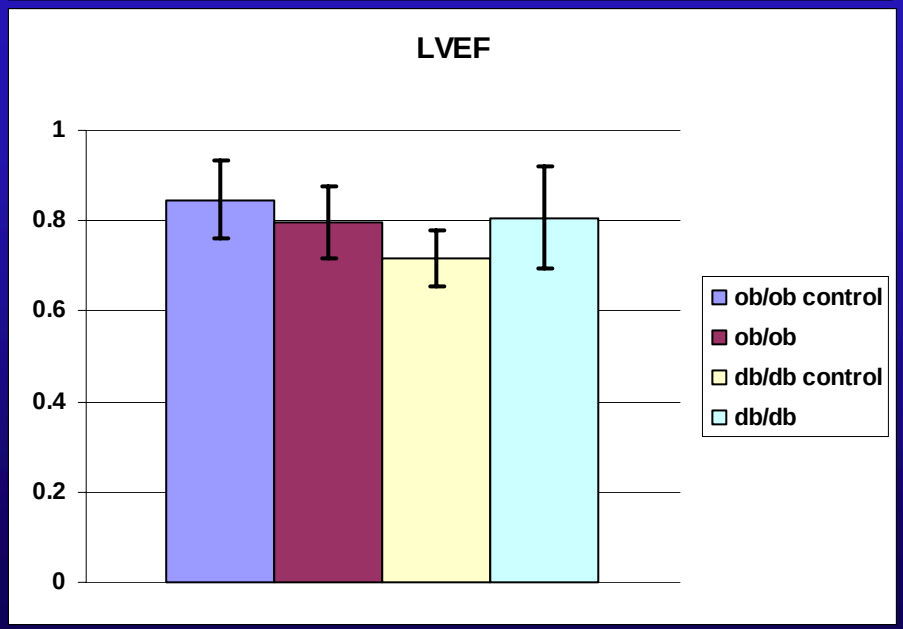
- Decreased Ejection Fraction
- Increased LV Mass
- LV Dilatation
- Increased dP/dT


LVEDP
*p<0.05
mmHg
20
15
10
5
0
4wk
8wk
ob/ob control
ob/ob
db/db control
db/db

4 wk ob/ob, db/db & control ECHO





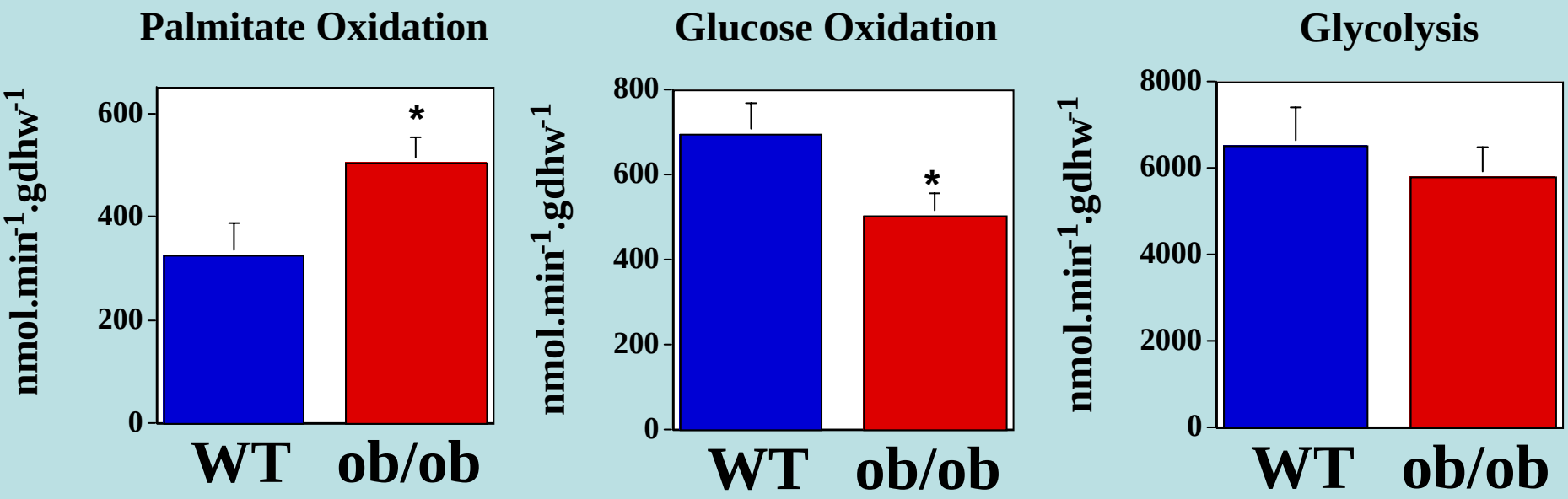


*** p < 0.05 vs. control**

Both ob/ob and db/db mice exhibit normal LV ejection fraction but decreased cardiac index at 4 weeks. In contrast, ob/ob mice exhibit LV dilation, while db/db mice exhibit decreased cavity size.

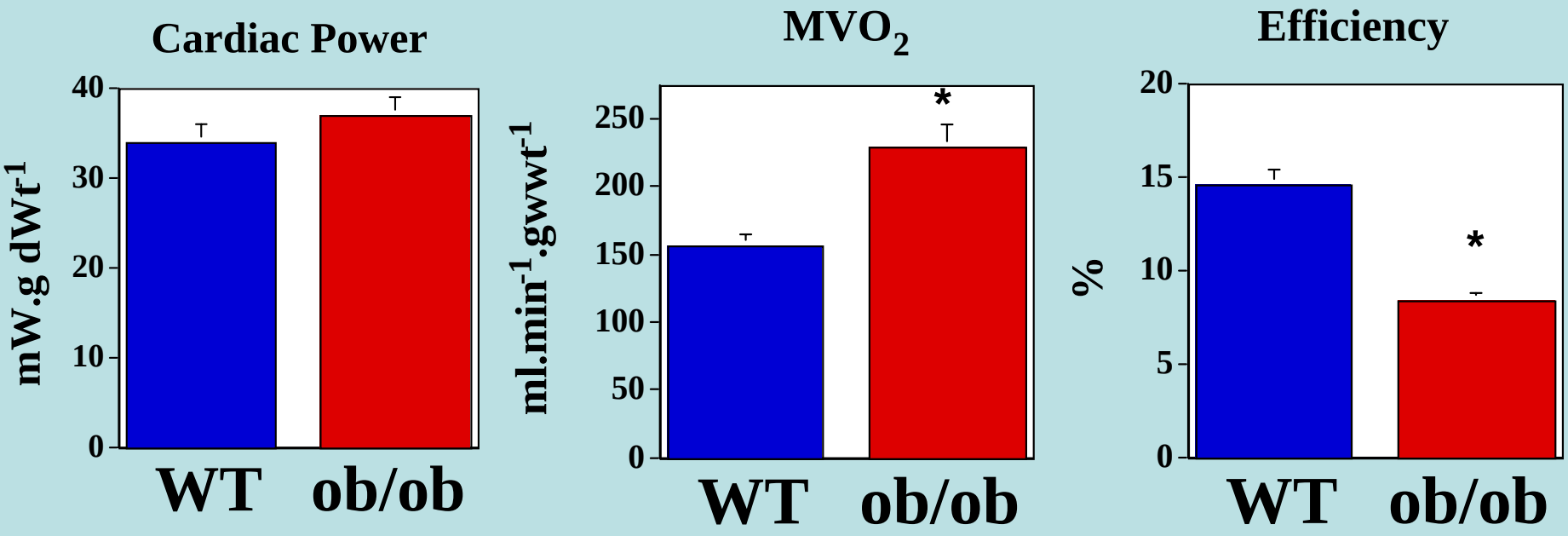
Myocardial Triglyceride Content of ob/ob Hearts

