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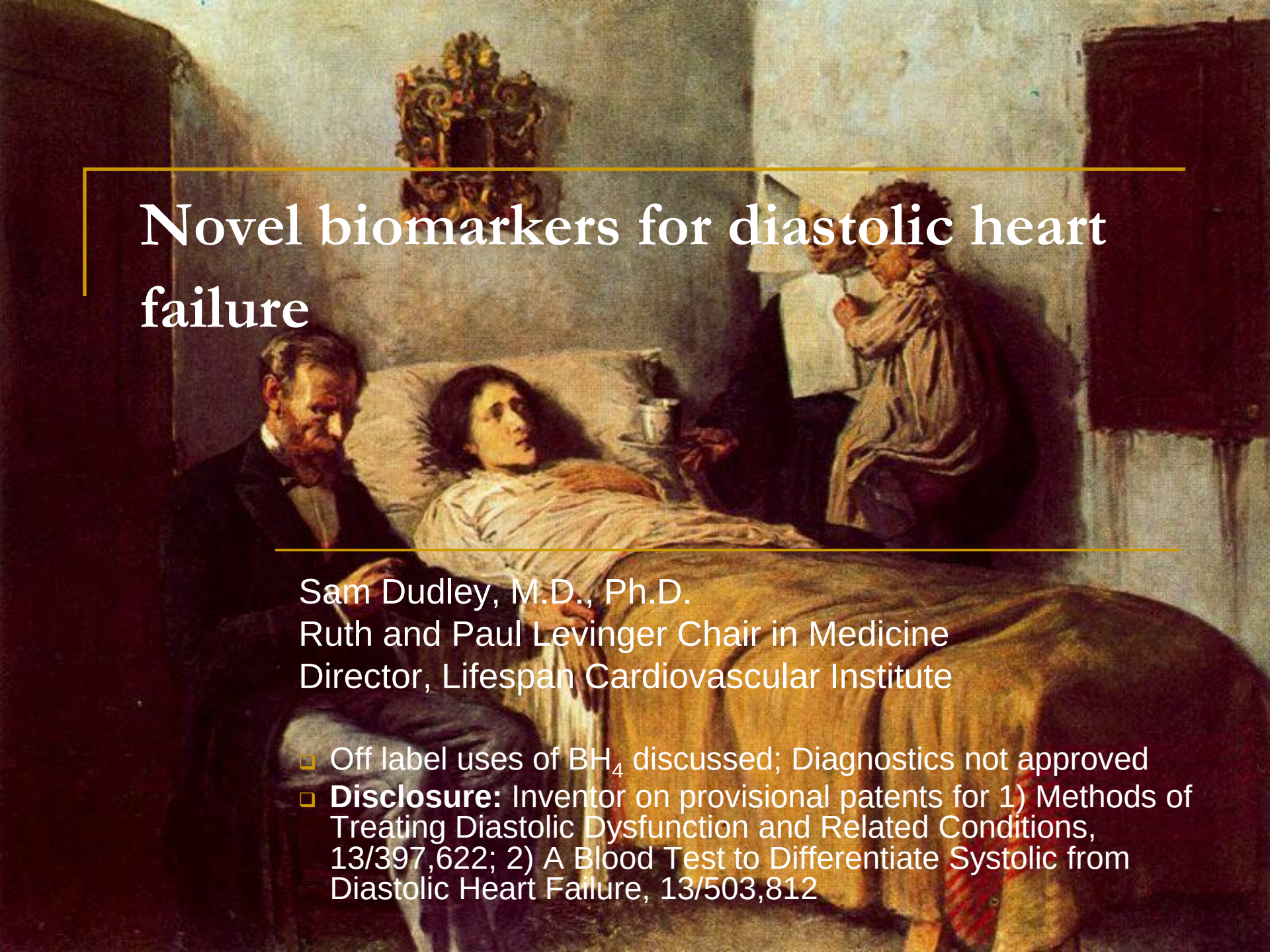


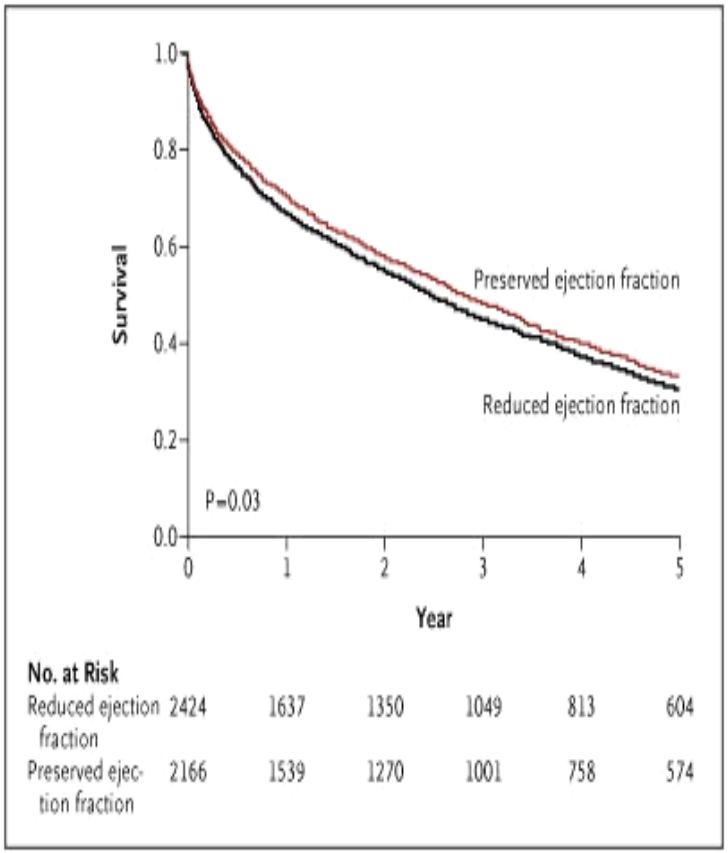
Novel biomarkers for diastolic heart failure

