About OMICS Group

OMICS Group is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 500 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 500 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

About OMICS International Conferences

OMICS International is a pioneer and leading science event organizer, which publishes around 500 open access journals and conducts over 500 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

.

Restoring thyroid hormone balance in the failing heart: Are we ignoring a hidden time bomb?



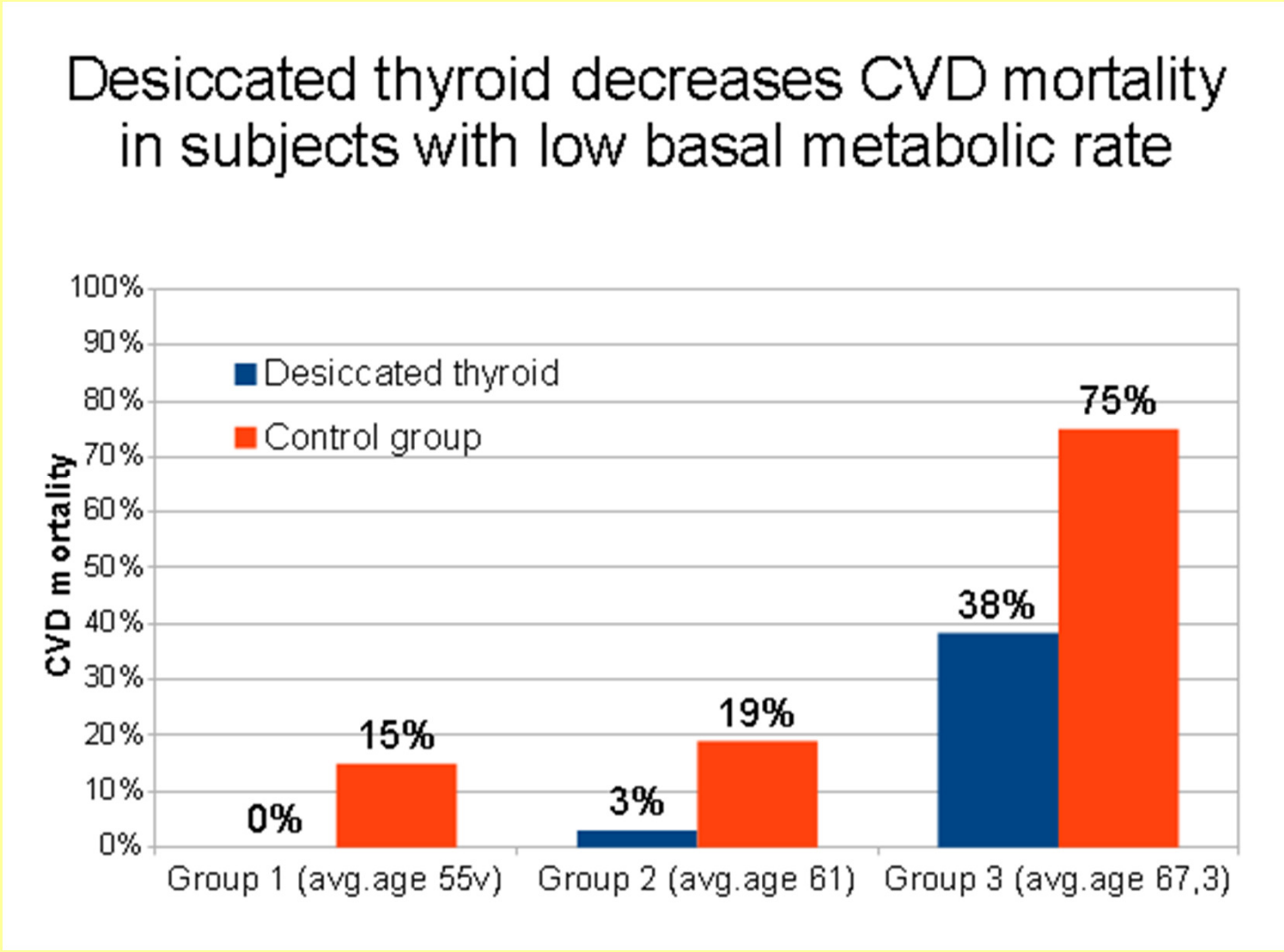
A Martin Gerdes, PhD, Professor/Chairman
Dept Biomedical Sciences, NYIT-COM
Old Westbury, NY 11771

Cardiology 2015

Experts have said:

- You need to stimulate the failing heart so we should try positive inotropes! Wrong
- You can't inhibit the failing heart with β-blockers- you will kill them! Wrong again
- If you give thyroid hormones to cardiac patients, you will trigger arrhythmias and may kill them!
- Are the experts wrong again?

WB Kountz , 1951, Thyroid function and its possible role in vascular degeneration.



5-year study with 268 subjects

Barnes BO, On the genesis of atherosclerosis,
J Am Geriatr Soc 21:350-4, 1973,

The occurrence of CVD in his 1500+ patients treated with desiccated TH was 94% lower than Framingham statistics would have predicted.

Thyroid hormone treatment of HF

- Old story, not yet translated to people. Why?
- Coronary Drug Project (1973)- Secondary prevention study in male MI survivors. Included analog **D-T4**.↑ arrhythmias, but **overdosed** with **D-T4**, contaminated with active L-T4.
- **DITPA** HF study (2009)- ↑HR/diarrhea, ↓BW, (overdose).
- FEAR OF OVERDOSING!
- T3, T4 are CHEAP GENERICS (NO $$$$ incentive)
- Clinicians need more information. T3, T4, both? Can cardiac T3 be restored WO inducing hyperthyroidism? How would you know WO cardiac biopsy? What are long-term effects?
- Basic and clinical grant proposals face hostile reviewers who feel the issue was settled long ago.
- Clinical studies focus on next $B drug/therapy/device.

