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OMICS Group International 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 400 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 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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Wrong about β-blockers! Wrong about positive inotropes! Wrong about Thyroid Hormone treatment of Heart Failure?

A Martin Gerdes, PhD, NYIT-COM, Old Westbury, NY



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Once upon at time,

B-blockers were contraindicated for HF.

It was believed that stimulating the failing heart with positive inotropes was a better idea.

WRONG! B-blockers save lives and positive inotropes kill.

Today, it is generally believed that

Thyroid hormones should be avoided in HF patients since the potential risk from triggering arrhythmias and sudden death from accidental overdose outweighs the potential benefits.

Is this true or are we overlooking what could be one of the biggest advances in the history of cardiology?

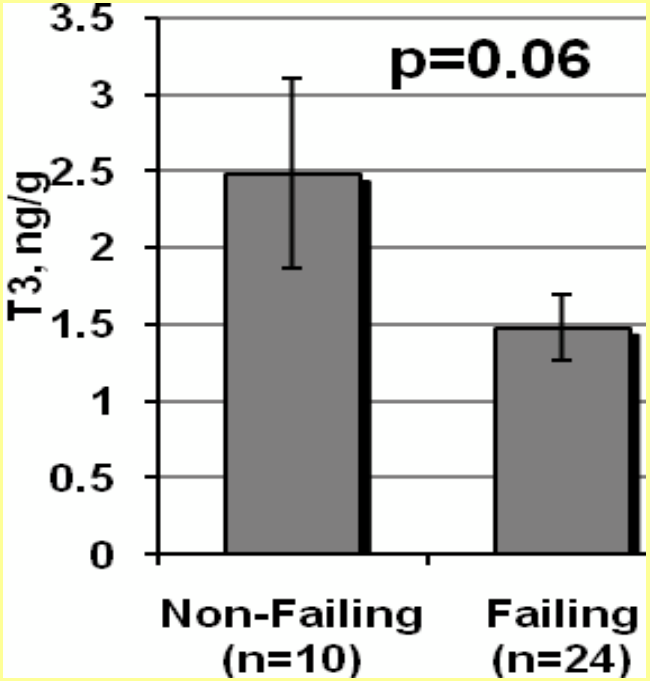
Thyroid hormones and the treatment of HF

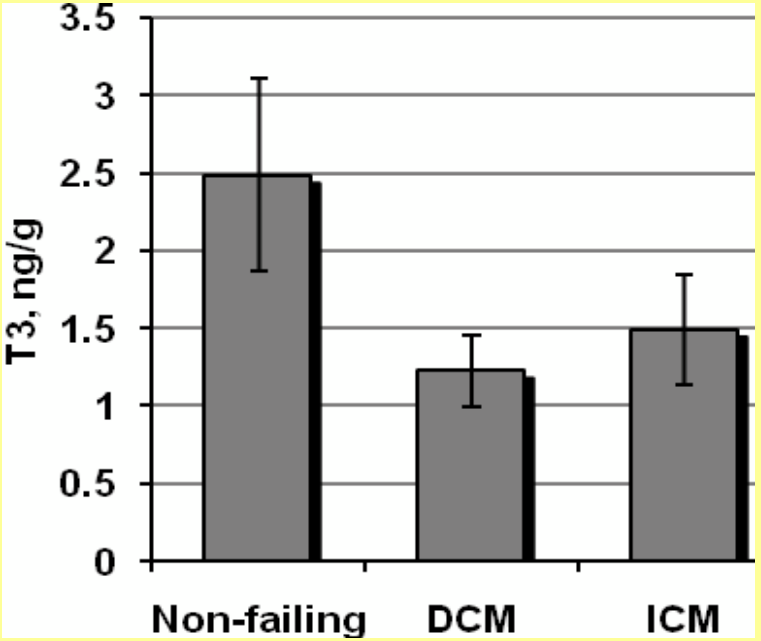
- Old story, not yet translated to people. Why?
- Coronary Drug Project (1973)- Aim was to reduce serum cholesterol and atherosclerotic heart disease with TH **analog, D-T4**. Result: ↑ arrhythmias, **BUT** D-T4 dose was excessive and contaminated with active L-T4.
- **DITPA** HF study (2009)- Some improvements but poorly tolerated. ↑HR/diarrhea, ↓BW suggest overdose.
- FEAR OF OVERDOSING. Possible ↑ arrhythmias drives clinical opinion.
- T3, T4 are CHEAP GENERICS (NO $$$$ incentive)
- **No therapeutic treatment/monitoring protocol showing benefits.**
- Clinicians need more information. T3 or T4? Can depressed cardiac T3 be restored WO inducing hyperthyroidism? How would you know with out cardiac biopsy? What are the long-term benefits?
- BS must target molecular mechanisms rather than set stage for trials.
- CS pressured to establish the next $B drug/device therapy.

Has critical new information surfaced recently?

- With heart diseases, the heart may actually make itself hypothyroid. Fetal gene re-expression = hypothyroidism?
- Animal studies show that in MI and hypertension, the heart activates D3, which converts T4 to rT3 and T3 to T2. (Confirmed by my lab, also in DM).
- Why? Could be evolutionary programming (starvation).
- Importantly, we have shown that chronic hypothyroidism alone eventually leads to dilated HF with impaired coronary blood flow. **Circulation** 2005:112:3122-30
- Does low cardiac T3 occur in humans?

Cardiac T3 from human hearts (U Penn- K Margulies)





Preliminary LV tissue T3 levels in human heart (ELISSA). Tissue T3 levels were reduced ~40% in this initial sample with similar changes in DCM and ICM. Differences between non-failing and failing did not quite reach statistical significance, apparently due to excessive variation in the selected non-failing group. *Note: relative reductions in LV tissue T3 of this magnitude in normal healthy rats causes severe LV dysfunction and eventually HF.*

Thyroid Dysfunction May Contribute to CV Disease and Progression to HF

- CV diseases (IHD, HT, DCM) > fetal gene program similar to hypothyroidism
- Older literature suggested that hypothyroidism > dilated, thin-walled, dysfunctional ventricle (HF)
- Sub-clinical hypothyroidism: risk factor for atherosclerosis and MI in women; IHD and ↑ mortality in men; ↑ mortality in HF
- MI>↓T3; greater ↓in THs = ↑ mortality
- Review: Thyroid replacement therapy and heart failure. AM Gerdes and G Iervasi, **Circulation** 2010.

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**
- CM hamsters develop subclinical hypothyroidism and die of HF at ~10 months of age
- TH treatment prevented the decline in LV function and attenuated LV dilatation
- Prevented progressive myocardial fibronecrosis
- Prevented loss of cardiac myocytes
- 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 vascular dysfunction a problem in human DCM?

- 2009, “Vascular dysfunction in idiopathic dilated cardiomyopathy” by S Roura, **Nature Reviews**
- Abnormal resting/maximum coronary blood flow.
- ↓ cardiac microvessels.
- Could this be due to tissue hypothyroidism??
- Other pertinent studies…
- 2012 study in *Thyroid*. Impaired coronary blood flow in asymptomatic patients with subclinical hypothyroidism.
- 2012 JACC. ↑ all cause and CV mortality in patients with subclinical-hypothyroidism (116,000 pts).
- 2013 JACC and 2013 JCEM. Low thyroid function linked to increased mortality in HF.