Sam Dudley, M.D., Ph.D.
Ruth and Paul Levinger Chair in Medicine
Director, Lifespan Cardiovascular Institute

- Off label uses of BH_4 discussed; Diagnostics not approved
- **Disclosure:** Inventor on provisional patents for 1) Methods of Treating Diastolic Dysfunction and Related Conditions, 13/397,622; 2) A Blood Test to Differentiate Systolic from Diastolic Heart Failure, 13/503,812

Clinical Significance of DD/DHF

- 5 million people in U.S. with Heart Failure (HF)
- ~ 1/2 of HF patients have preserved LVEF
- High morbidity and mortality in DD/DHF
- No proven treatment for patients with DD/DHF



Owan et al. *NEJM* 2006
Zile & Brutsaert. *Circ.* 2002

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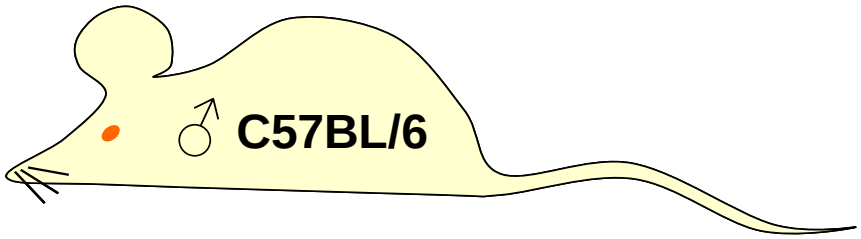
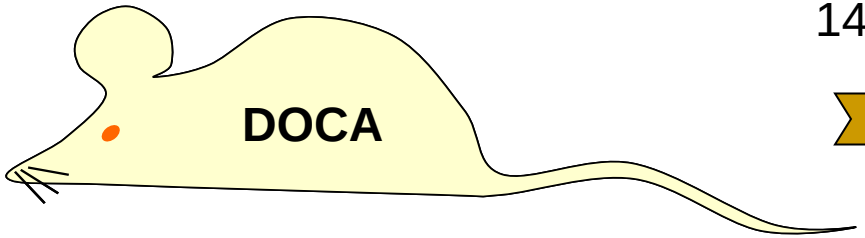
The one kidney/DOCA/salt water model



Nephrectomy, DOCA pellet insertion, salt water, ± BH_4



14 days

Model characteristics

- mild/moderate HTN
- preserved ejection fraction
- no hypertrophy
- no valvular regurgitation

- echocardiogram
- invasive hemodynamics
- tissue harvest

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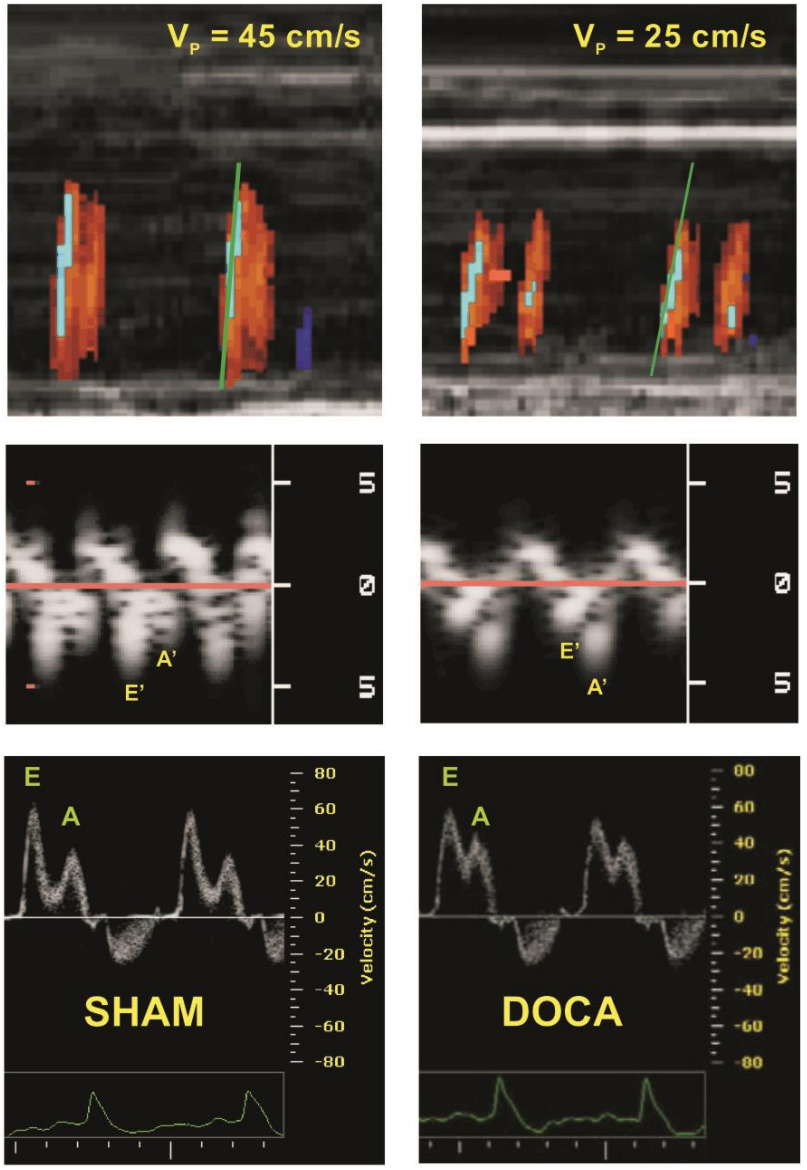
Hypertensive mice showed diastolic dysfunction by echocardiographic techniques