Thyroid Dysfunction May Contribute to CV Disease and Progression to HF

- CV diseases (IHD, HT, DCM, DM) > fetal gene program similar to hypothyroidism
- Older literature suggested that hypothyroidism > dilated, thin-walled, dysfunctional ventricle (HF)
- Sub-clinical hypothyroidism is risk factor for atherosclerosis and MI in women and IHD and ↑ mortality in men
- ↓T3 post-MI; greater ↓in T3 = ↑ mortality
- Reviews: AM Gerdes & G Iervasi, **Circulation** 2010 and AM Gerdes, **Am J Physiol** 2015

More recent clinical study results

- **↑TSH leads to worse clinical outcomes in HF.** S Chen et al, 2014
- **Subclinical hypothyroidism is associated with ↑ risk in HF patients.** CM Rhee, 2013
- **Both subclinical hypo- and hyperthyroidism lead to ↑ atrial fibrillation in patients with cardiovascular disorders.** DM Tanase, 2013
- **Low THs associated with ↑ mortality in HF.** JE Mitchell, 2013
- **Low T3 is independent predictor for all cause and cardiac mortality in HF**. CP Chuang 2014.
- Hypothyroidism, LT3, ScHypo, but not ScHyper lead to ↑ mortality in DCM. W Wang, **JCEM** (In Press)
- Note: several studies showed no association. **Why?**

Serum THs likely underestimate cardiac T3 levels

- Resting coronary blood flow is ~4-5% of CO.
- Blood leaving heart is diluted ~20X
- No available information for THs from coronary sinus blood in HF
- But, animals studies show that heart diseases promote cardiac tissue hypothyroidism (MI, hypertension, DM).
- **Fetal gene re-expression = hypothyroid heart?**

Chronic hypothyroidism eventually leads to HF

- PTU treatment for 1 yr in rats
- Severe systolic dysfunction
- Increased chamber diameter/wall thickness despite reduced heart mass
- Chamber dilatation with series sarcomere addition (hallmark phenotype of HF)
- Severely impaired coronary blood flow
- Extensive loss or dedifferentiation of small myocardial arterioles
- YD Tang et al, **Circulation** 2005;112:3122-30

TH treatment of BIO-TO2 CM Hamsters from 4-6 Mo:

- **Summary**
- TH treatment prevented the decline in LV function and attenuated LV dilatation in DCM
- Prevented myocardial fibronecrosis
- Prevented myocyte loss
- Restored impaired resting and maximum coronary blood flow to normal
- **Am J Physiol** Khalife et al, 2005;289:H2409-H2415

- Is there evidence that low cardiac thyroid function and impaired coronary blood flow occurs in humans with “non-ischemic” DCM?

Is impaired coronary blood flow a problem in humans with "non-ischemic" HF (IDCM)?

- 2009, "Vascular dysfunction in idiopathic dilated cardiomyopathy" by S Roura, **Nature Reviews**
- Abnormal myocardial perfusion at rest and impaired perfusion reserve (PET scan).
- ↓ cardiac microvessels.
- Could this be due to tissue hypothyroidism??
- Other pertinent studies…
- 2012; *Thyroid;* 22:245-51. Impaired coronary blood flow in asymptomatic patients with subclinical hypothyroidism.

Thyroid Hormones and MI

- MI promotes low T3 in patients; greater the drop in serum T3, ↑mortality; Worse outcome as serum rT3 increases in patients with MI. Friberg L et al, *Am J Med* 2001.
- ↑ cardiac D3 deiodinase (converts T4 to rT3 and T3 to T2) and ↓ LV T3 after MI in rats and mice.
  Olivares EL et al, *Endocrinology* 2008 and Pol CJ et al, *Endocrinology* 2011.
- T4 treatment of rats with MI- ↑ myocyte survival, improved myocyte shape, ↑ LV function. Chen YF et al, JTM 2013

- See following talk by V Rajagopalan on therapeutic T3 in rats with MI

General Hypothesis

Chronic heart diseases lead to:

↓ cardiac T3 levels,

impaired LV function,

maladaptive myocyte and vascular remodeling, and

accelerated progression to HF.

Evidence suggests low cardiac T3 in hypertension, DCM, and ICM.

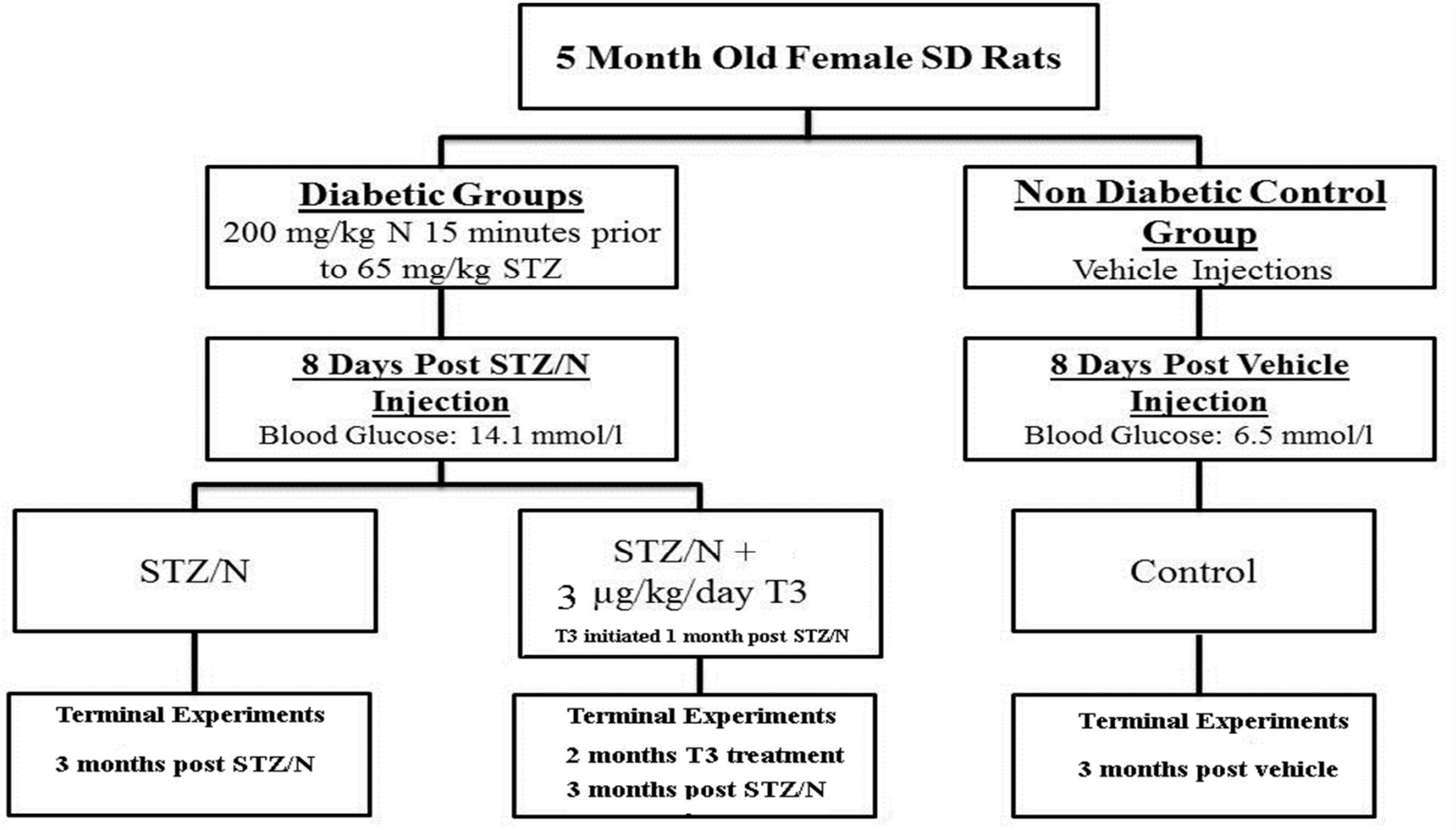
But, what about Diabetes?