Thyroid Hormones and MI

- ↓ serum T3 after MI in patients; greater 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

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.

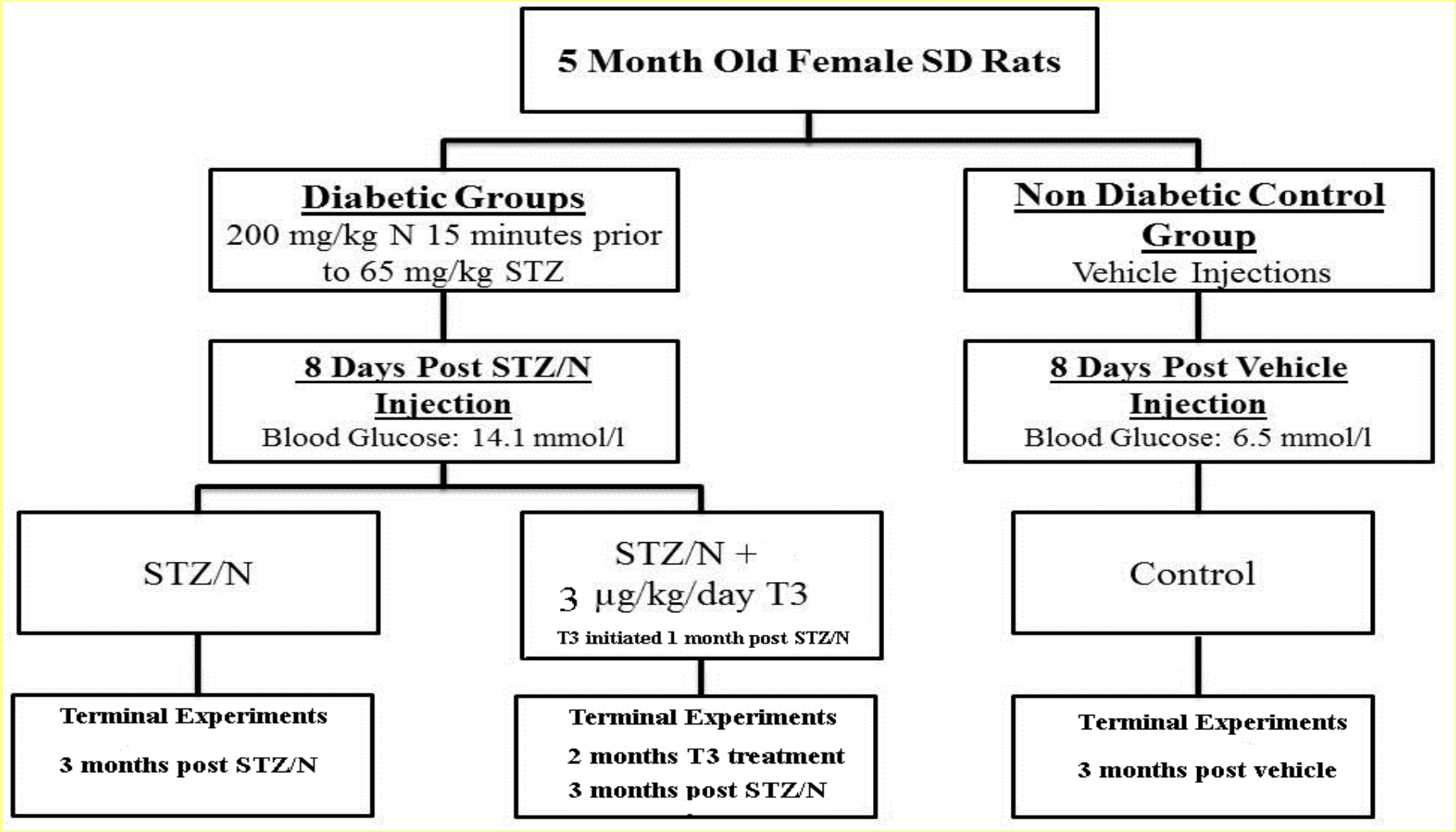
But, what about Diabetes?

DM and Thyroid Dysfunction

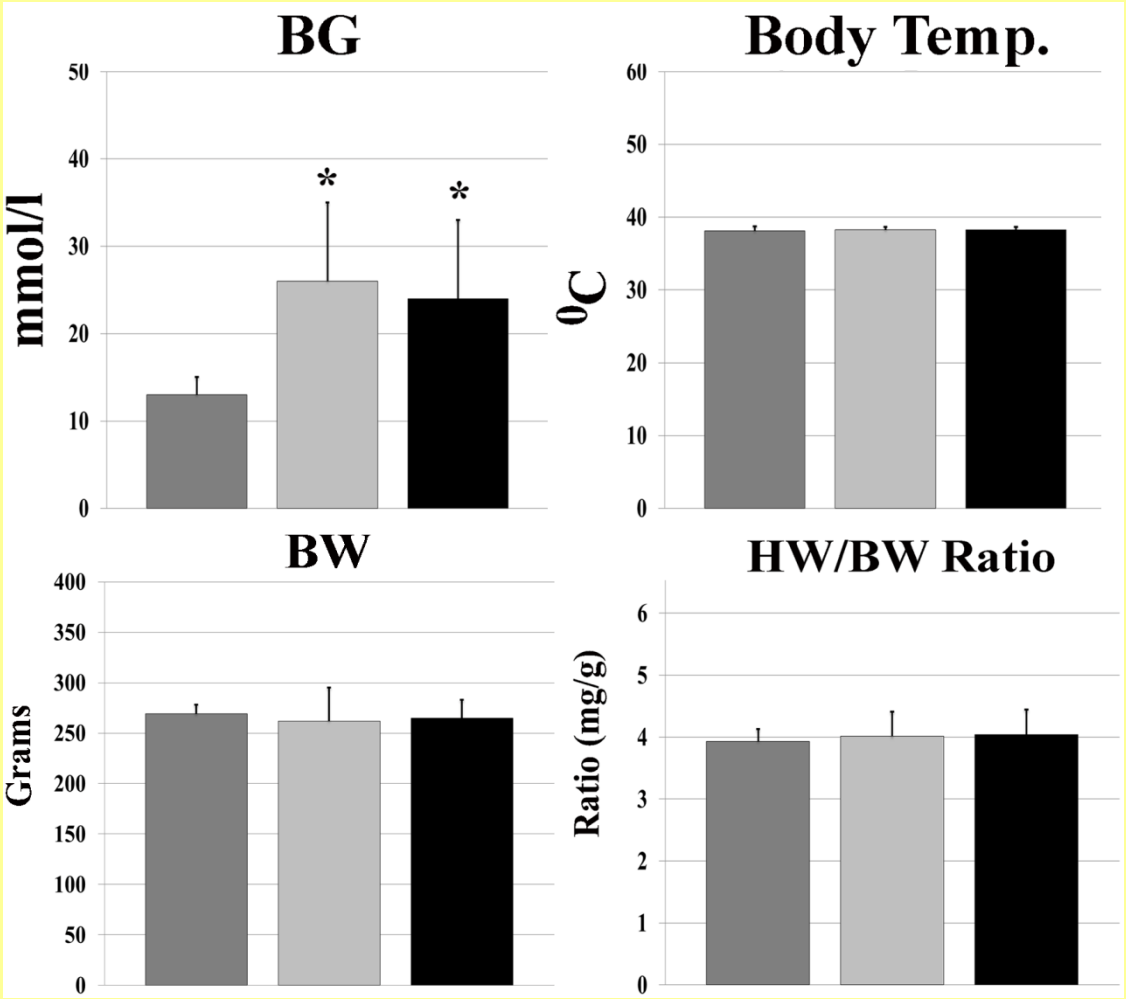
- **Risk of developing HF ↑↑ in diabetics**
- **Diabetics have ↑ frequency of clinical and subclinical hypothyroidism**
- **DM and hypothyroidism produce a similar phenotype of cardiac impairment**
  - Impaired contractility and relaxation abnormalities
  - Ca^{2+} handling abnormalities
  - Re-expression of fetal genes
  - Microvascular and blood flow abnormalities
- **↑ cardiac events and worse outcomes in DM + low thyroid function**
  - ↑ 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