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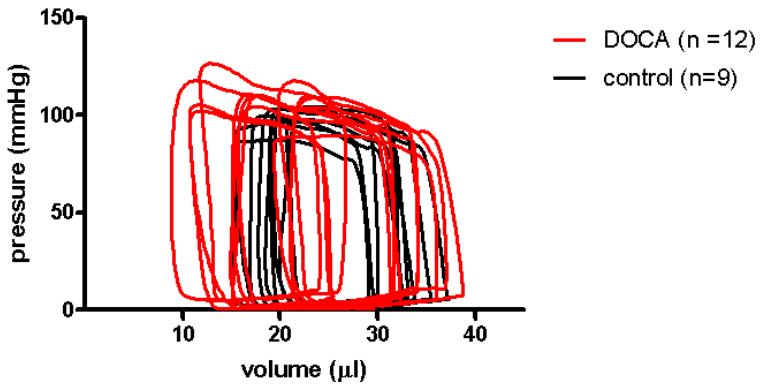
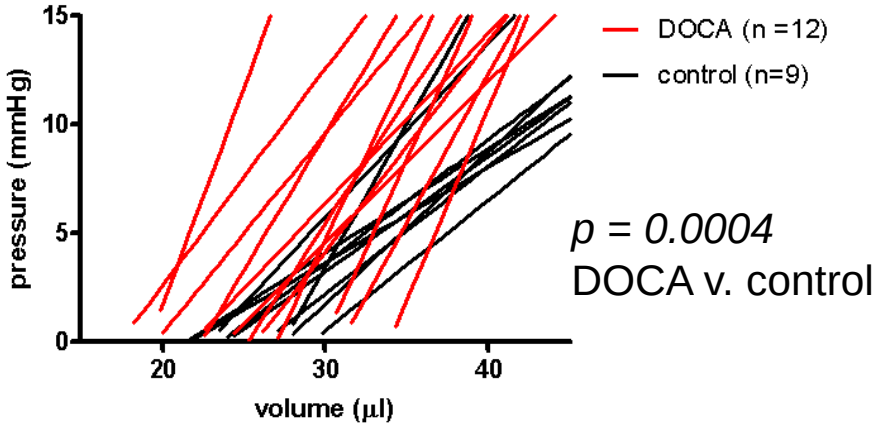
DOCA mice show abnormal hemodynamics