Substrate Metabolism in Hearts of 4-week-old ob/ob Mice



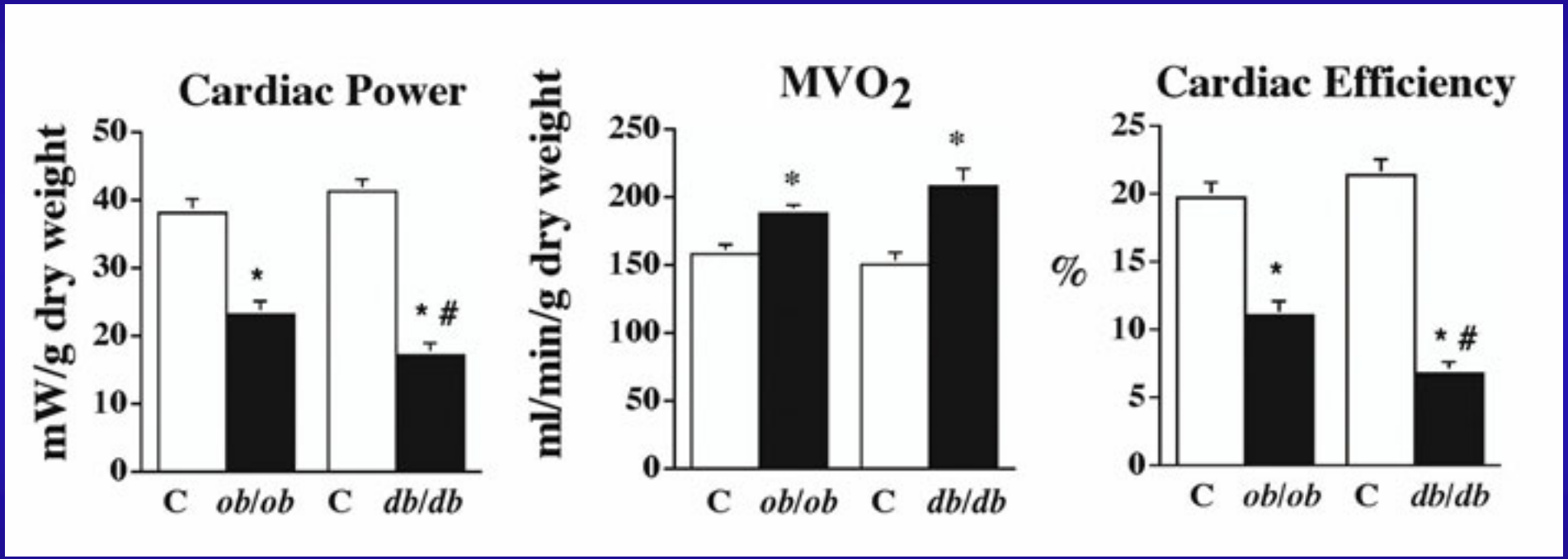
Perfusion conditions: 11mM Glucose, 1mM Palmitate, 1nM Insulin

Cardiac Performance and Myocardial Oxygen Consumption in the Hearts of 4-week-old ob/ob Mice



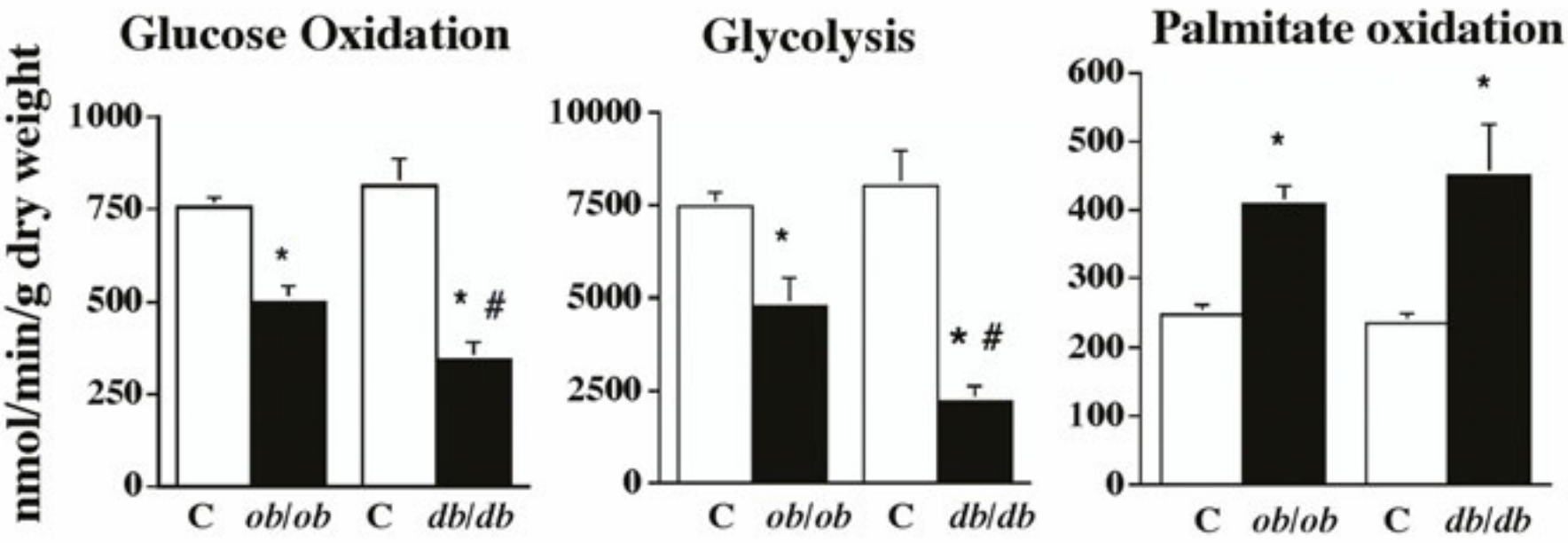
Perfusion conditions: 11mM Glucose, 1mM Palmitate, 1nM Insulin

Cardiac Performance and Myocardial Oxygen Consumption in the Hearts of ob/ob and db/db Mice at 8-10 weeks of age



Perfusion conditions: 11mM Glucose, 1mM Palmitate, 1nM Insulin

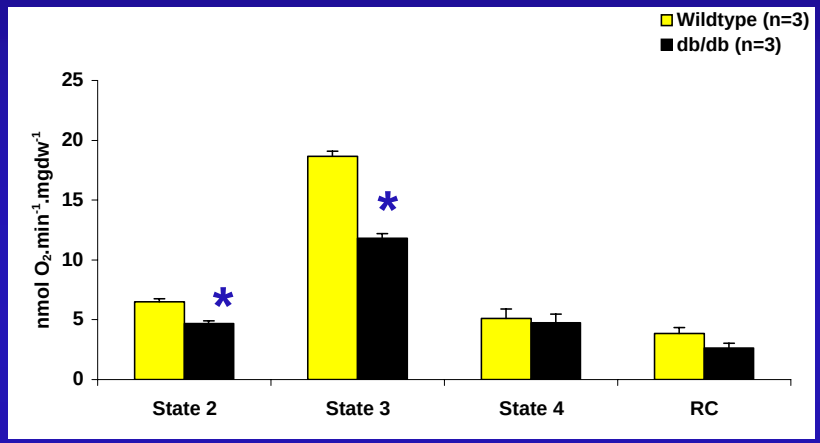
Substrate Metabolism in the Hearts of ob/ob and db/db Mice at 8-10 weeks of age