DM and Thyroid Dysfunction

- **Diabetics have ↑ frequency of clinical and subclinical hypothyroidism**
  - Reported DM prevalence: 11-31%
  - General population prevalence: 2-5%
- **DM and hypothyroidism produce a similar phenotype of cardiac impairment**
  - Impaired contractility and relaxation abnormalities
  - Ca^{2+} handling abnormalities
  - Re-expression of fetal genes
  - Microvascular and blood flow abnormalities
- **↑ cardiac events and worse outcomes in DM + thyroid dysfunction**
  - ↑ incidence of MI, ↓ Survival

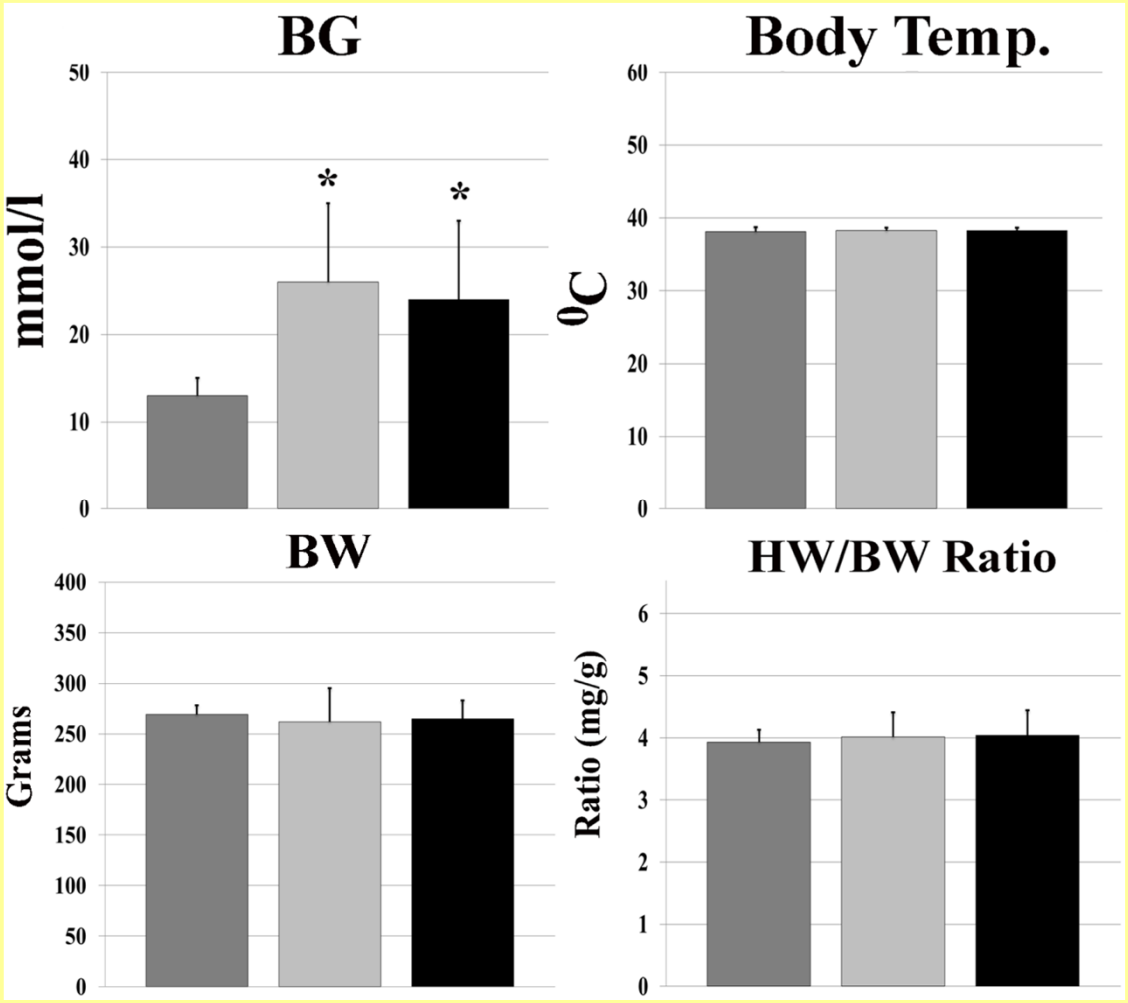
Duntas et al. Clinical Endocrinology. 2011; 75:1-9
Falcao-Pires & Leite-Moreira Heart Fail Rev. 2011; 17:325-44