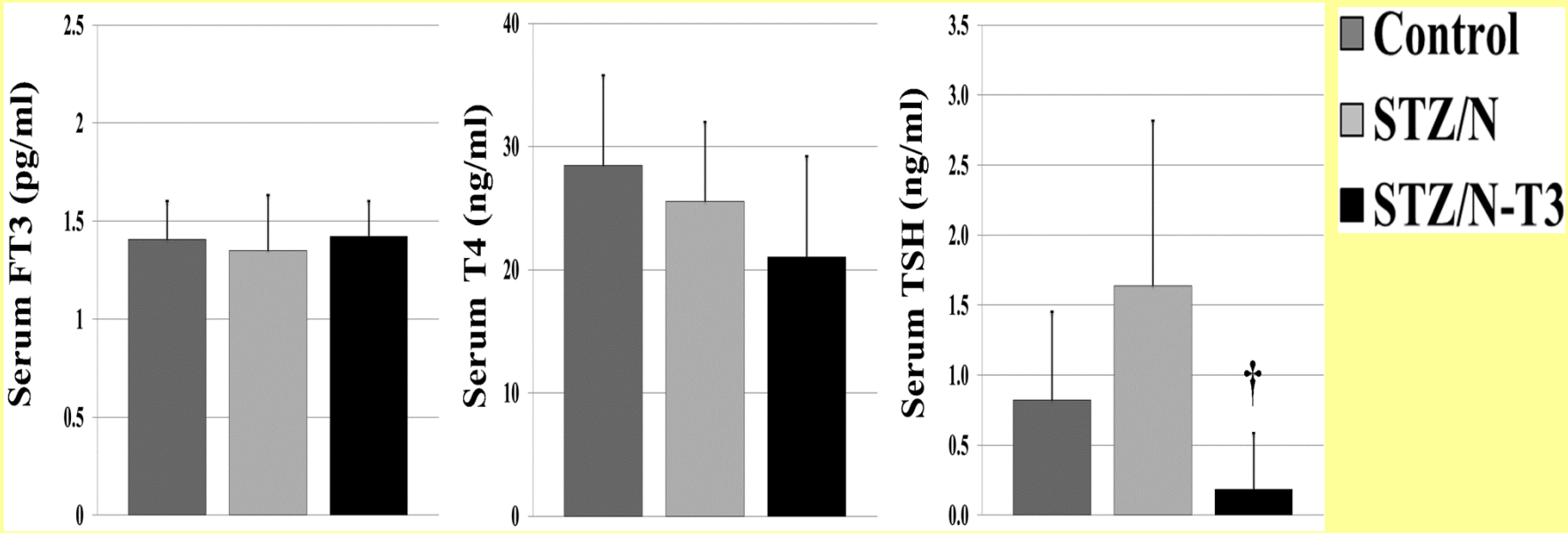


Physiologic T_3 replacement does not induce a hypermetabolic state



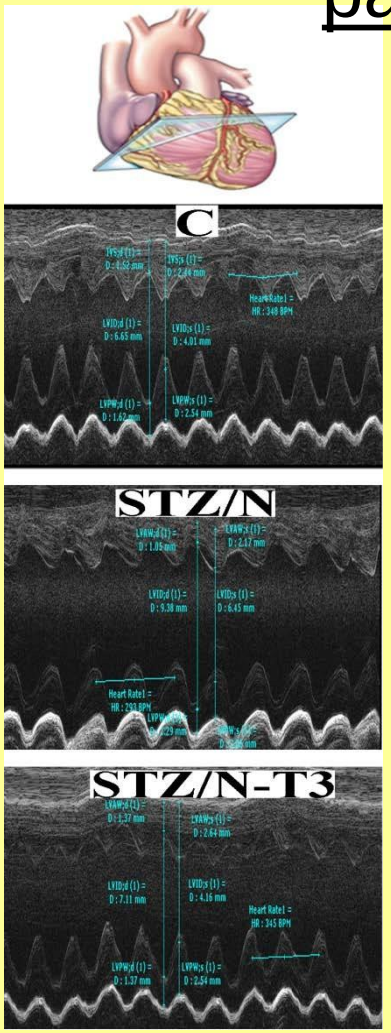
Means (SD). N=9-10
***, p<0.05 vs. Control**

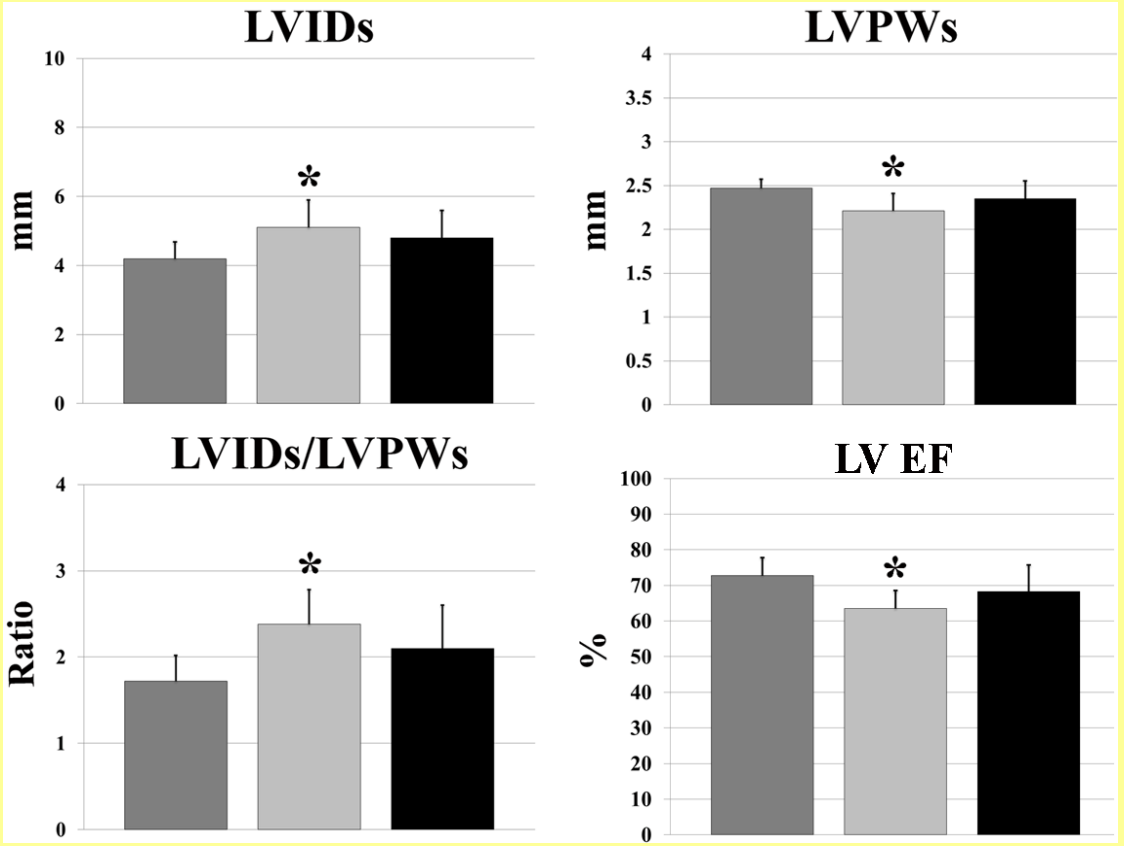
Experimental DM (STZ/N) does not to lead to a serum phenotype of hypothyroidism