Baseline

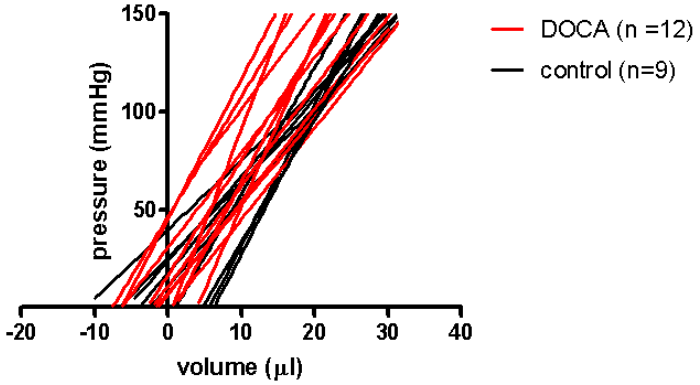


EDPVR

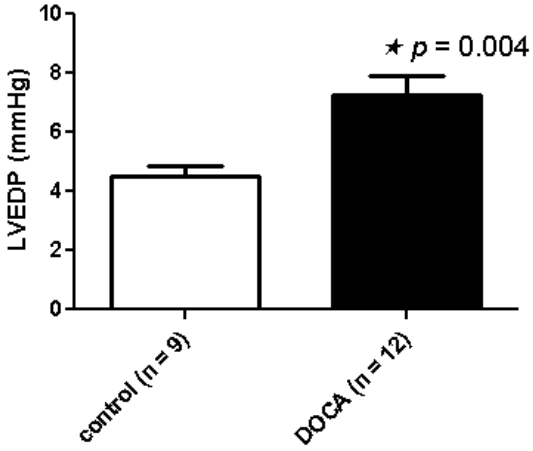


p = 0.0004
DOCA v. control

ESPVR



LVEDP



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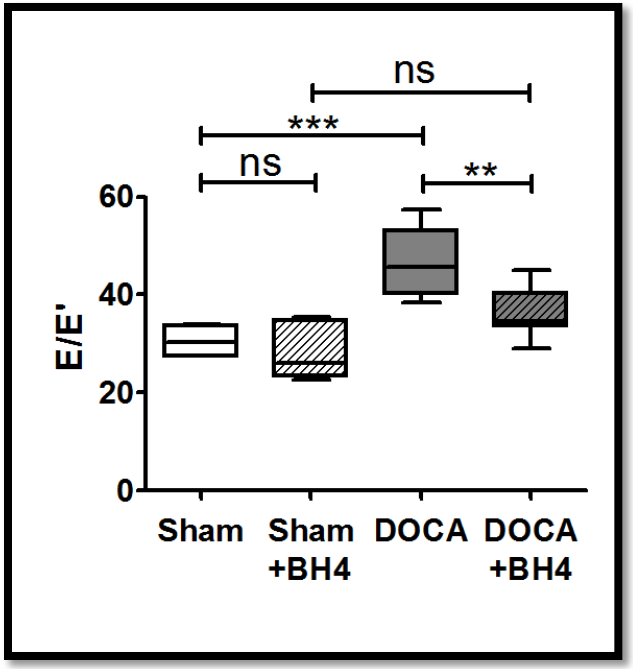
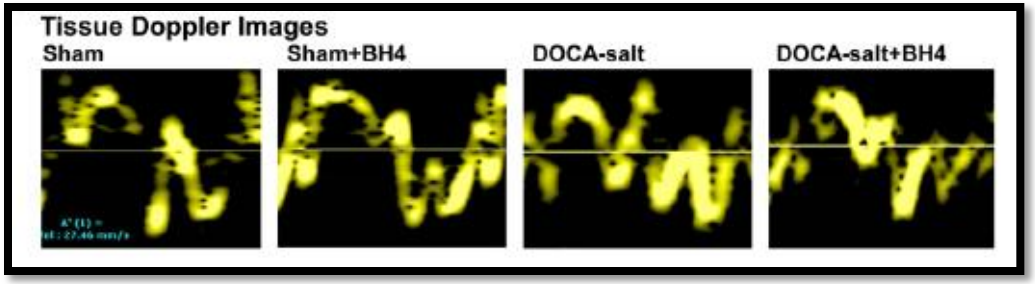
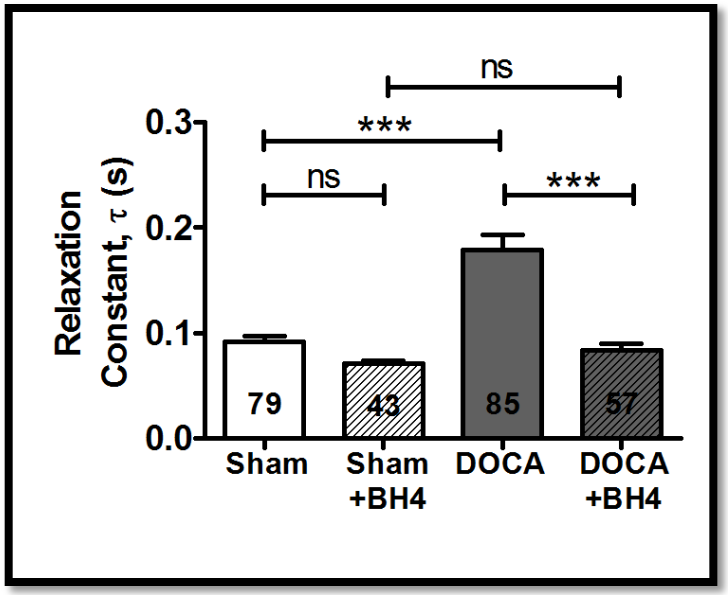
BH_4 Improves Diastolic Function and Cardiomyocyte Relaxation

