CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

A Clinical Perspective on basic science: Gender aspects

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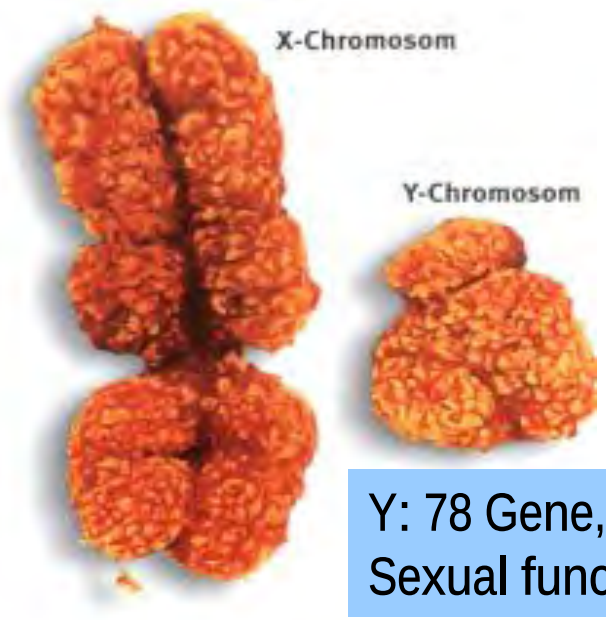
& Center Cardiovascular Research, & DHZB