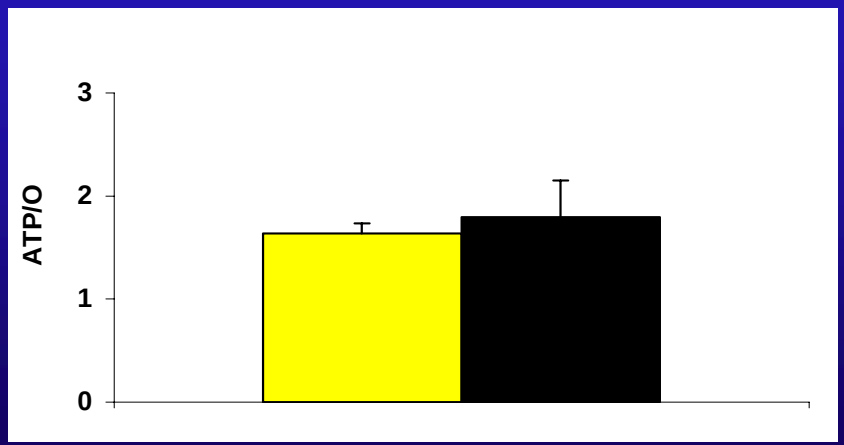


Perfusion conditions: 11mM Glucose, 1mM Palmitate, 1nM Insulin

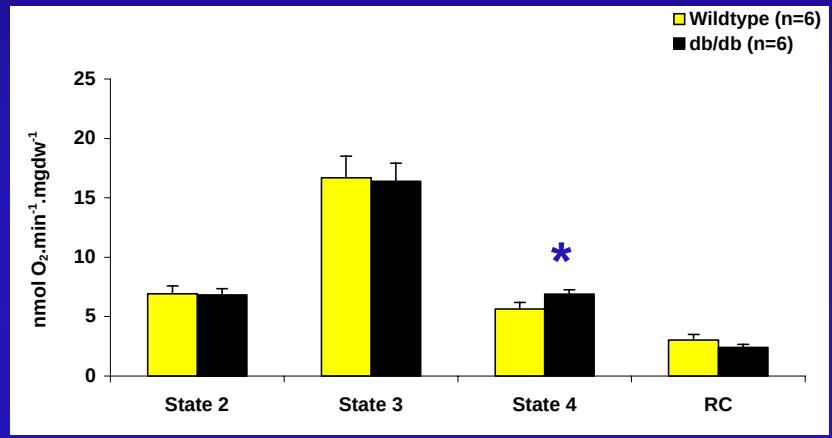
Mitochondrial Dysfunction and Increased Uncoupling in Cardiac Mitochondria from db/db Mice