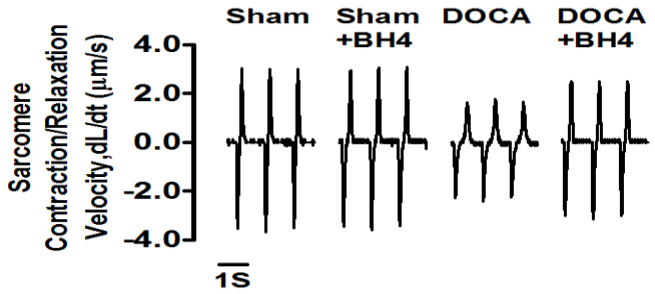
In vivo





Cellular





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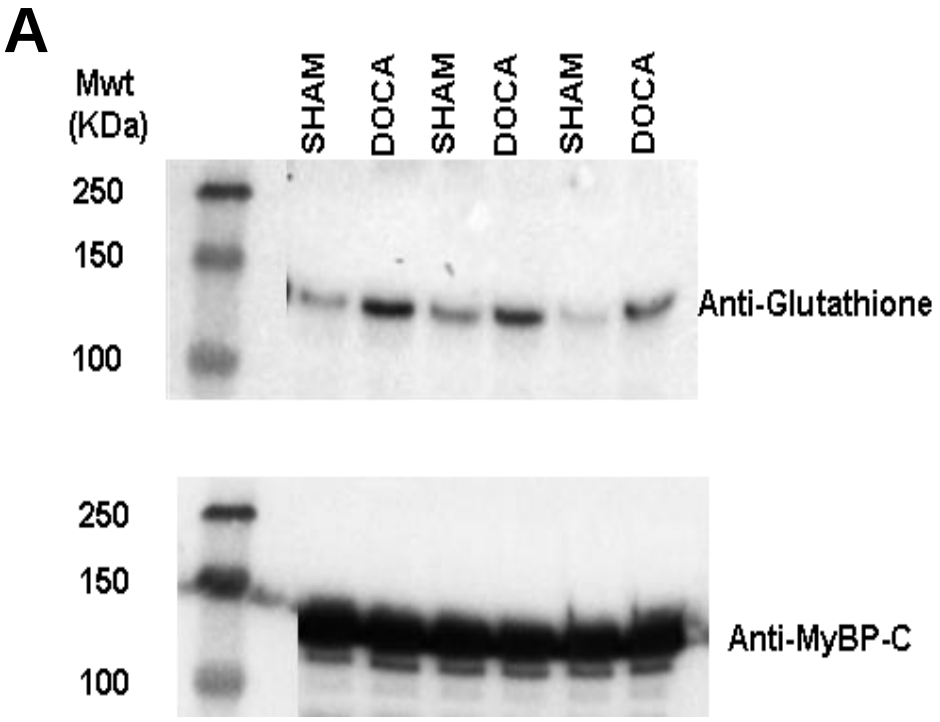
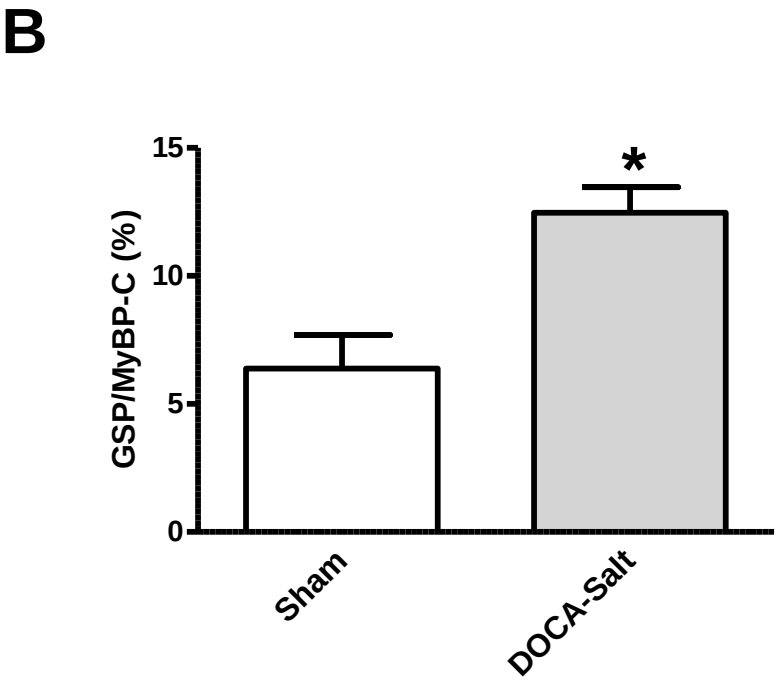
Glutathionylation of myosin binding protein C (MyBP-C) in diastolic dysfunction





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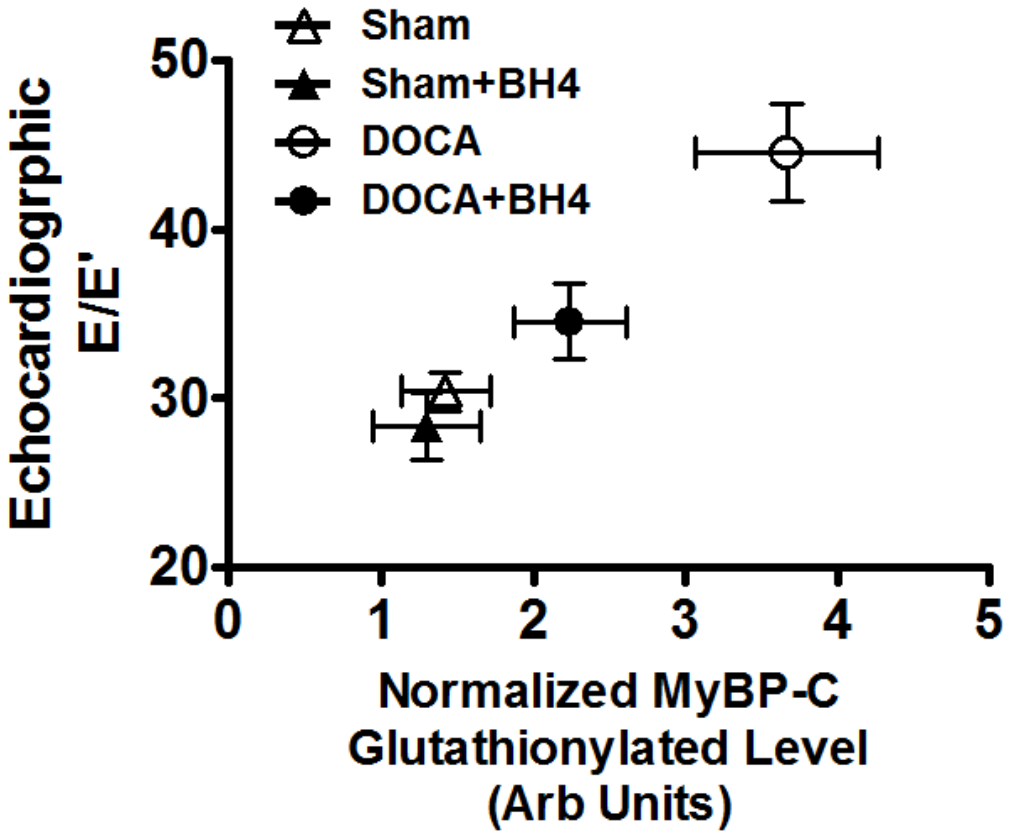
S-Glutathionylation of cMyBP-C Correlates with Diastolic Relaxation