Charité

Sex and Gender Differences in Medicine

Sex – biological facts
Genes and Hormones

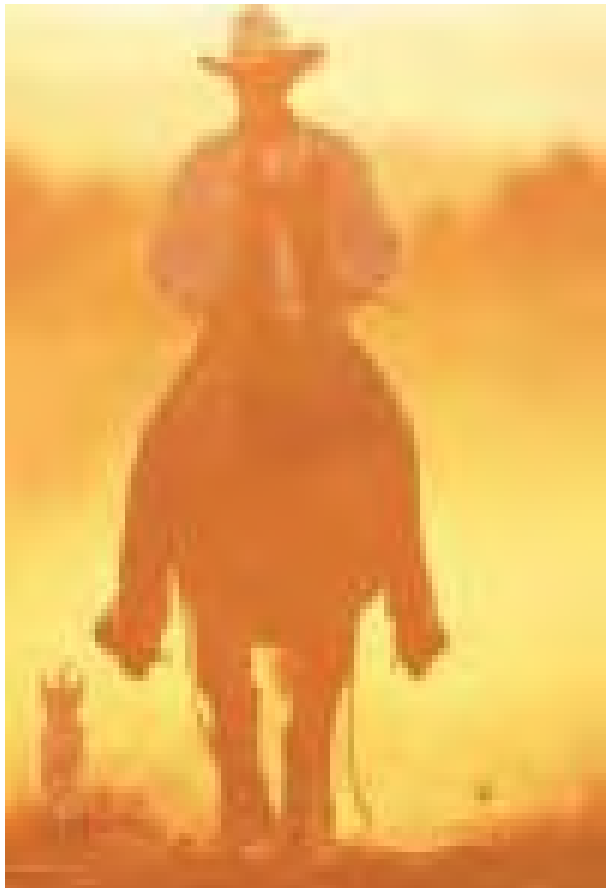


Y: 78 Gene,
Sexual function

X: ca 1500 Gene
Heart-, Brain-, Immune function

Environment leads to epigenetic DNA and chromatin modifications

Gender –
Socio-cultural facts

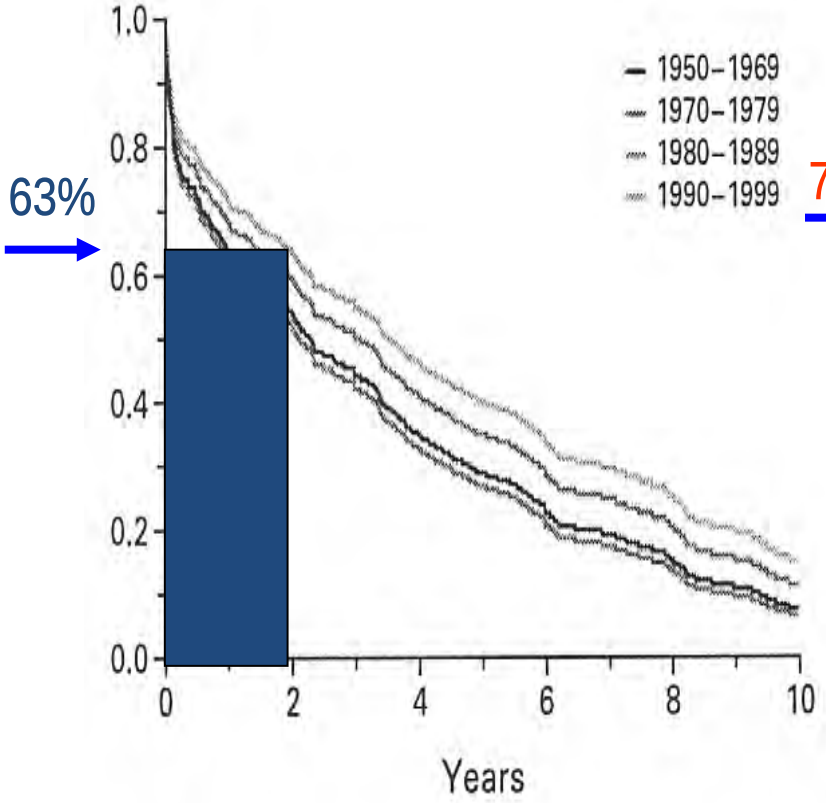


Gender medicine aims at benefit for women and men

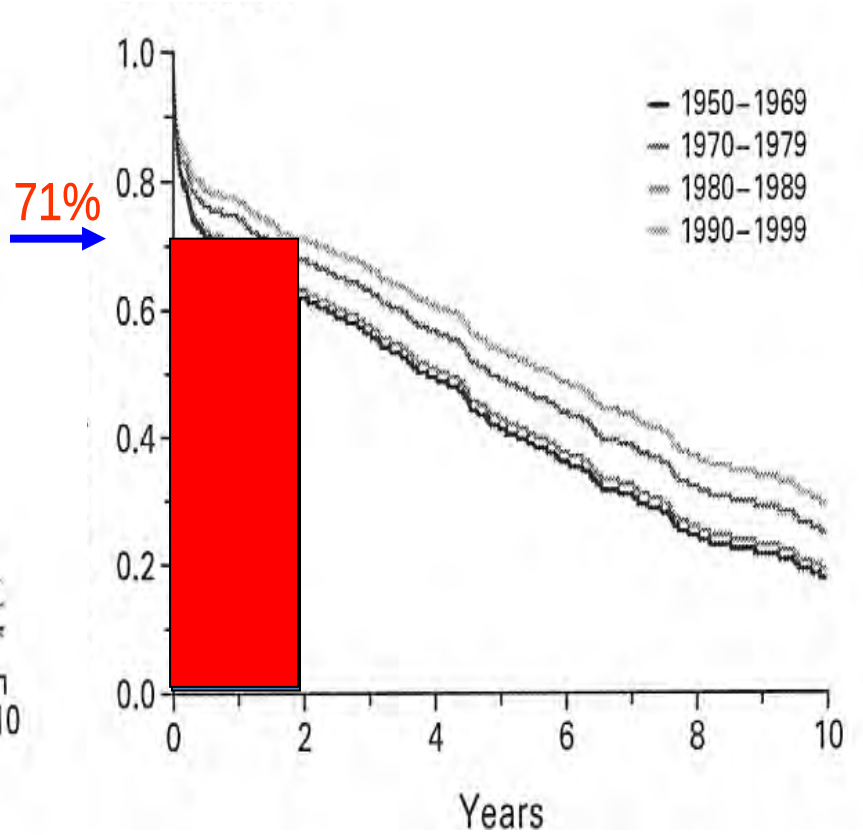
Survival after onset of HF in the population is improving and better in women