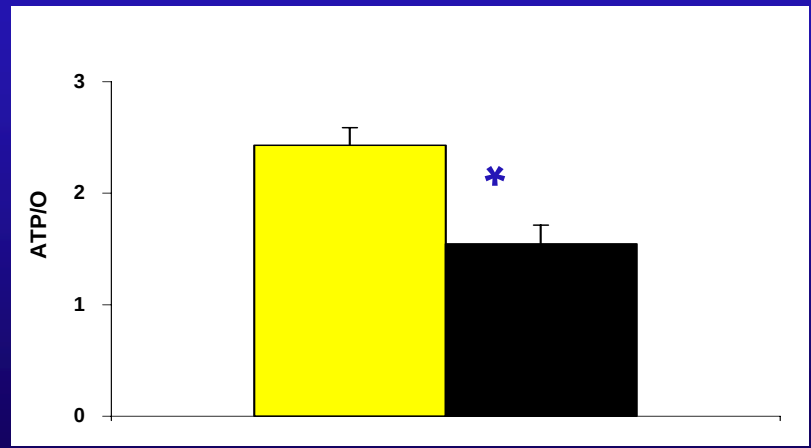
Glucose Perfused





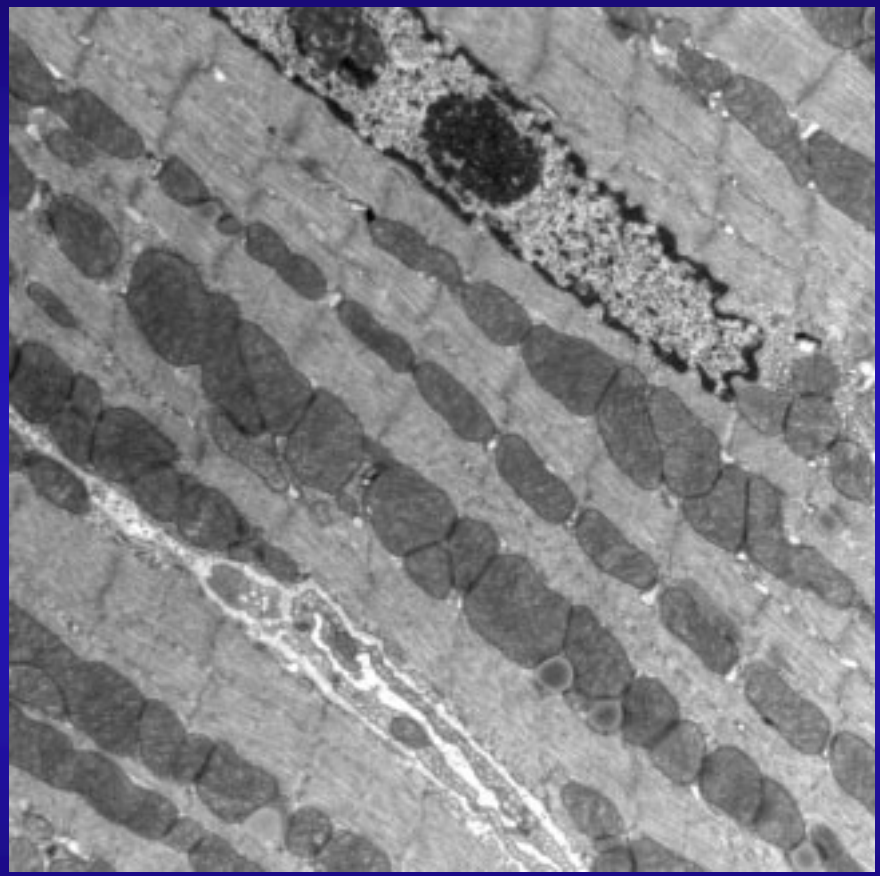
Glucose and Palmitate Perfused



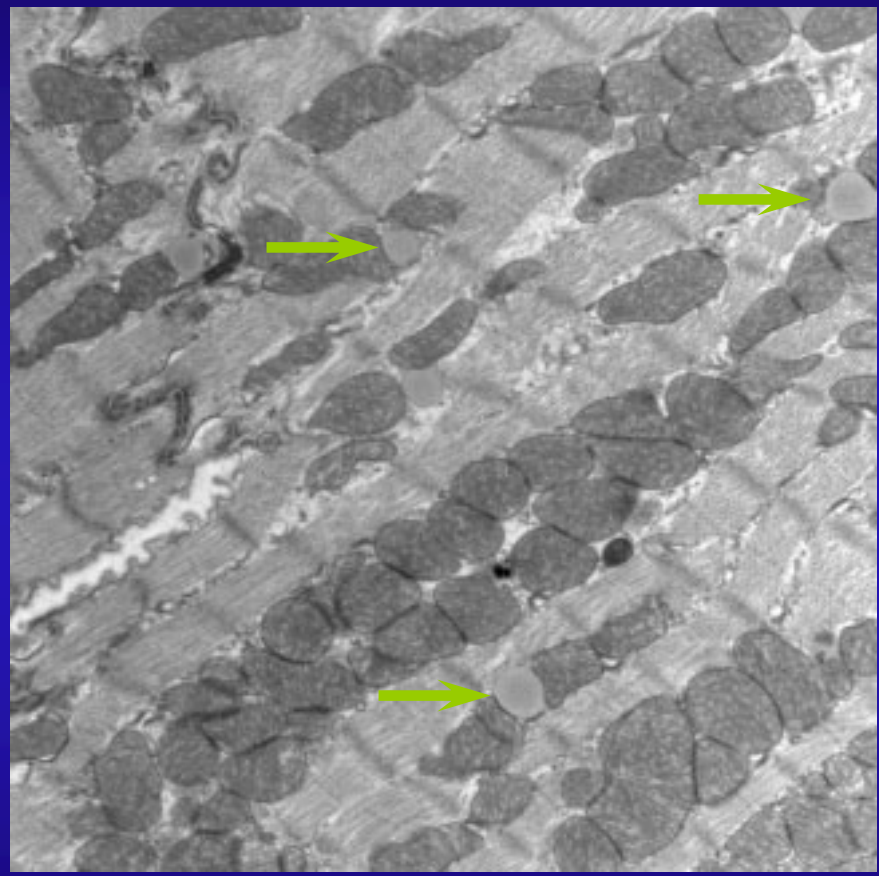


Mitochondrial respiration determined in the presence of 20 µM palmitoyl-L-carnitine