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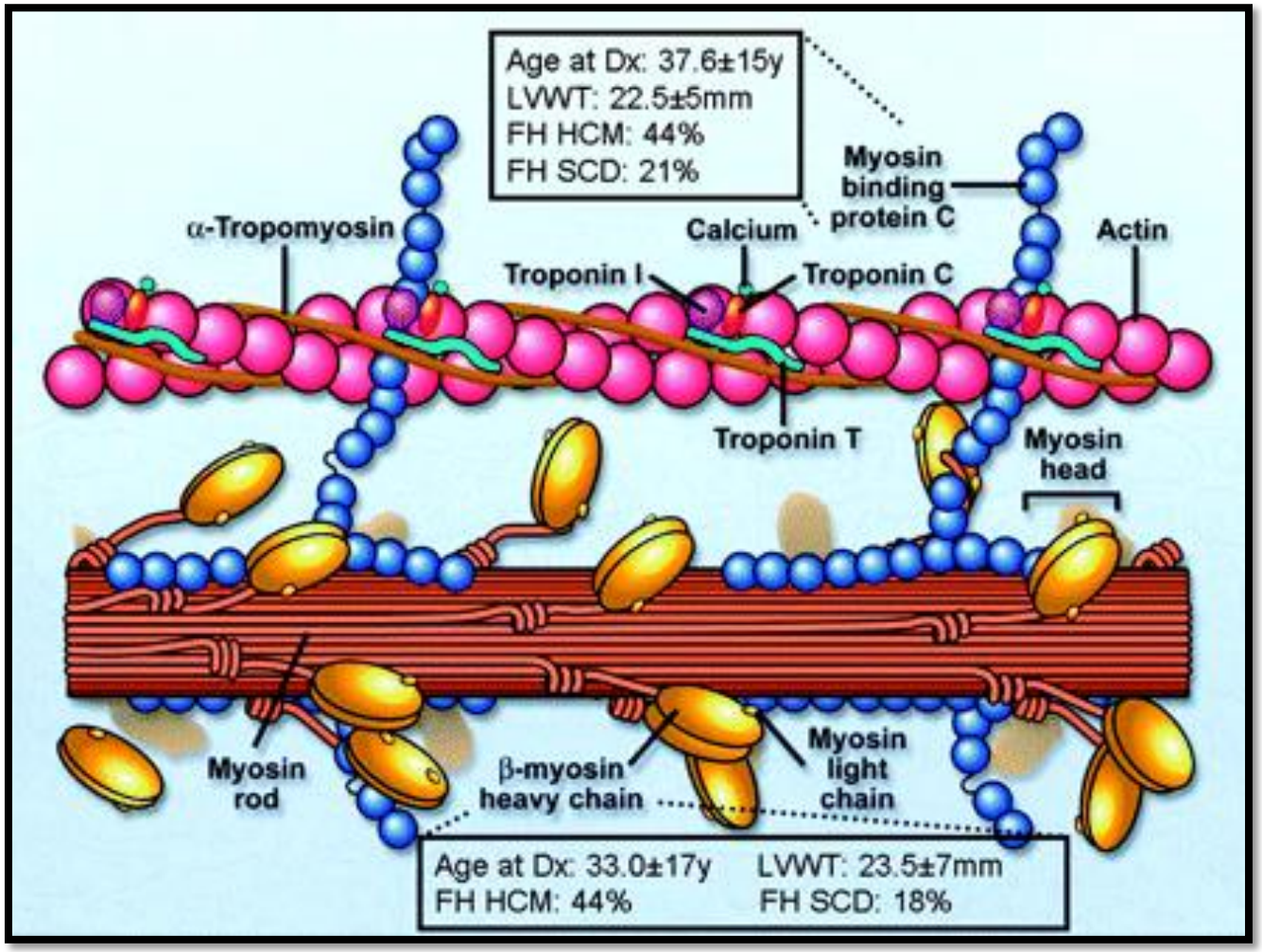
Cardiac myosin binding protein C (MYBPC3)