Framingham cohort: 2- year survival is 71 % in women and 63 % in men

Men, 2 years mortality 37 %



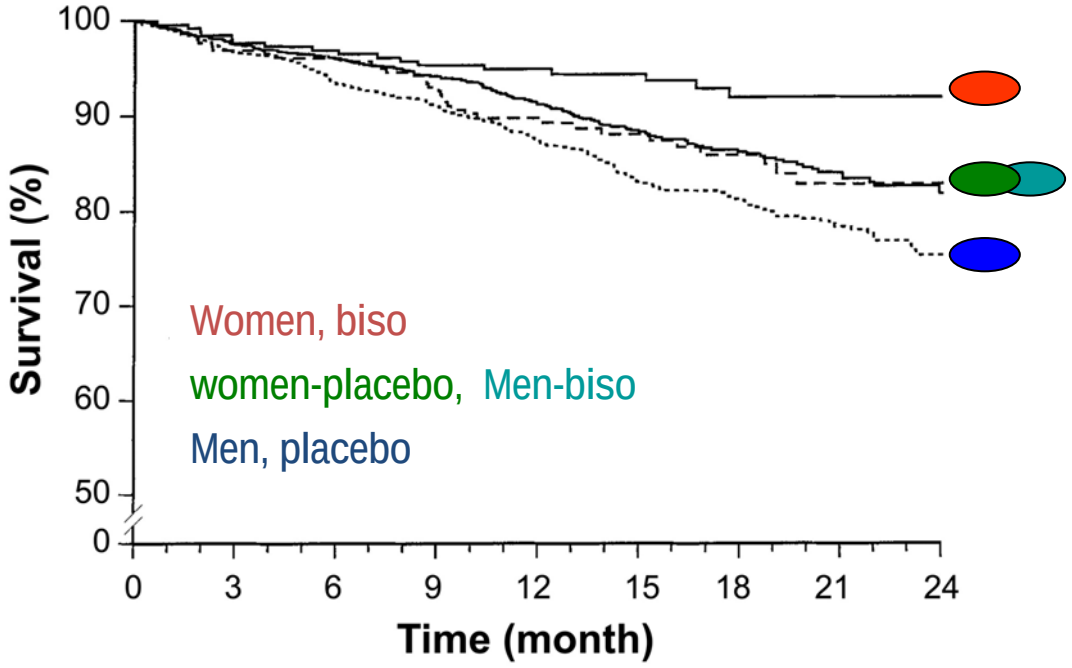
Women, 2 years mortality 29 %



Levy, NEJM 2002

Survival in systolic HF in clinical studies is better than in the population and better in women than in men

Cardiac Insufficiency Bisoprolol Study (CIBIS) II, men (n=2132) women (n=515)



Female sex is as good as a β-blocker or an Angiotensin receptor blocker (CHARM study)

Reasons for better outcome of women: unclear

Simon T et al, Circulation 2001

Survival in men with systolic HF is predicted by serum estrogen levels

501 men with chronic HF, LVEF 28+8 %, age 58+12 y were classified according to quintiles of serum estrogen levels. Significant differences existed after adjustment for all clinical variables and serum androgens.