Ultrastructural Changes in ob/ob Mouse Hearts

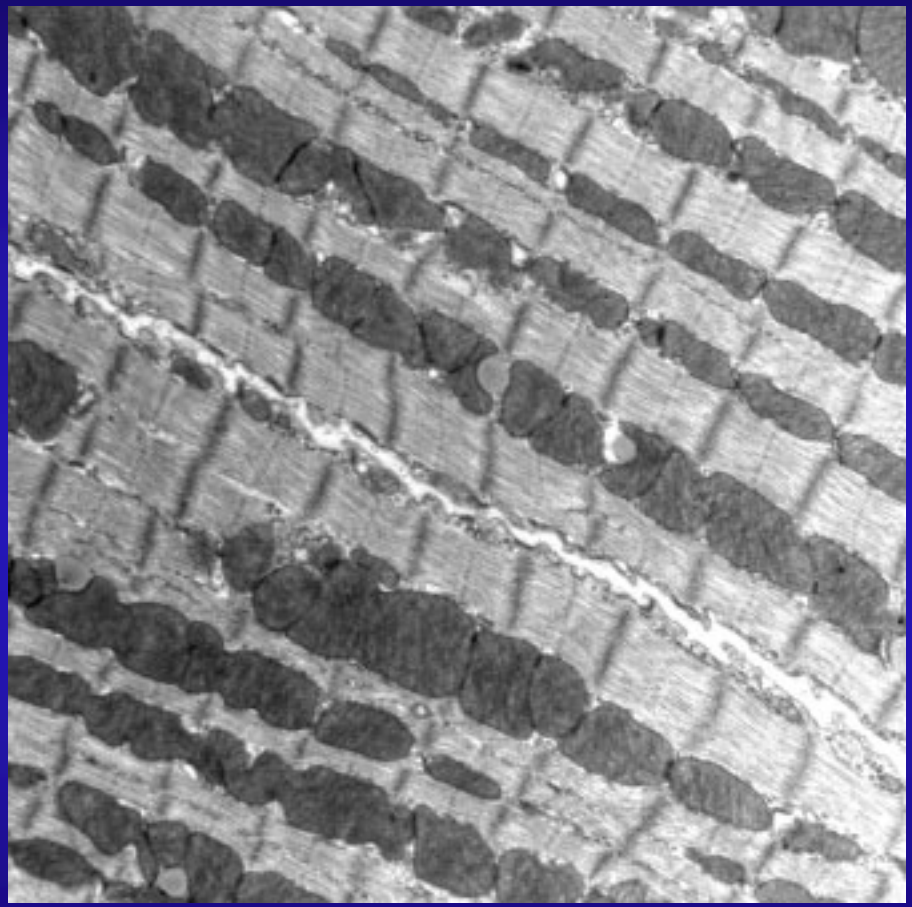


Wildtype

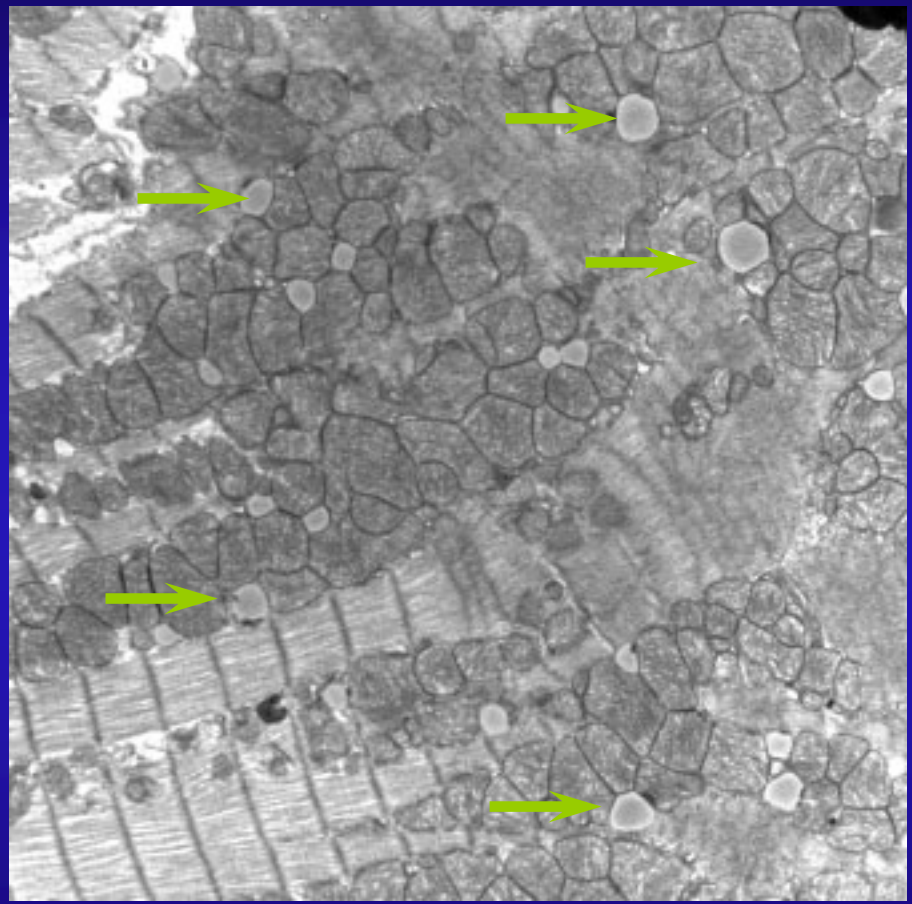


Ob/ob

Ultrastructural Changes in db/db Mouse Hearts

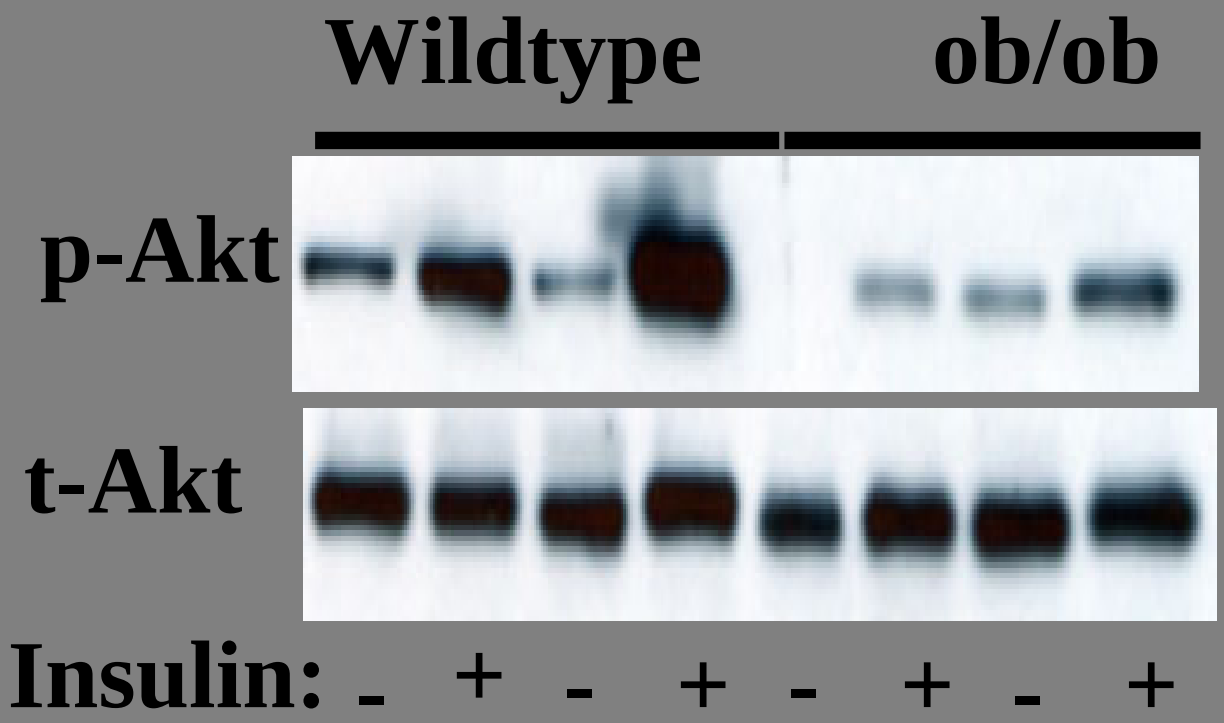


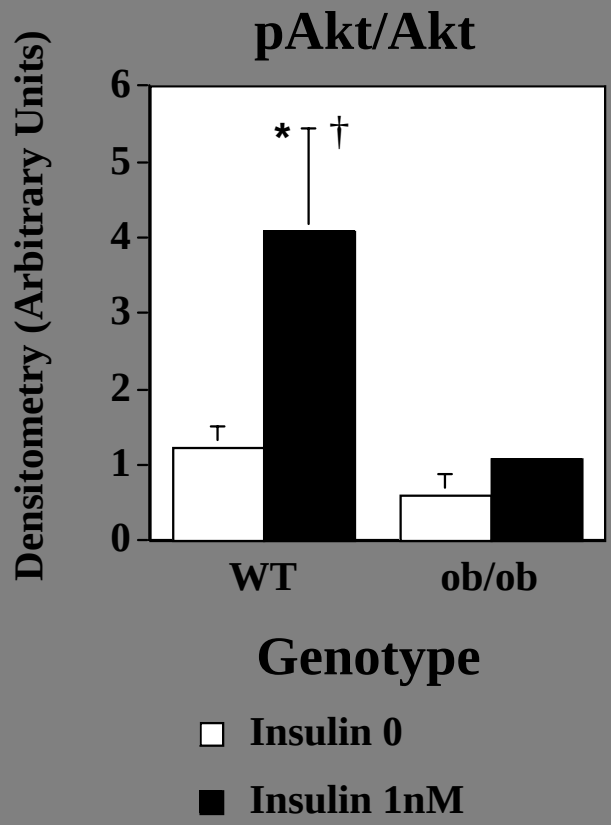
Wildtype



Db/db

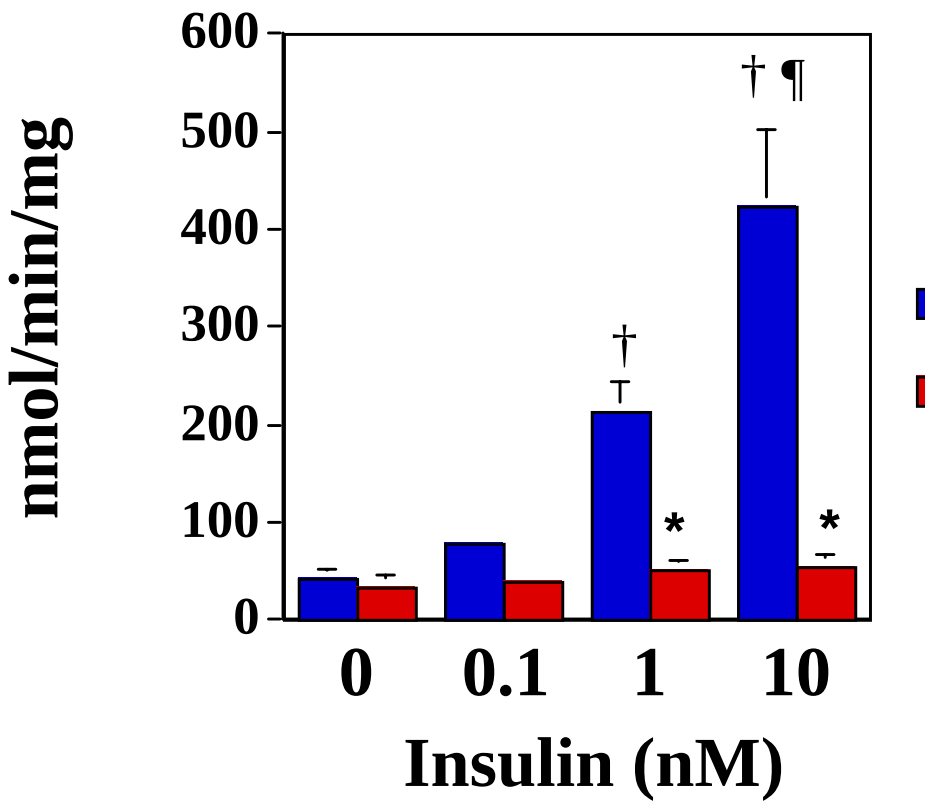
Insulin-Stimulated Activation of Akt is Impaired in ob/ob mouse hearts