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

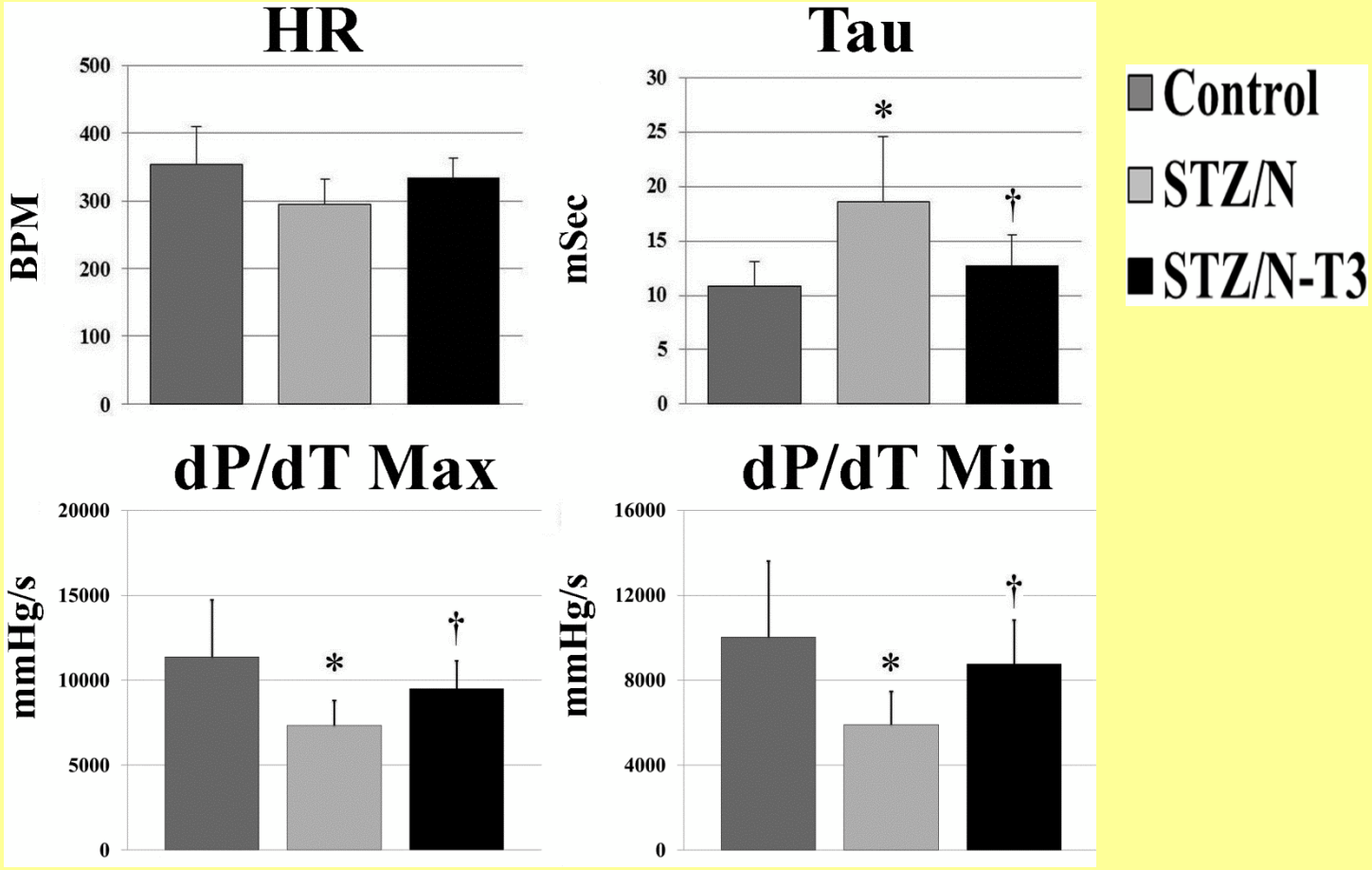
DM leads to impaired LV function and elevated parameters of anatomical wall stress





Mean (SD). N=10/group
***, p<0.05 vs. Control**

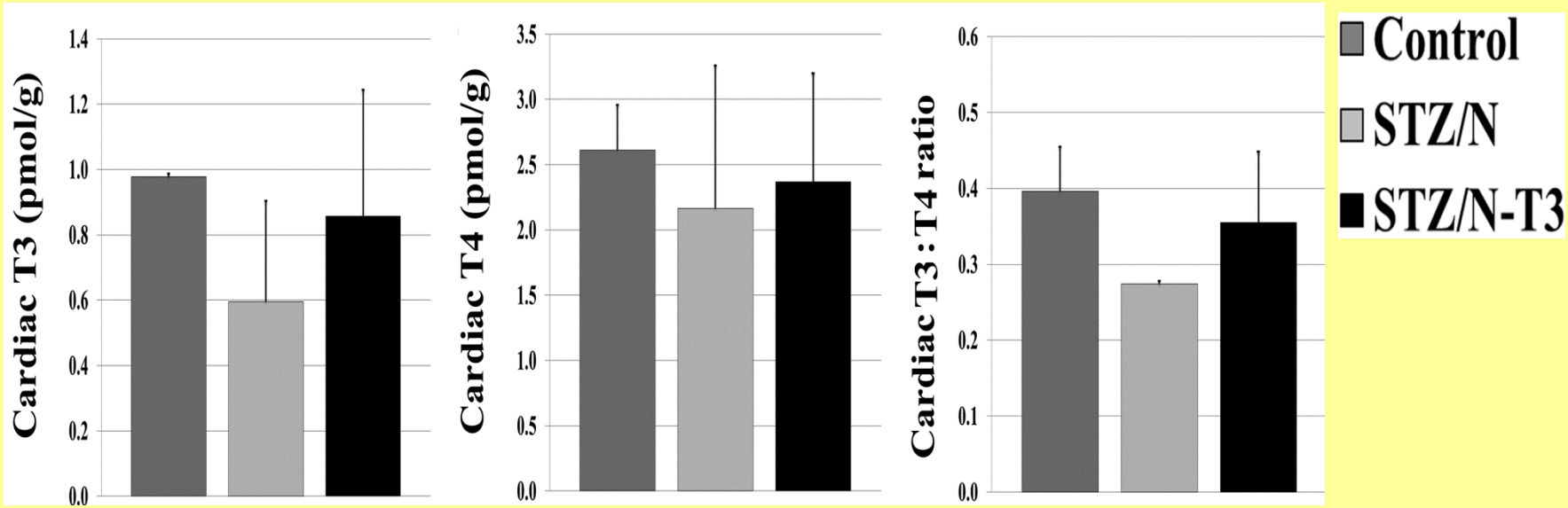
T_3 attenuates hemodynamic dysfunction and improves parameters of cardiac relaxation