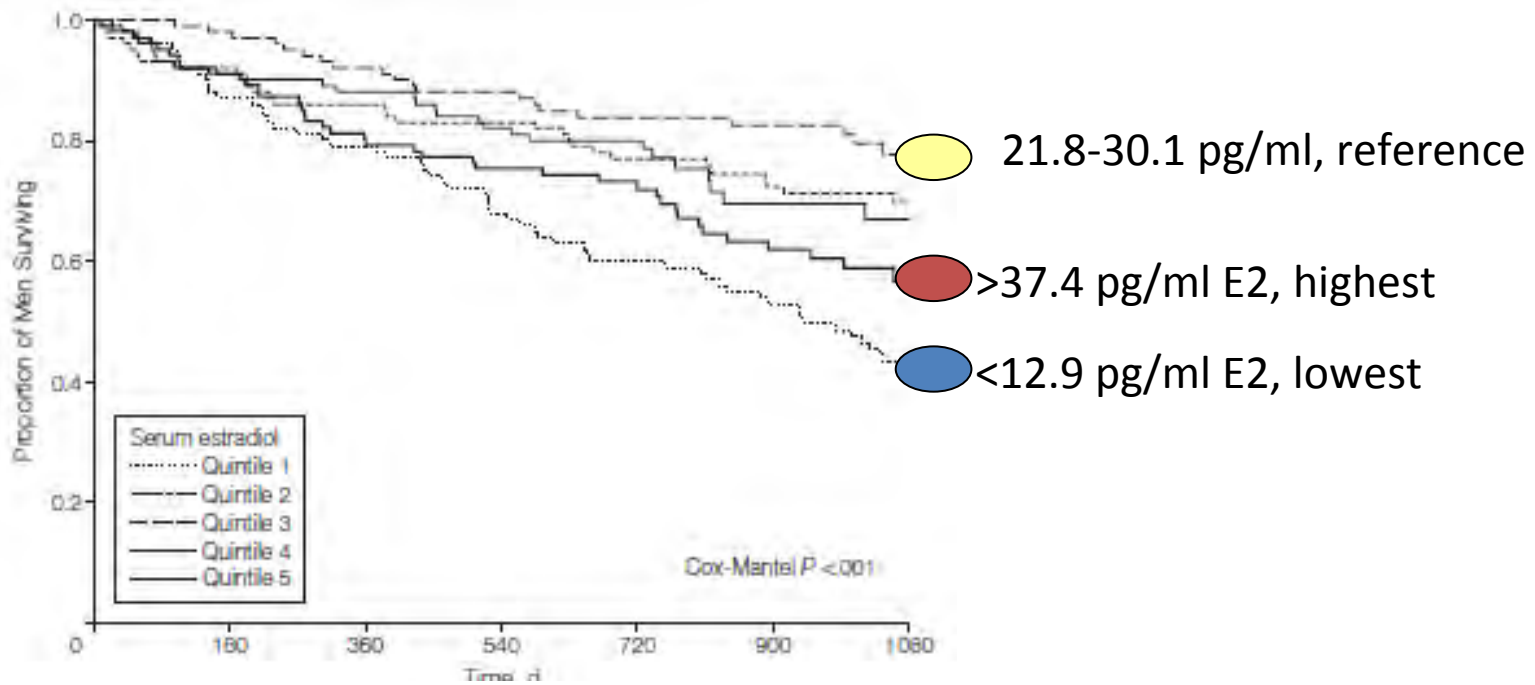


Figure 2. Kaplan-Meier Curves Reflecting 3-Year Cumulative Survival Rates in Men With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction According to Subsequent Quintiles of Serum Estradiol