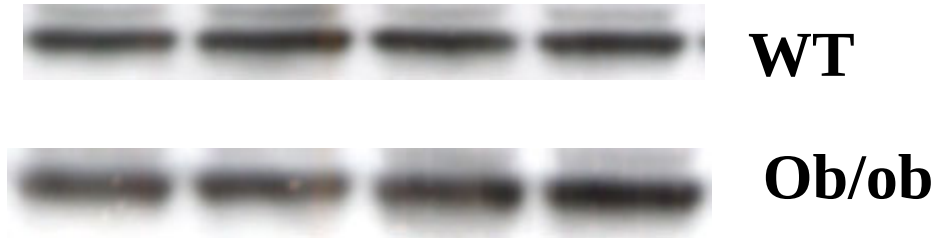


Insulin Resistance in ob/ob Cardiomyocytes

Glucose Uptake



GLUT4



Summary

- Cardiac Function is Impaired in the Hearts of obese, Insulin Resistant and Diabetic Mice
- These Changes Occur Prior to the Onset of Hyperglycemia
- Cardiac Dysfunction is Associated with Altered Substrate Metabolism (decreased glucose utilization and increased fatty acid utilization)
- Oxygen Consumption is Increased - Decreased Myocardial Efficiency
- Increased Oxygen Consumption is Due in Part to Fatty Acid Induced Mitochondrial Uncoupling
- The Bioenergetic Deficits are Associated with Mitochondrial Proliferation

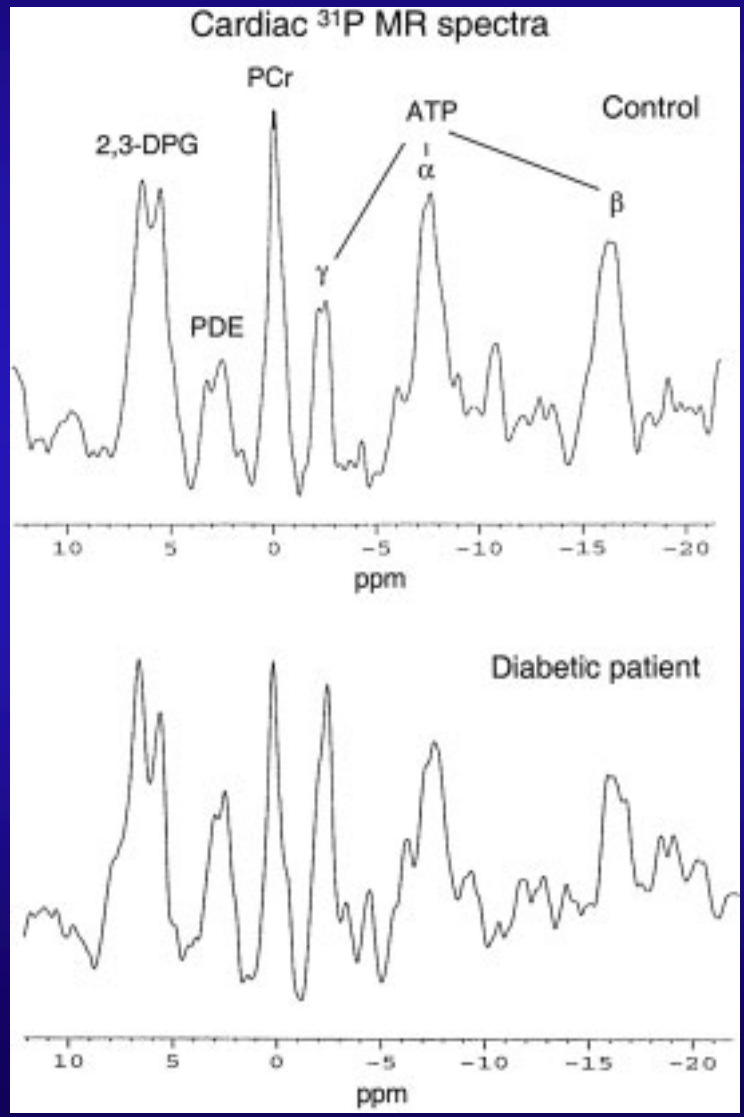
Mice versus Men

Evidence for Altered Myocardial Substrate Utilization, Insulin Resistance and Impaired Myocardial Energetics in Humans with Obesity and Diabetes

Mechanistic Observations Human Studies

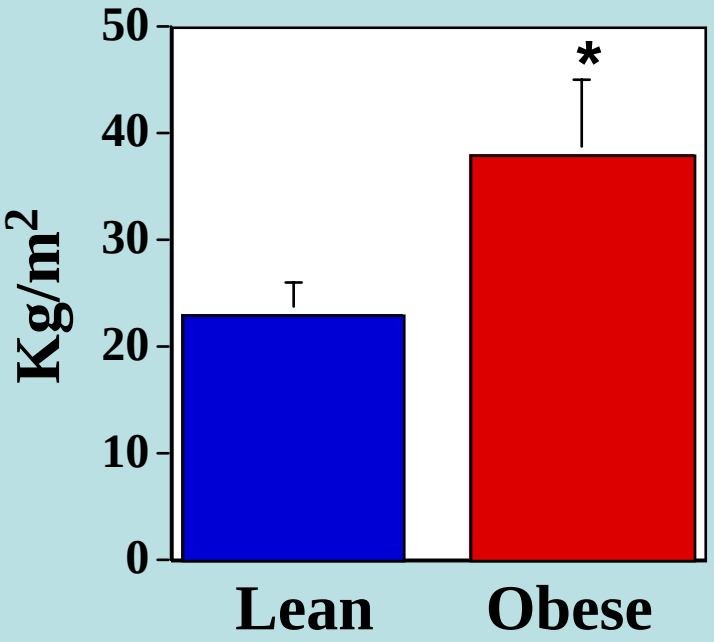
--Using NMR spectroscopy individuals with type 2 diabetes were recently shown to have reduced myocardial high energy phosphate content that was inversely associated with circulating levels of FFA (Scheuermann-Freestone M et al. Circulation 107:3040, 2003), suggesting mitochondrial dysfunction

--Using MR spectroscopy a strong association between obesity and increased myocardial triglyceride accumulation was described. Indeed myocardial TG content was positively associated with LVH and inversely associated with LV function (Szczepaniak et al. Magnetic Resonance in Medicine 49:417, 2003).