STZ/N model of experimental DM



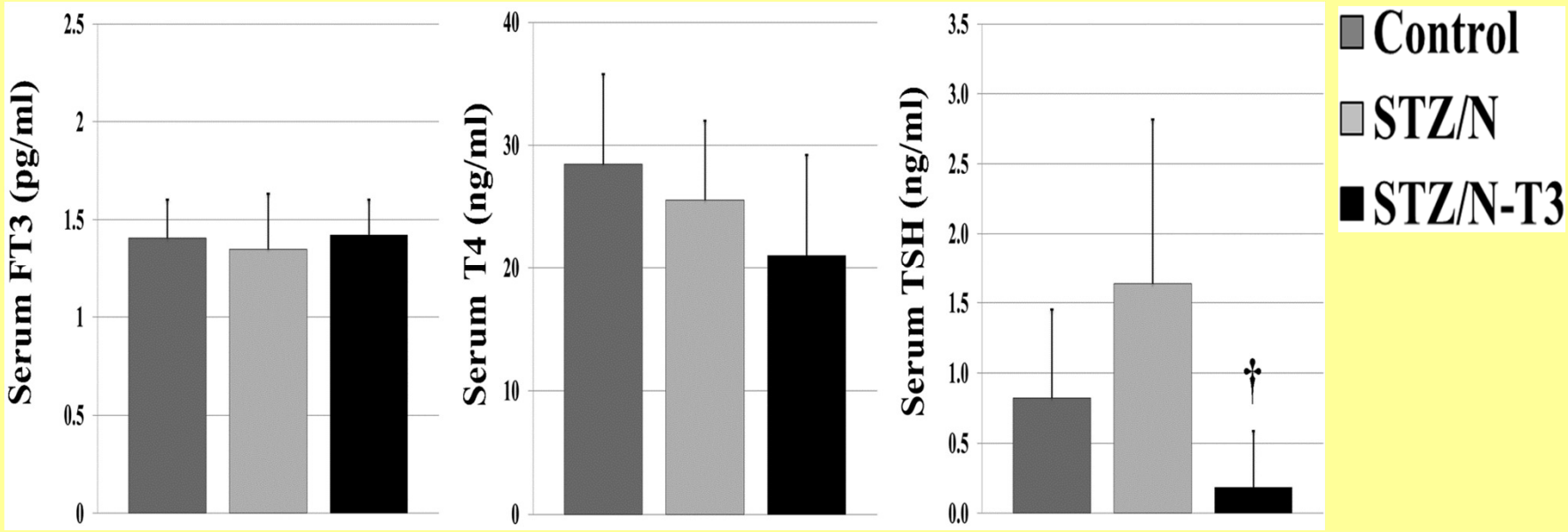
2014 Mol Med 20:302-312, NY Weltman et al

Physiologic T_3 replacement does not induce a hypermetabolic state



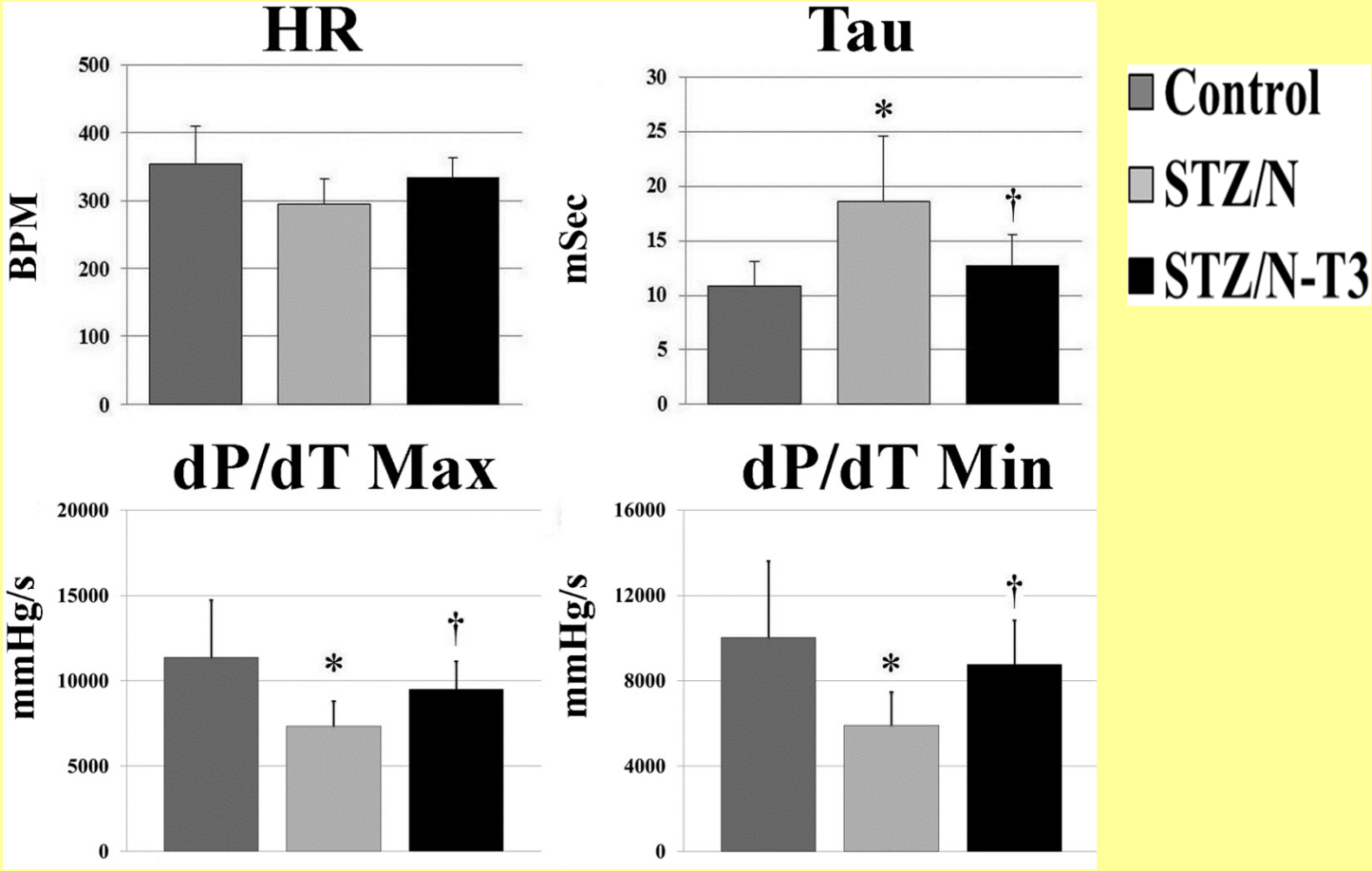
Means (SD). N=9-10
***, p<0.05 vs. Control**