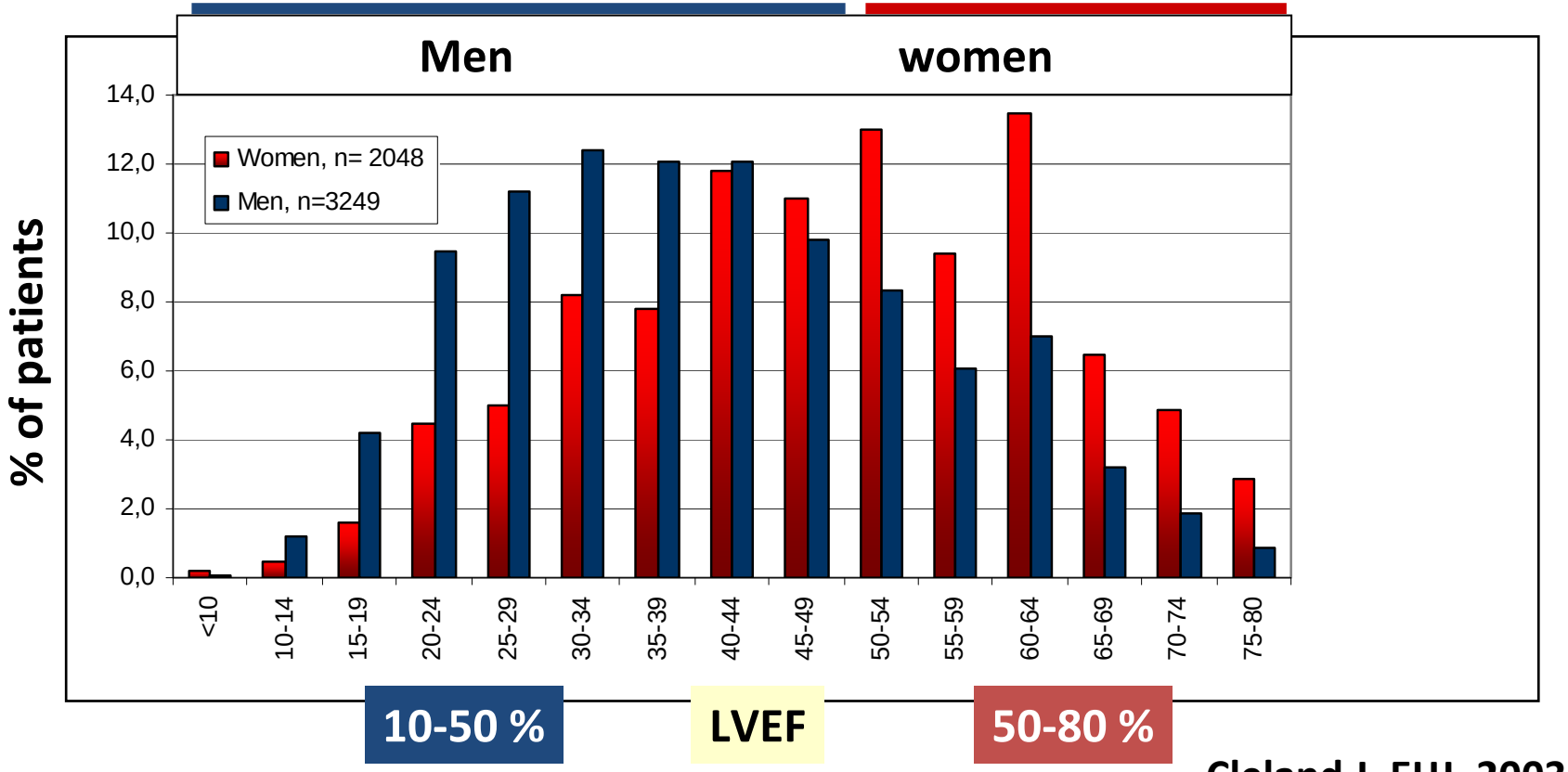
Jankowska E, JAMA 2009

EuroHeart Survey: Women have more heart failure (HF) with normal EF, men HF with reduced EF (systolic)