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

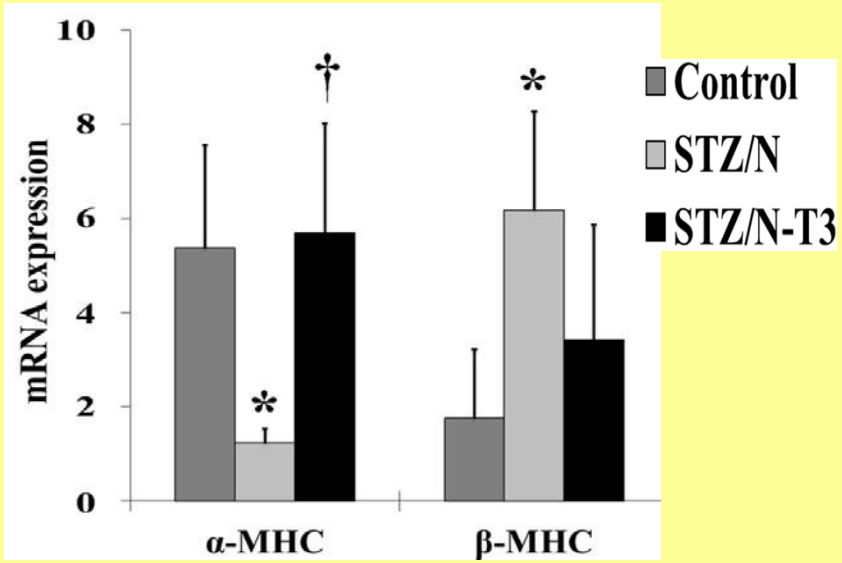
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**

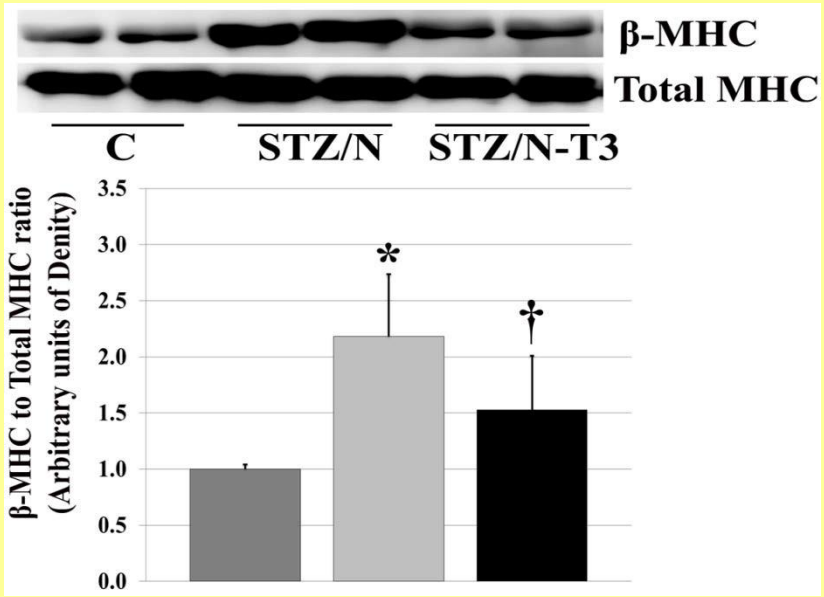
DM (STZ/N) leads to cardiac tissue hypothyroidism despite NORMAL serum TH levels

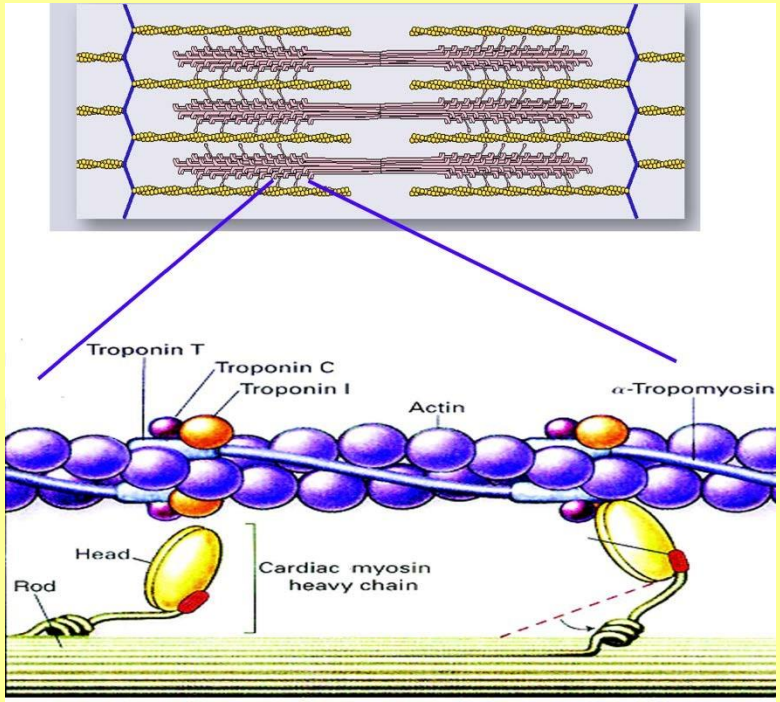


Mean (SD). N=2-3 pooled LV samples/group (6-8 hearts/group); Statistical analysis was not performed