Experimental DM (STZ/N) does not to lead to a serum phenotype of hypothyroidism



Means (SD). N=5-10/group
†, p<0.05 vs. STZ/N

T_3 attenuates hemodynamic dysfunction and improves parameters of cardiac relaxation

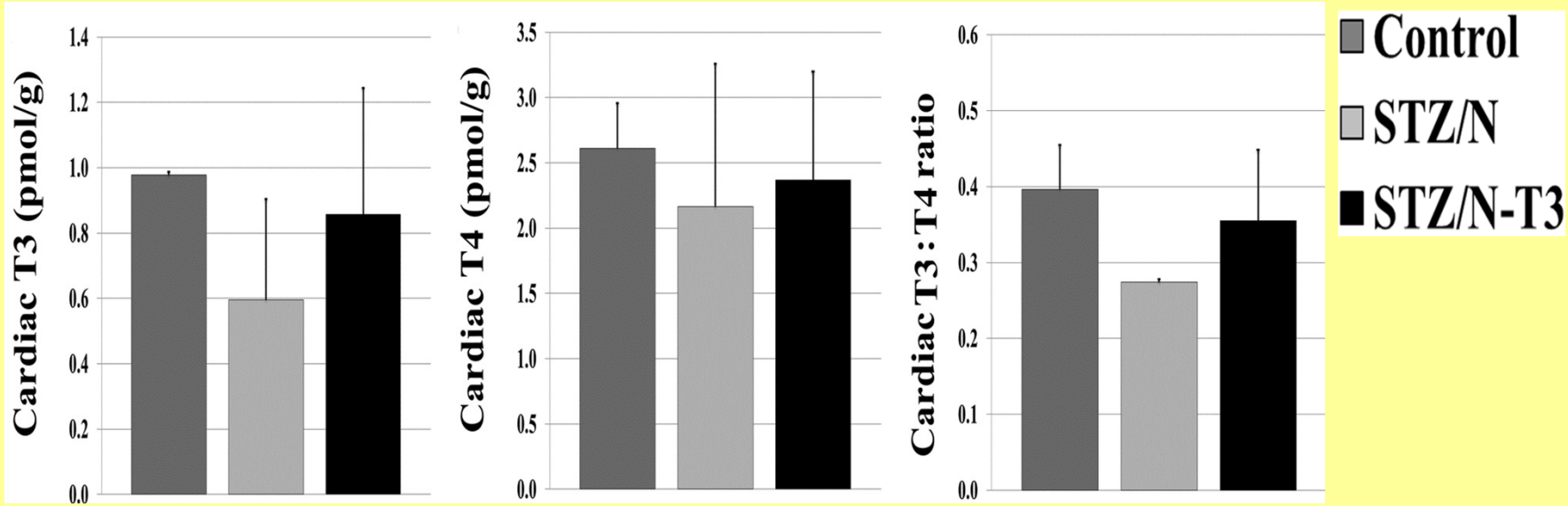


Mean (SD). N=9-10/group

***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**

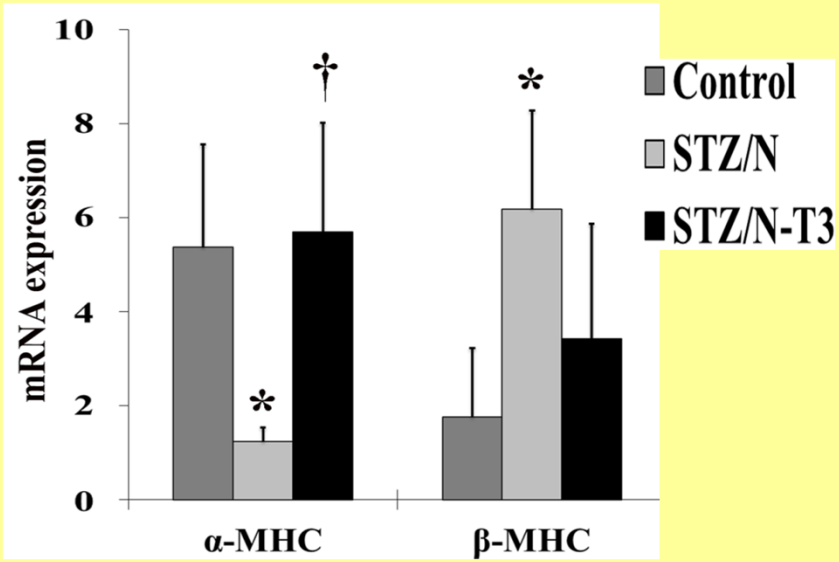
Cardiac Tissue TH Levels

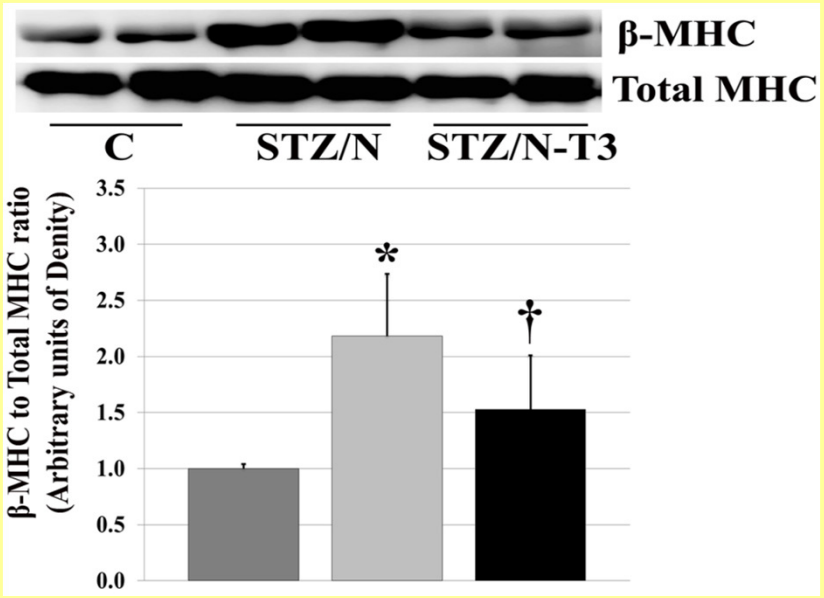
DM (STZ/N) leads to cardiac tissue hypothyroidism despite NORMAL serum TH levels