Sex differences in HF-hospitalized patients in 115 European hospitals

Men (n=2048): more systolic dysfunction

Women (n=3249): more diastolic dysfunction

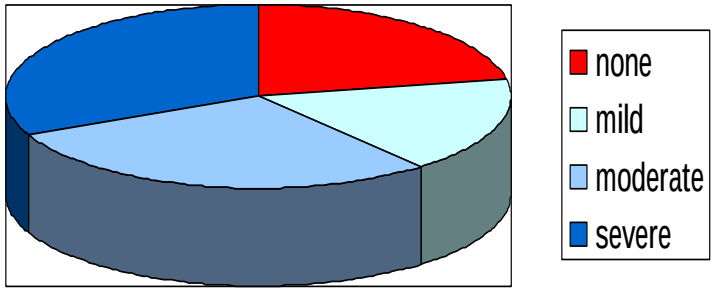


Cleland J, EHJ, 2003

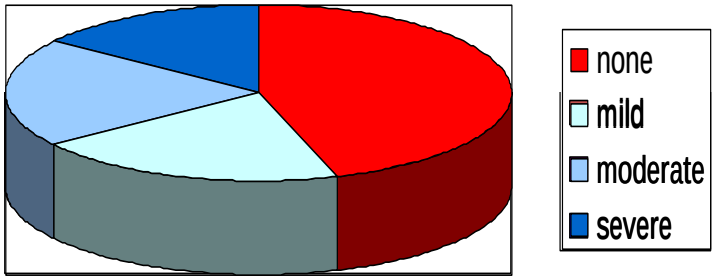
Men have more systolic heart failure; women more “diastolic” HF (HF with preserved EF)