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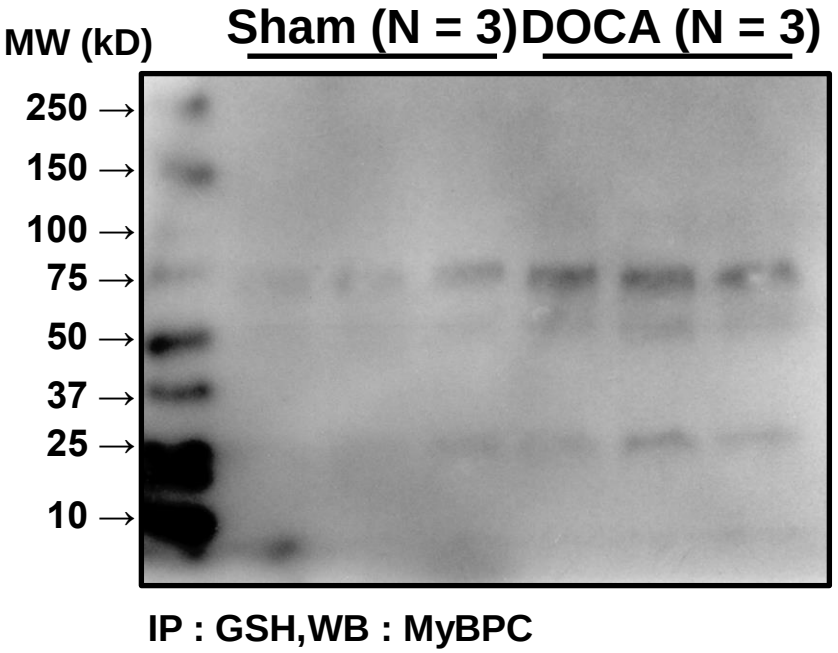
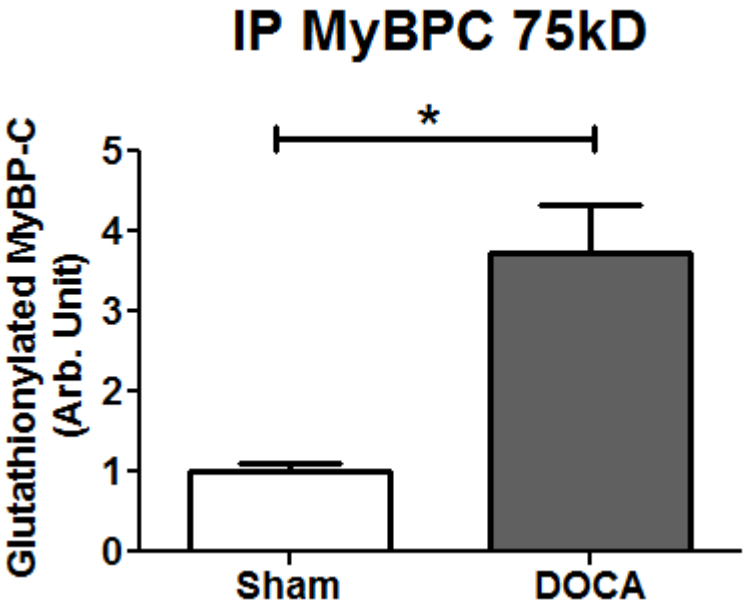
Landstrom and Ackerman, Circulation. 2010; 122: 2441-2450

Plasma cMyBP-C-glutathionylation from DOCA-salt mice





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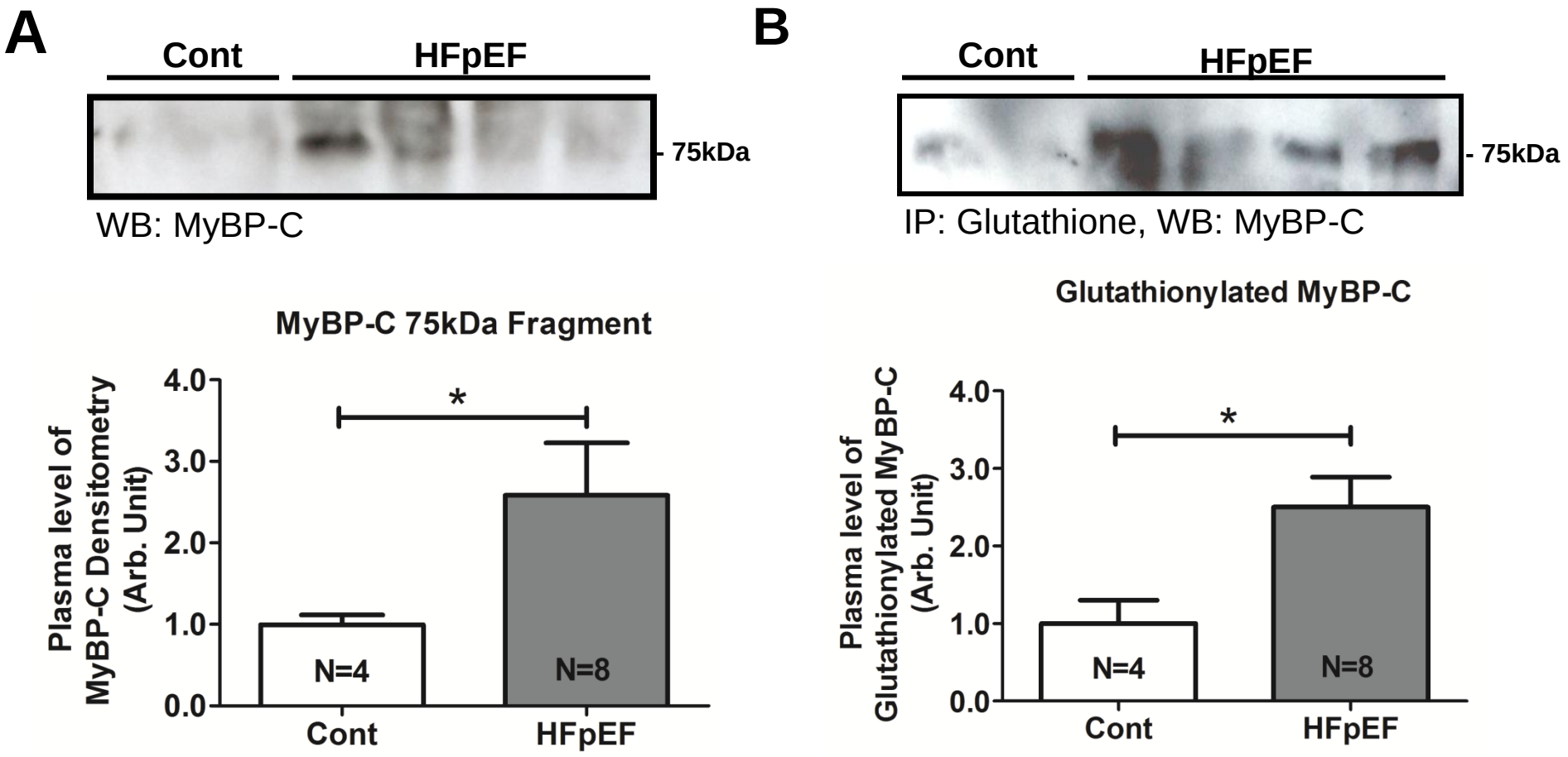
Oxidized cMyBP-C in human blood