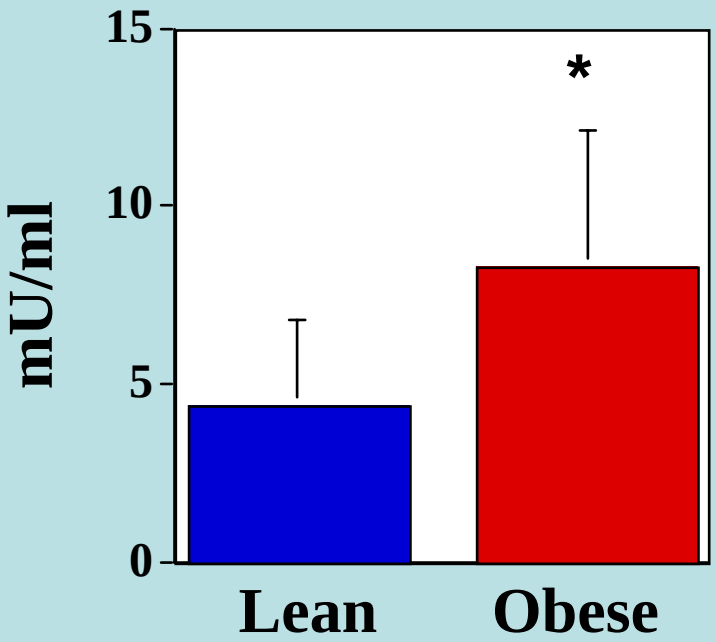


Characteristics of Study Cohort

Body Mass Index



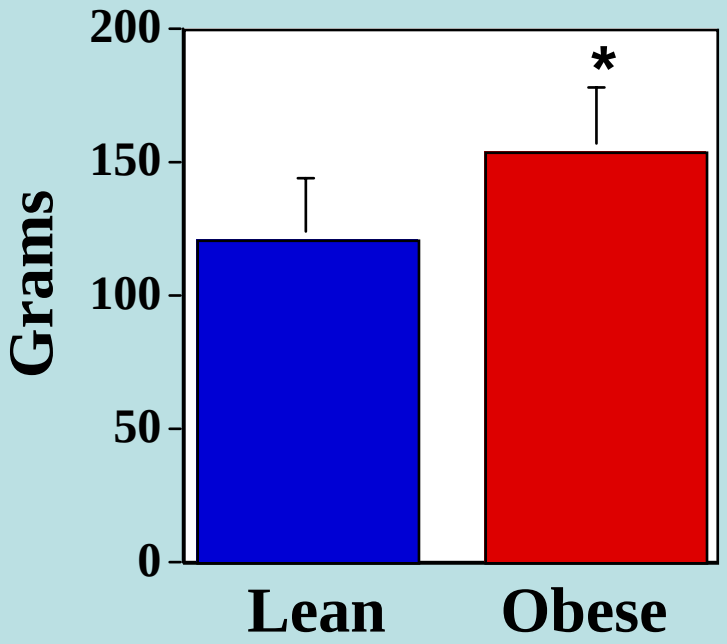
Serum Insulin



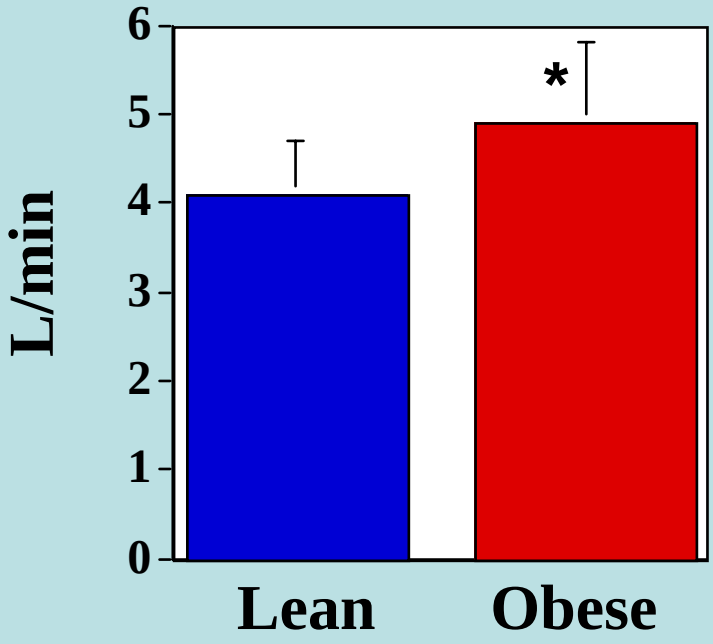
Peterson L et al - Circulation 2004;109:2191-96

Cardiac Structure/Function

LV Mass



Cardiac Output



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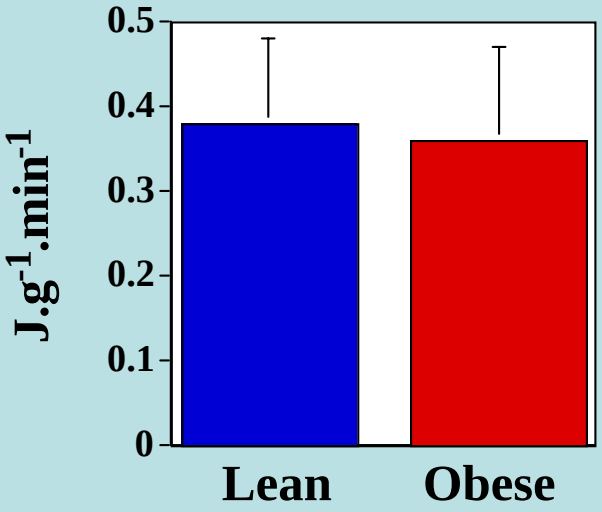
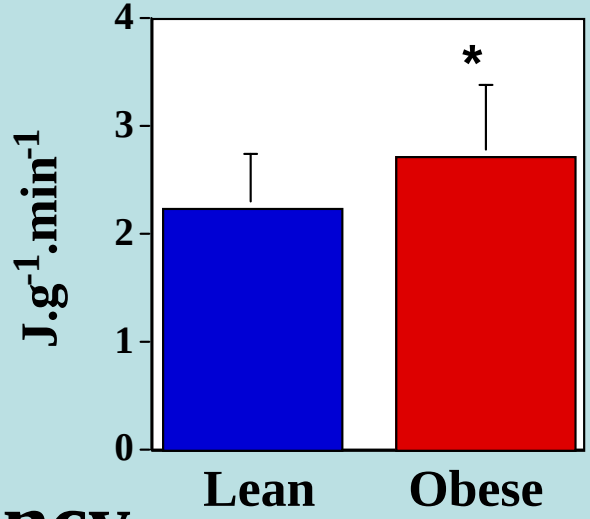
Cardiac Bioenergetics