DM leads to altered expression of contractile proteins

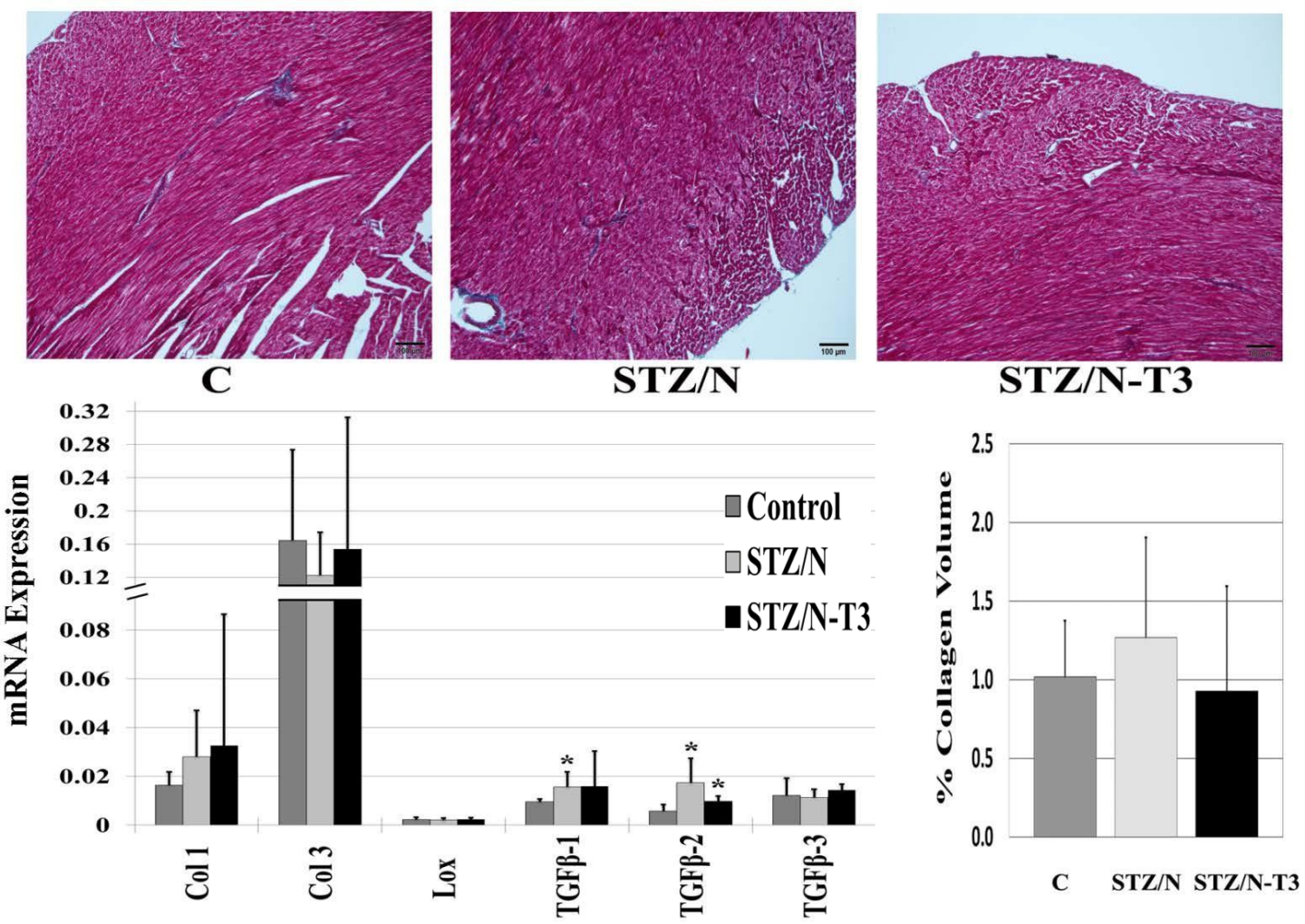






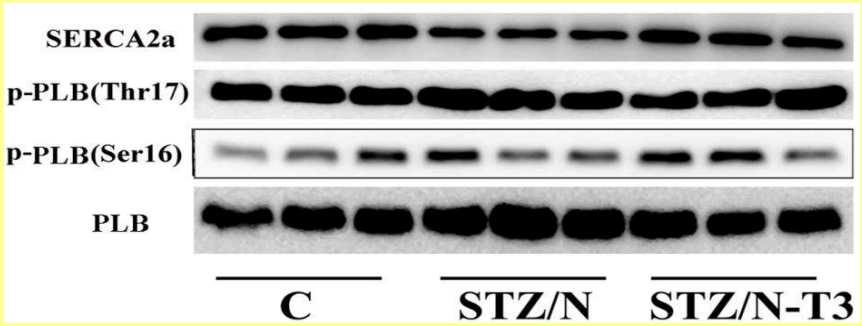
Means (SD). N=4-8/group
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**

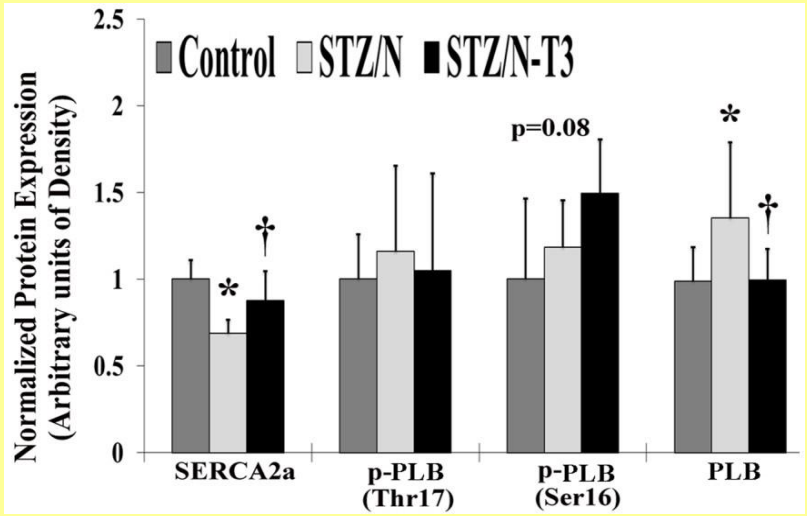
LV relaxation abnormalities do not appear to be the result of increased LV collagen deposition



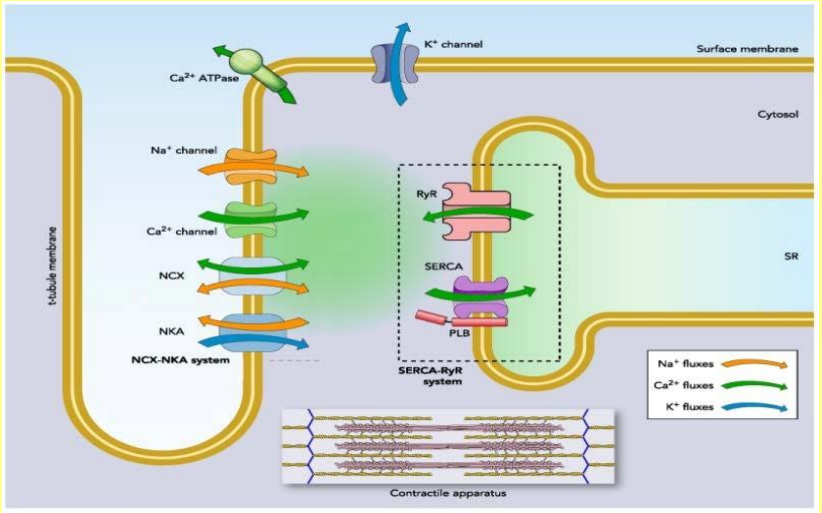
Means (SD). N=5-10/group
***, p<0.05 vs. control**