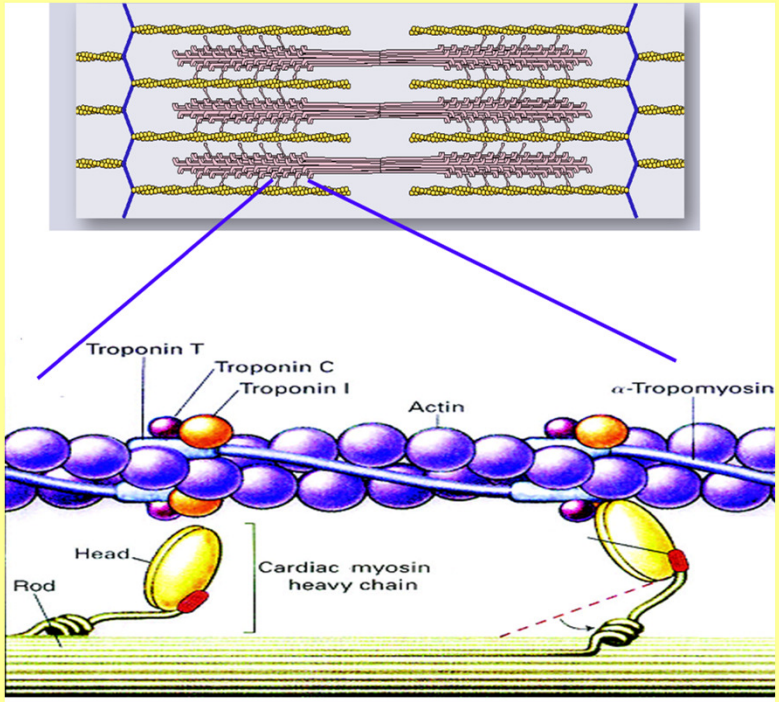


Mean (SD). N=2-3 pooled LV samples/group (6-8 hearts/group);
Statistical analysis was not performed

DM leads to altered expression of contractile proteins

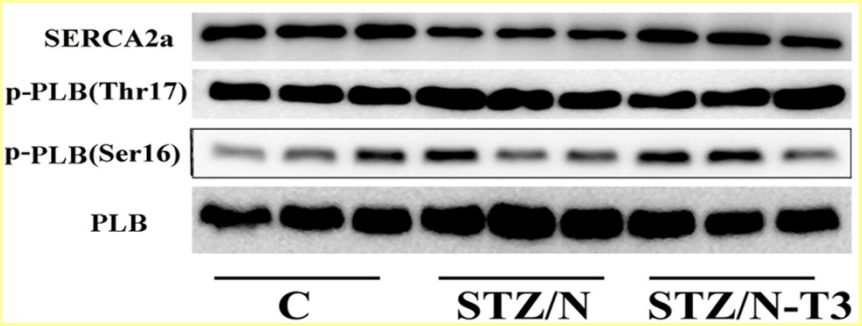


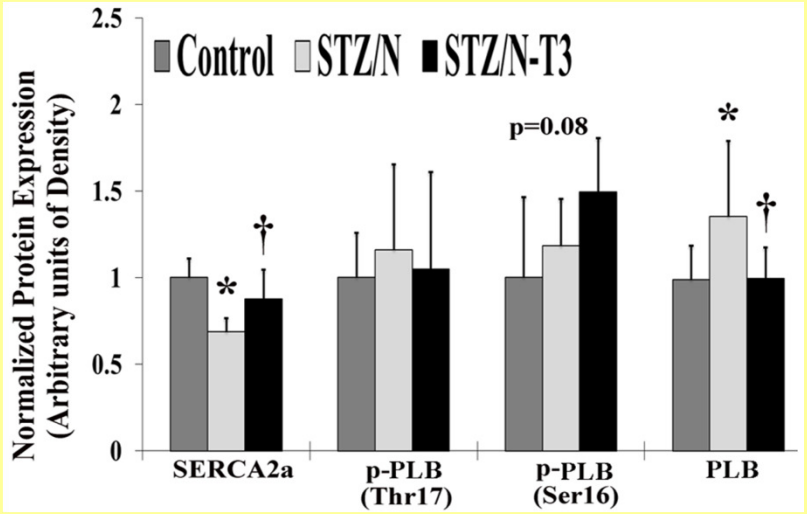




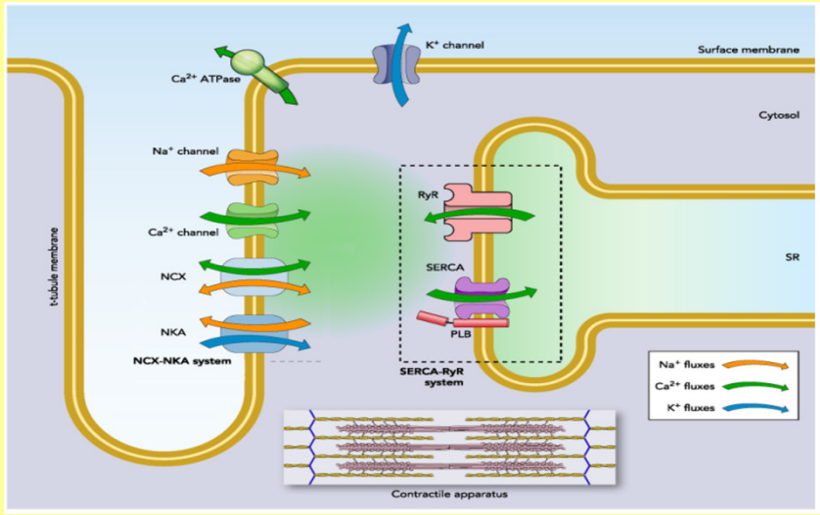
Means (SD). N=4-8/group
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**