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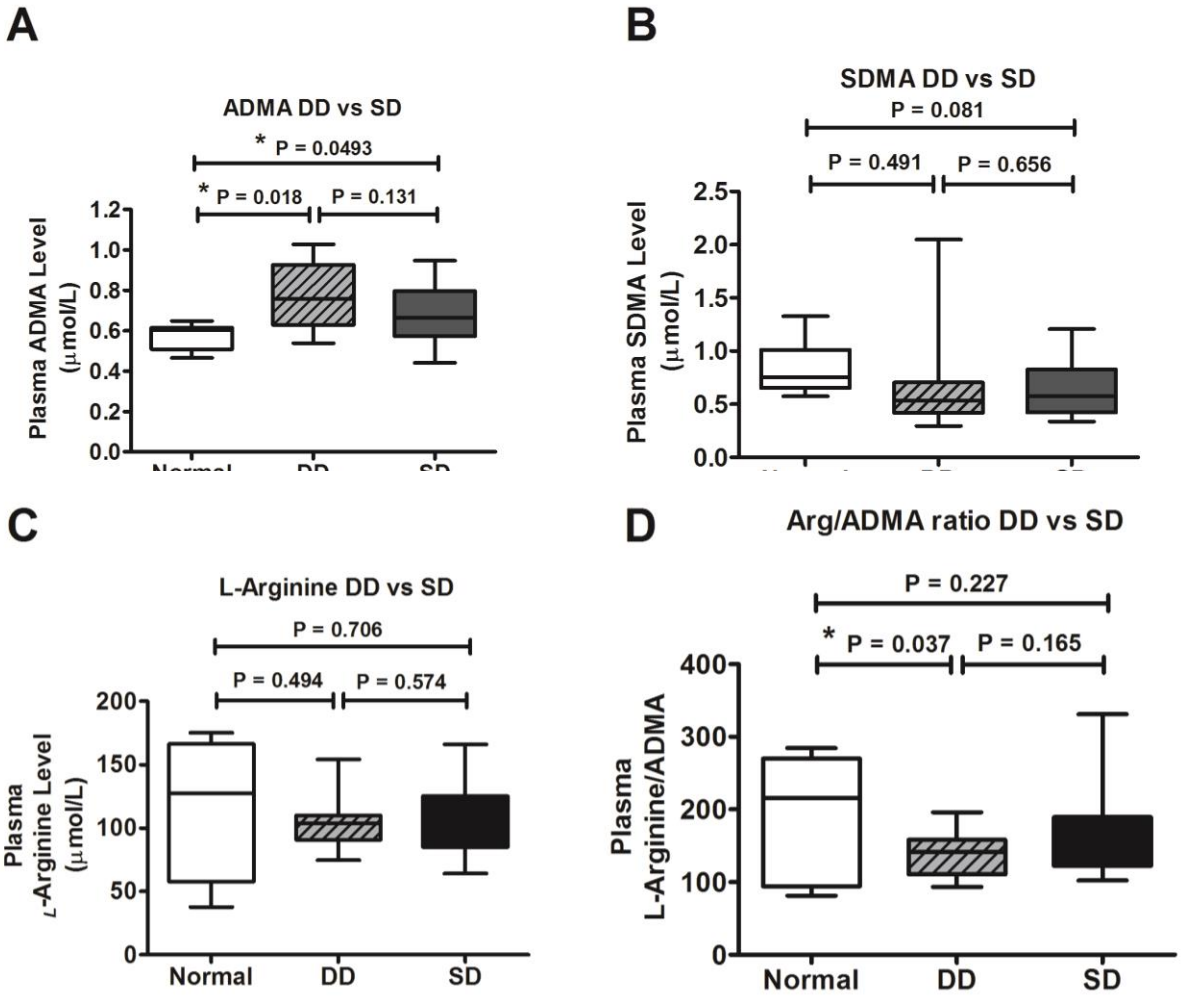
Asymmetric dimethyl arginine (ADMA) is lower in HFpEF



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Summary

- Hypertension-induced diastolic dysfunction cardiac BH_4, increased cardiac oxidation, uncoupled nitric oxide synthase (NOS), and reduced nitric oxide (NO)
- BH_4 prevents or reverses diastolic dysfunction
- Hypertension-induced diastolic dysfunction is associated with glutathionylation of cardiac myosin binding protein C (cMyBP-C)
- Diastolic dysfunction results in elevated plasma cMyBP-C and modified cMyBP-C
- Diastolic dysfunction is associated with elevated ADMA, consistent with NOS uncoupling

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Thanks' for your kind attention!!!!!

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