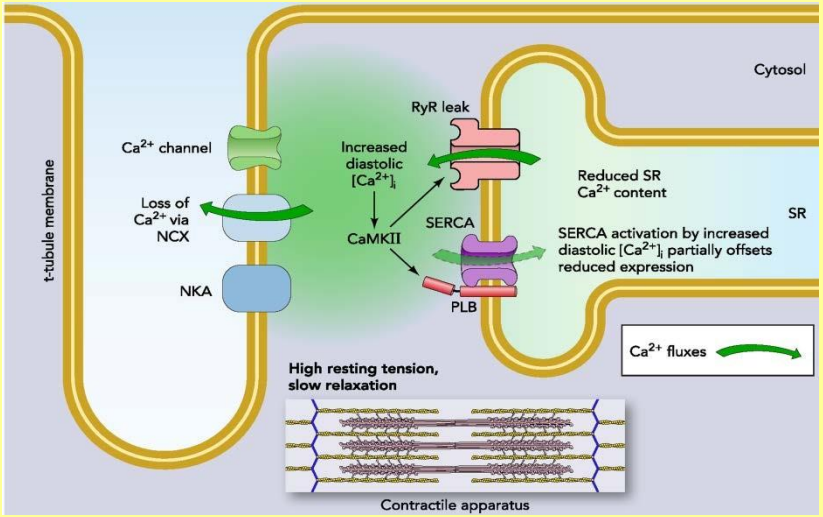
T_3 preserves the expression of myocardial Ca^{2+} handling proteins





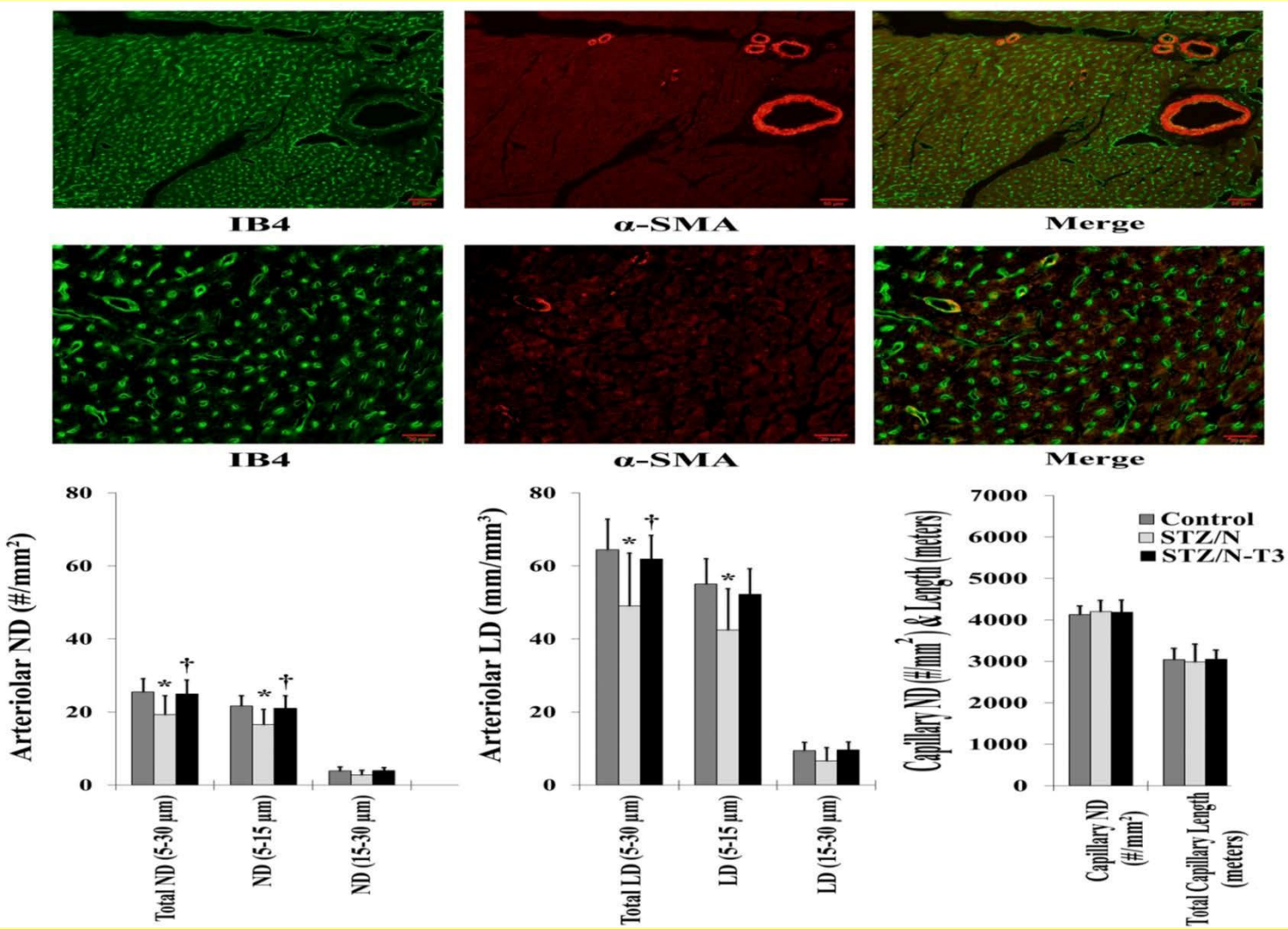
Means (SD). N=4-6/group
***, p<0.05 vs. Control; †, p<0.05 vs. STZ/N**





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

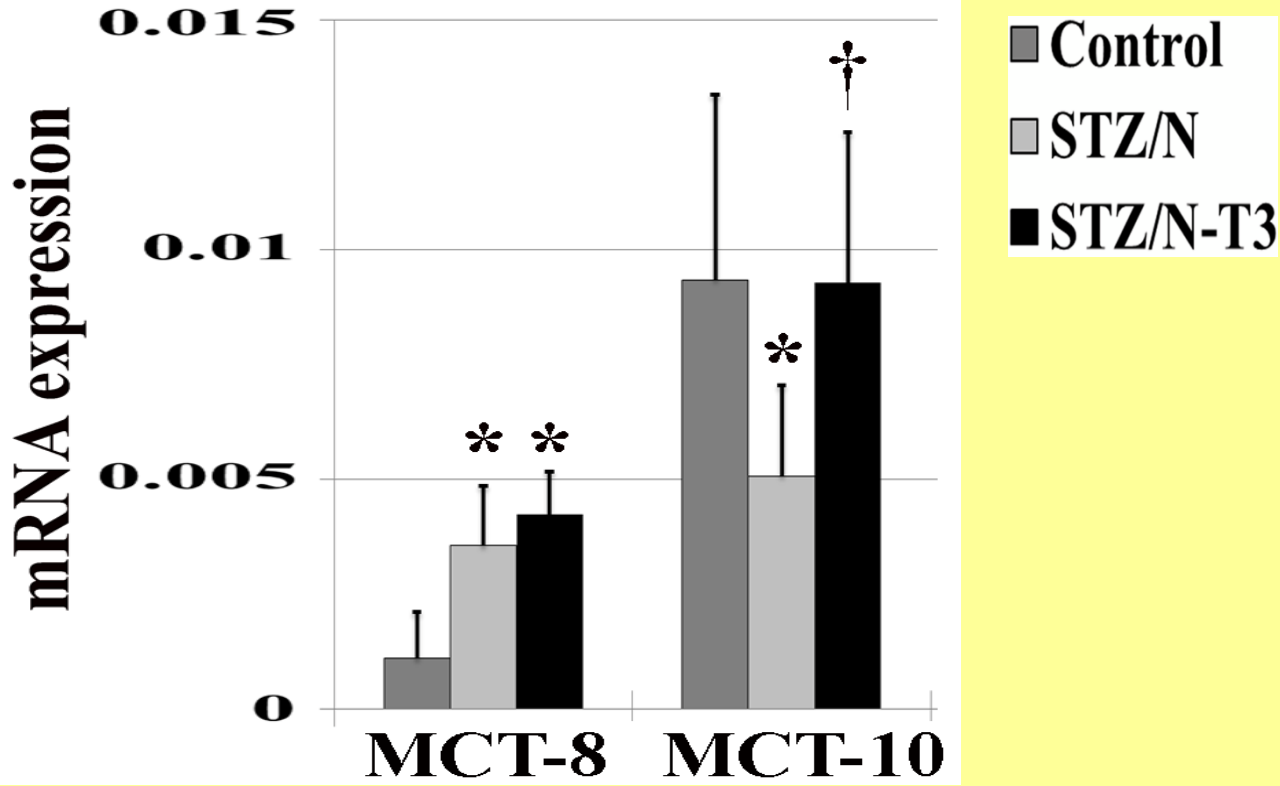
Loss of small arteriolar resistance vessels in the diabetic myocardium is prevented with T_3 treatment