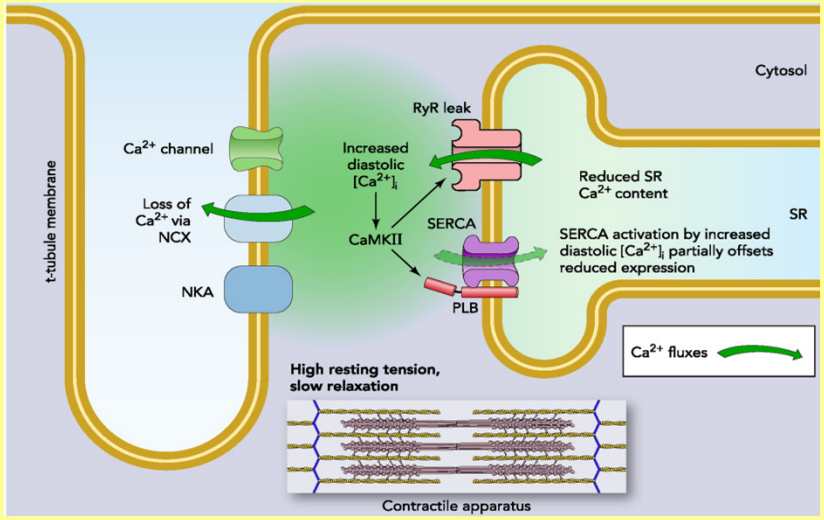
T_3 preserves the expression of myocardial Ca^{2+} handling proteins





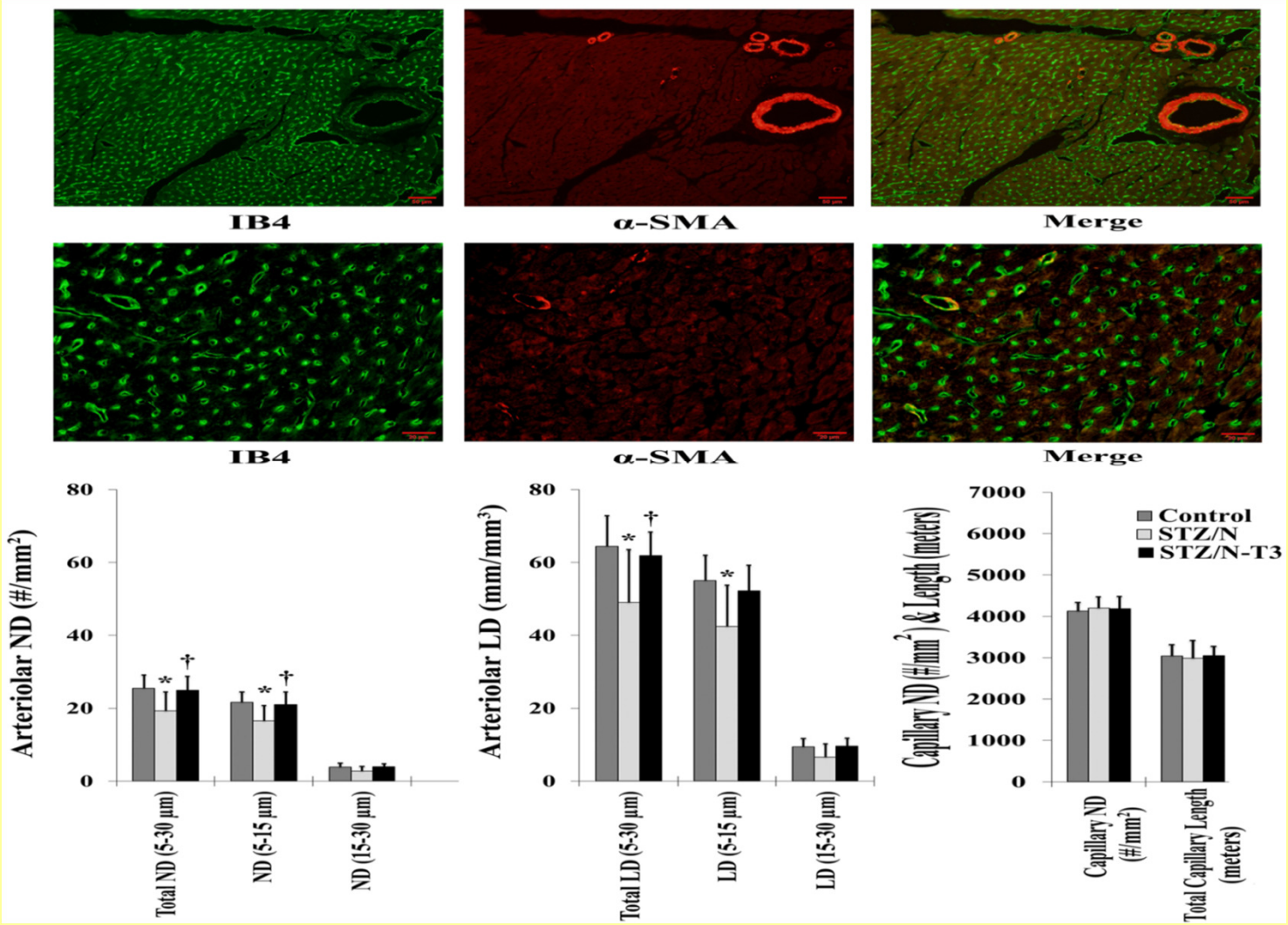
Means (SD). N=4-6/group
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**