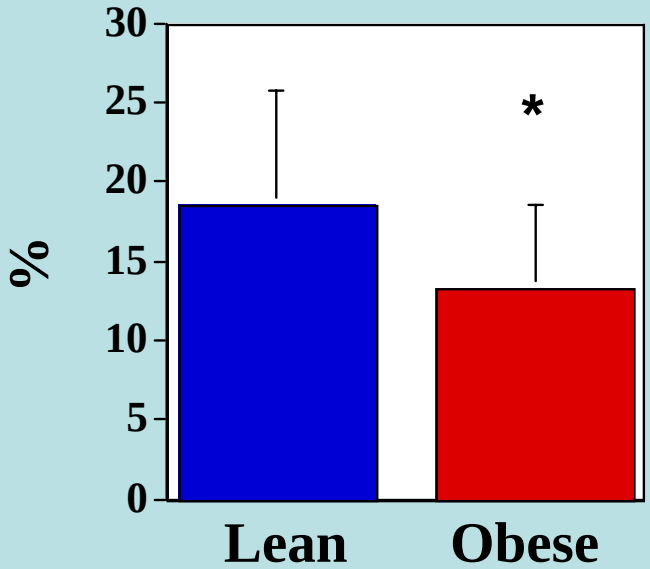
Cardiac Work



MVO_2



Cardiac Efficiency



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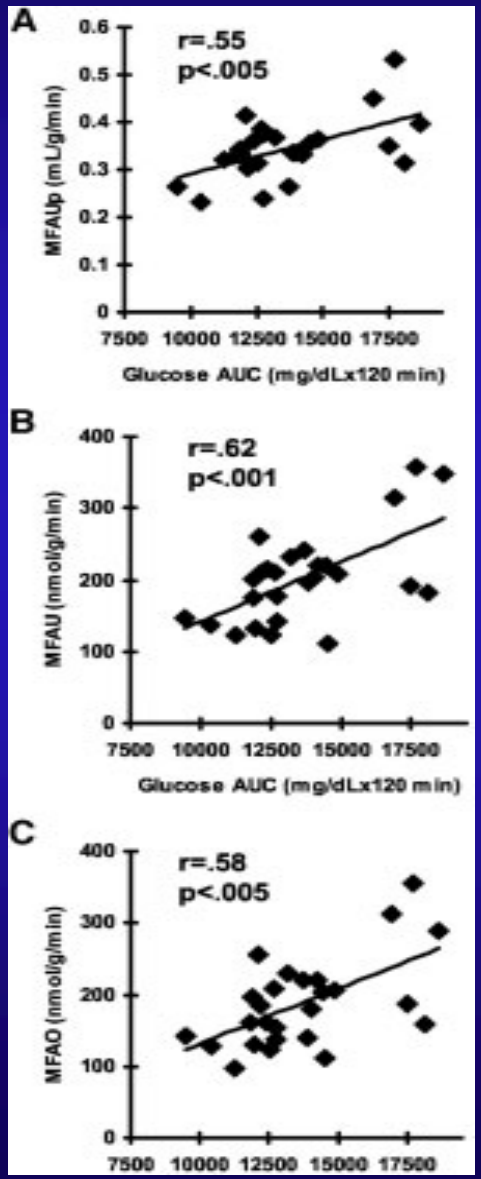
Fatty Acid Utilization



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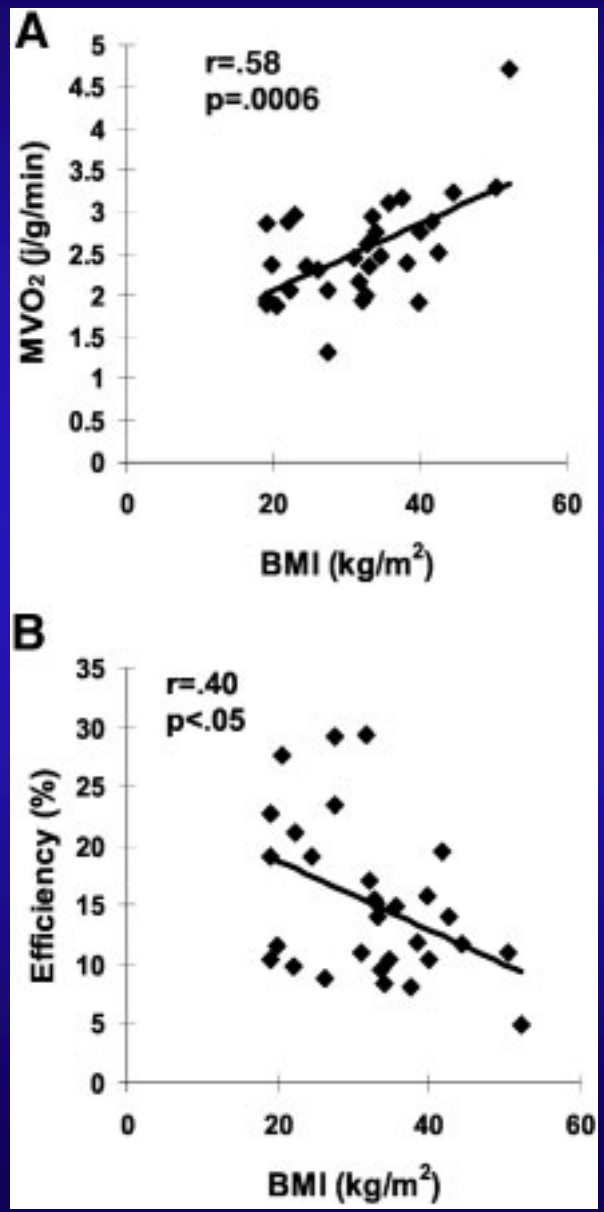
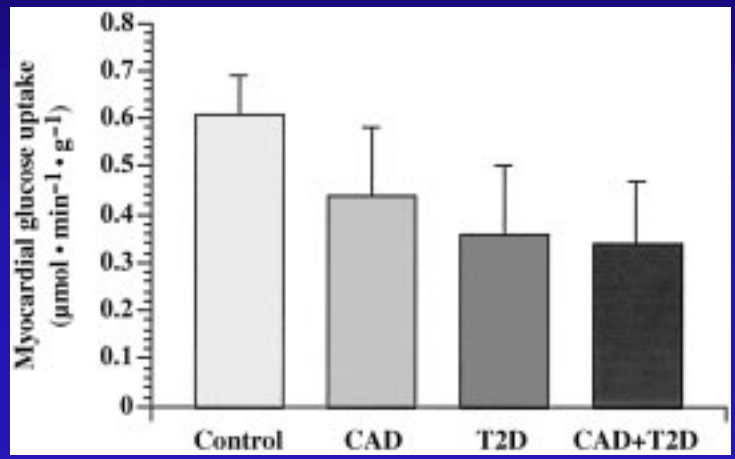
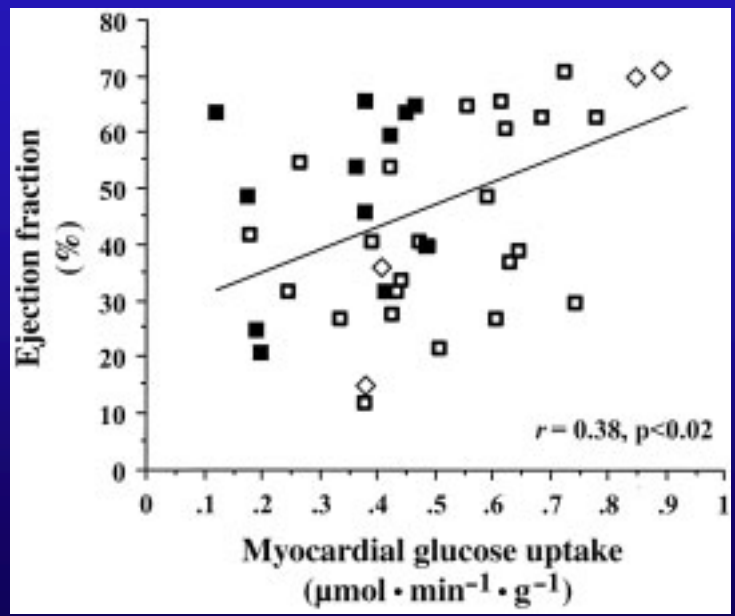


Does Insulin Resistance Occur in the Human Heart?

- Using euglycemic clamps and PET scanning (under physiological levels of insulin), the hearts of individuals with type 2 diabetes demonstrates reduced insulin stimulated glucose uptake that was equivalently decreased in subjects with and without CAD. And a positive correlation was observed between myocardial glucose uptake and LV ejection fraction (Iozzo P et al. Diabetes 51:3020, 2002).





Metabolic Basis for Cardiac Dysfunction in Diabetes and Obesity