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

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

ExperimentalDM↓expressionofMCT-10 (main TH membrane transporter)



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

Chronic DM leads to myocardial D3 deiodinase expression



Overall Summary

- The STZ/N model produces a cardiac phenotype resembling diabetic cardiomyopathy
- May be ↑ increased risk of ↓ cardiac tissue T3 in DM despite normal serum THs
- Low cardiac tissue T3 levels contribute to cardiac systolic/diastolic dysfunction, fetal gene re-expression, and vascular rarefaction in DM (STZ/N rats)
- Physiologic T_3 replacement appears to be a safe and effective adjunctive therapy in the treatment of diabetic heart disease
- <u>Oral T3 treatment, monitoring protocol:</u> Look for feedback inhibition of T4/TSH with all serum THs in normal range

Clinical Significance

May have cardiac tissue hypothyroidism despite normal serum THs

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

What about arrhythmias and THs?

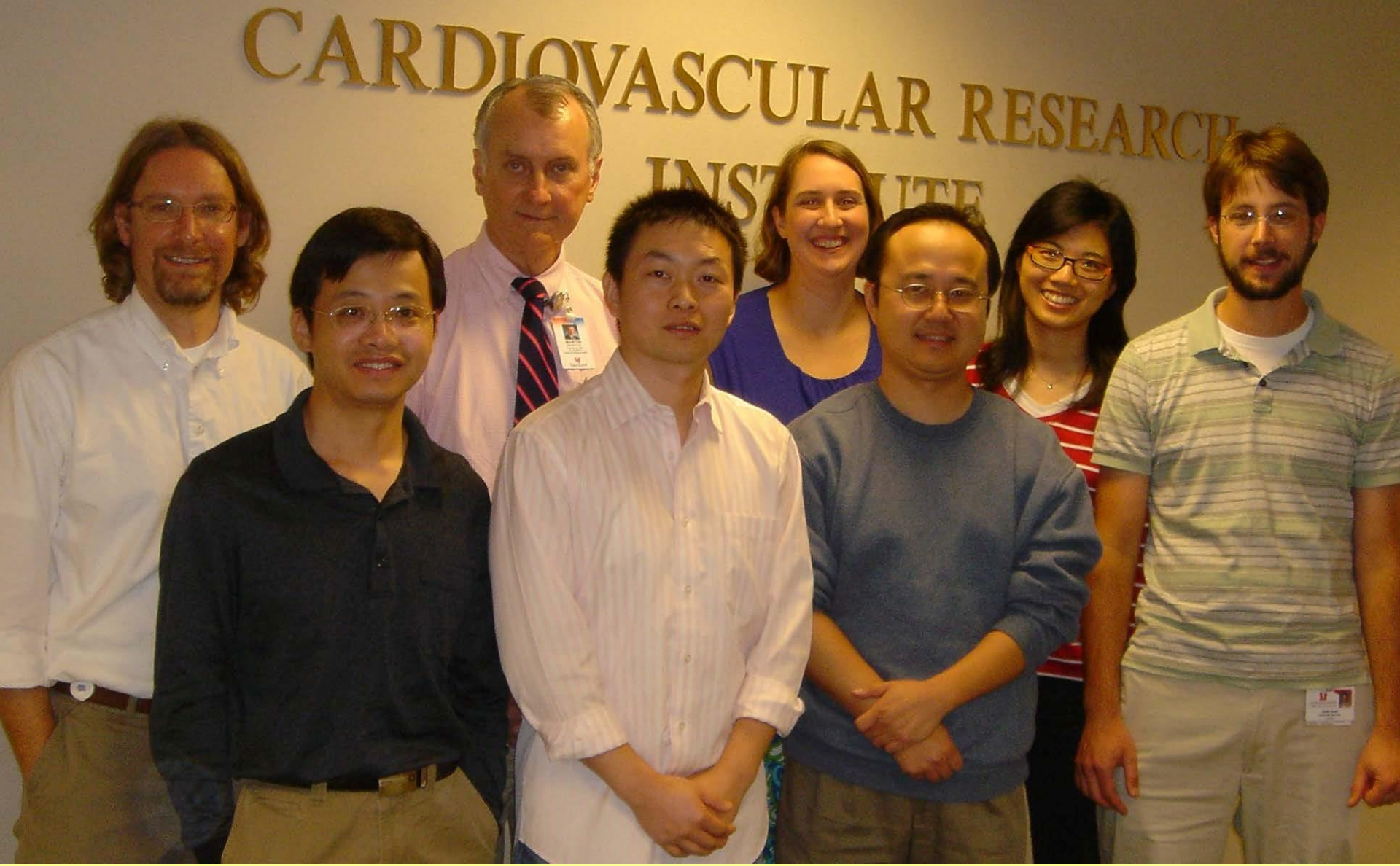
- Using RV catheter, we have been testing arrhythmia induction in rats
- Data recently showed that both hypothyroidism and hyperthyroidism are pro-arrhythmic (Y Zhang et al. 2013. ***Circulation: Arrhythmias and Electrophysiology***
- Other recent experiments are showing reduced susceptibility to arrhythmia generation in MI rats treated with either T4 or T3

Overall conclusion

Cumulative data overwhelmingly suggest that heart diseases promote low cardiac T3, adverse changes in heart function, myocyte and vascular remodeling, gene expression, possibly arrhythmias, **and HF**.

Finally, we have a safe, T3 treatment-monitoring protocol that can be easily translated to humans (Note: Efficacy of same protocol recently confirmed in 2 other rat HF models).

What are we waiting for?



Steve Ortmeier Martin Gerdes Rebecca Redetzke Jessie Liu

Yuefeng Chen Jinghai Chen David Wang Garth Aasen

Thank you!

Questions?

30

Thanks' for your kind attention!!!!!



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