Louch et al. Physiology 2012; 27:308-323

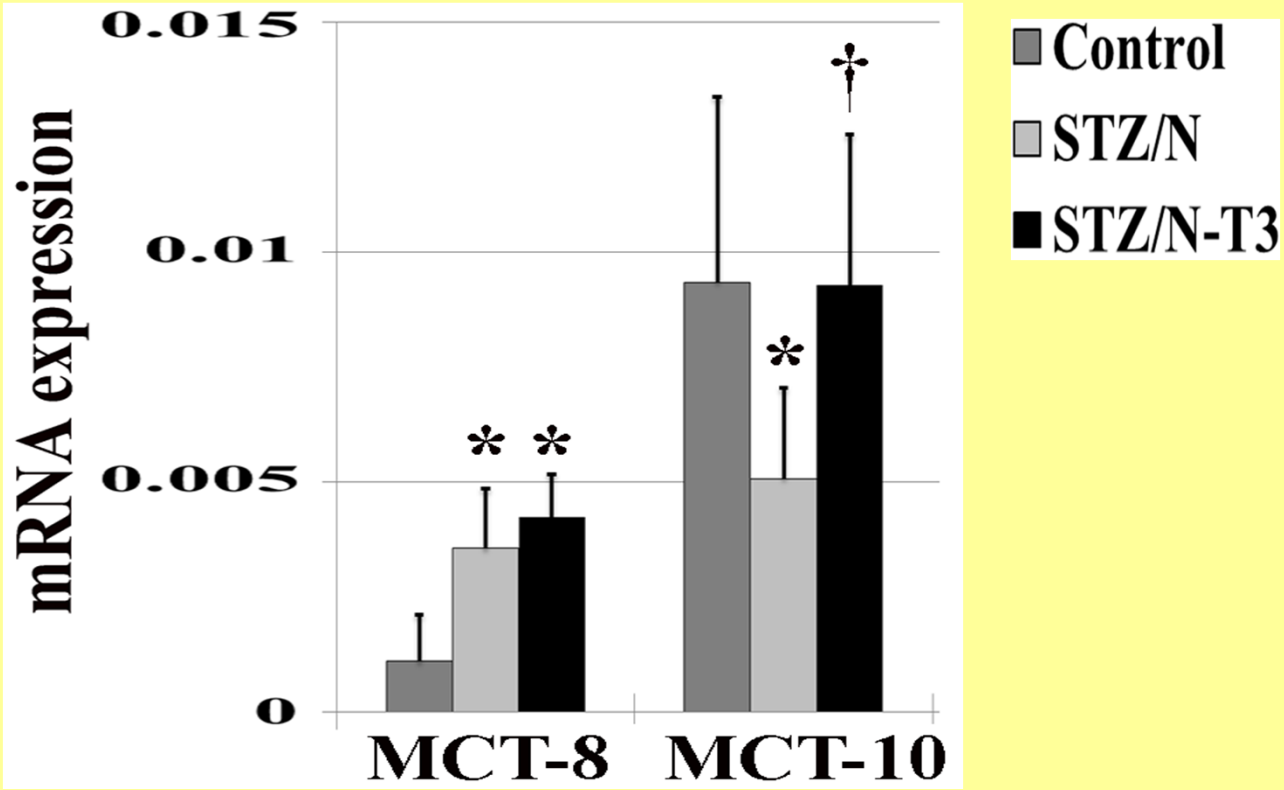
Loss of small arteriolar resistance vessels in the diabetic myocardium is prevented with T_3 treatment



Mean (SD). N=7-8/group.

***, p<0.05 vs. control; †, p<0.05 vs. STZ/N**

Experimental DM significantly reduces the expression of **MCT-10** (T3 membrane transporter)



Means (SD). N=5/group
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**

TH degradation via D3 Deiodinase

- Converts T4 to rT3
- Expressed during fetal development
- Re-expressed in MI, PO, pathological LVH
- Results:
- D3 ↑STZ/N
- Normalized w T3

Part III: Summary

Potential mechanisms responsible for reduced tissue TH levels in the diabetic myocardium:

- Reduced plasma membrane TH transport into the cell
- Excessive intracellular TH inactivation via D3 deiodinase

Summary: T3 treatment of DM

- Serum THs normal but ↓ cardiac T3 in DM.
- Cardiac T3 restored w safe low dose oral T3.
- Prevented LV systolic and diastolic dysfunction.
- Prevented fetal gene re-expression.
- Prevented adverse vascular remodeling.
- Improved T3 bioavailability by preventing changes in MCT-10 and D3.

- **While rats remained diabetic, T3 prevented the associated cardiomyopathy**

Clinical Significance

1. Cardiac tissue TH imbalance may not be reflected in routine serum TH assays.

2. If the animals examined in our experiments were patients, thyroid dysfunction would have been ruled out as a potential contributor!

3. Study demonstrates an effective T3 treatment-monitoring protocol that can be easily implemented in people

What about the risk of arrhythmias and T3 treatment?

See talk by Youhua Zhang

Summary of benefits that can be safely achieved

- ↑ coronary blood flow and angiogenesis
- ↑ myocyte remodeling and survival
- ↓ myocardial fibrosis
- ↓ atherosclerosis
- ↓ arrhythmias
- ↑ systolic/diastolic function, Ca+ handling
- ↑ kidney function
- Other likely benefits
- ↓ depression (?)
- ↑ survival (?)
- ↑ overall quality of life (?)

Misdirected priorities?

Every 5 seconds someone in the world dies of HF.

What are we waiting for?



Thanks

James Kuzman
Jessie Liu
Jinghai Chen
Rebecca Redetzke
XJ Wang
S Said
BE Anderson
EH Schlenker
S Kobayashi
A Pingitore
E Dedkov
K Ojamaa
Nathan Weltman
Yuefeng Chen
Steve Ortmeier
V Rajagopalan
Faqian Li
TA Thomas
WI Khalife
Q Liang
YD Tang
OV Savinova
Y Zhang
R Zucchi

Thanks' for your kind attention!!!!!!



Let Us Meet Again

We welcome you all to our future conferences of OMICS International

Please Visit:

http://cardiology.conferenceseries.com

http://www.conferenceseries.com/

http://www.conferenceseries.com/clinical-research-conferences.php