Systolic dysfunction dominates in men and diastolic dysfuntion in women

men



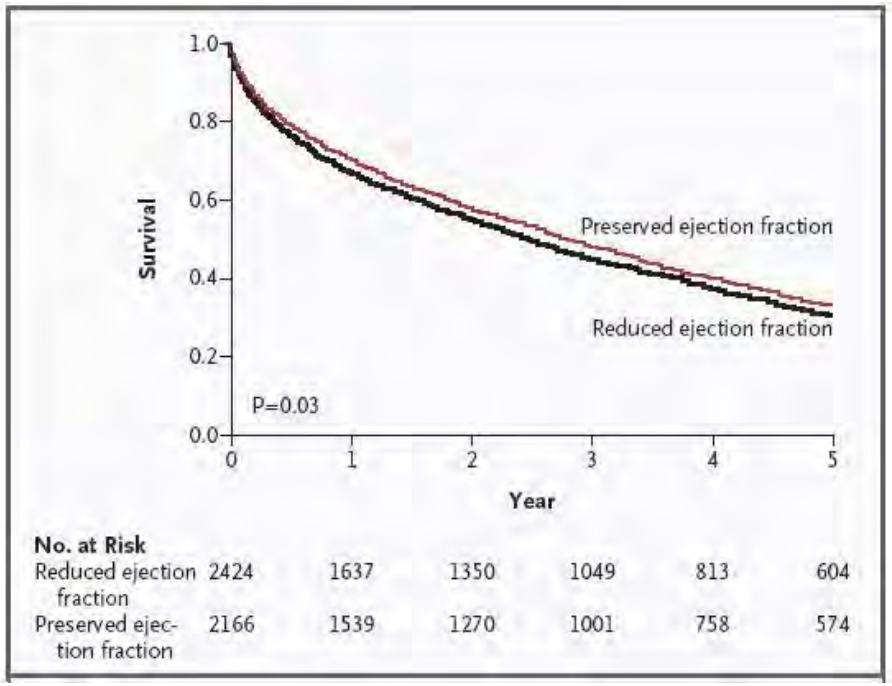
women



Euro heart failure survey

Cleland, Europ H J, 2003

Both are bad



Olmstead county study

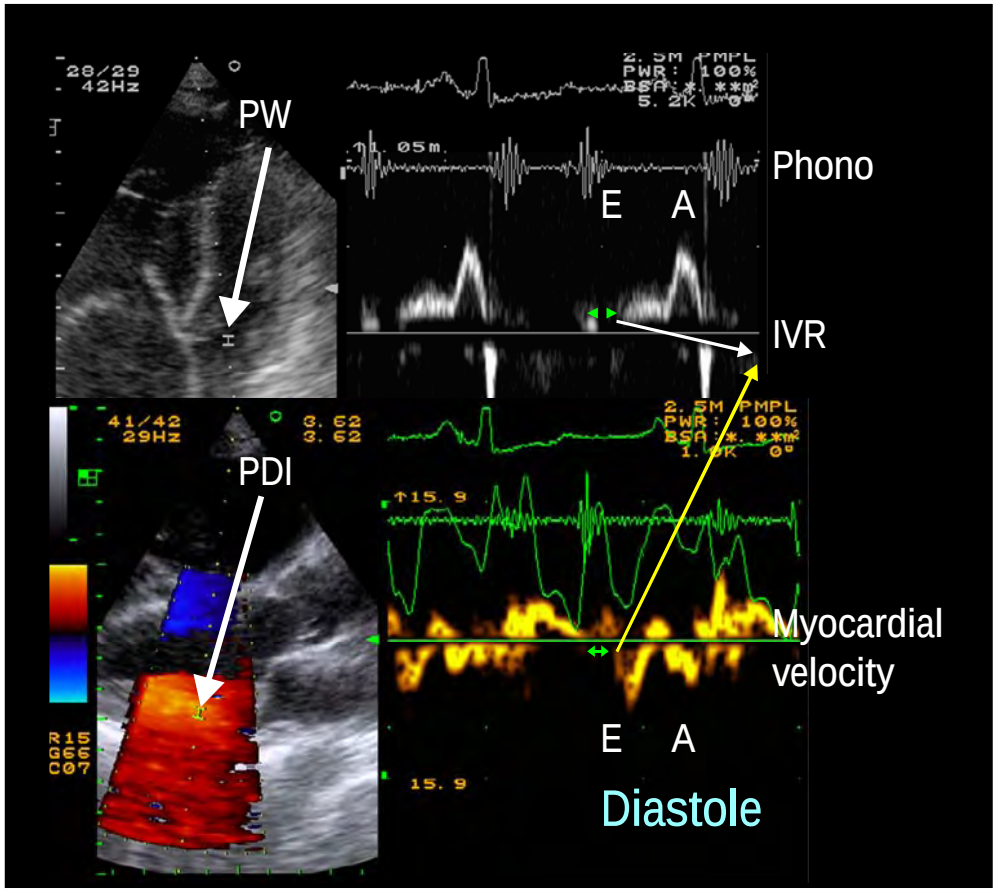
HFPEF: 46 % of all patients,
65 % women

Owan, NEJM 2006

Diastolic HF and HF with preserved EF _ novel entities

Risk factors:

female gender, old age, diabetes, hypertension



The diagnosis

Signs and Symptoms

Dyspnoe, exercise intolerance

congestion

Echo: normal systolic function

impaired diastolic filling

Mitral flow - PW

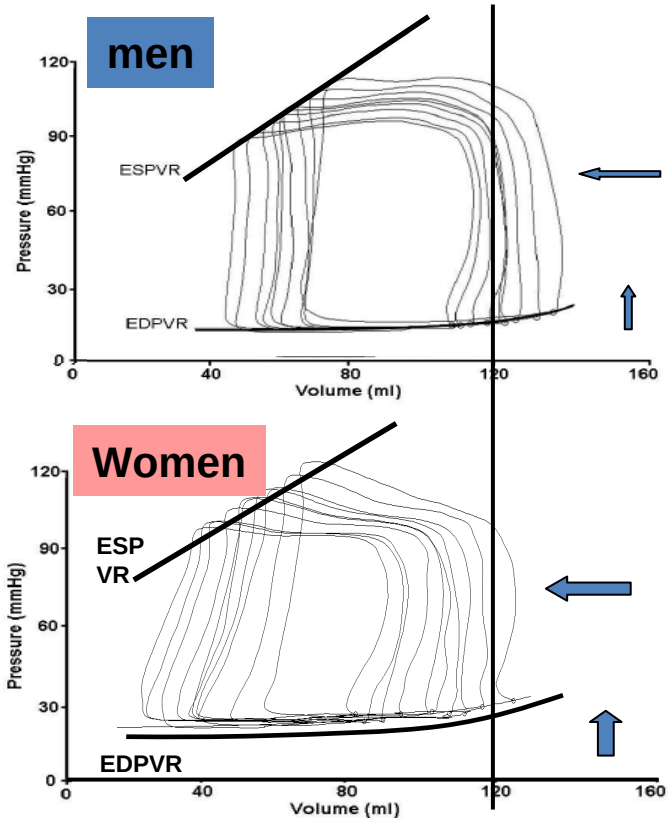
Doppler,

disturbed Relaxation

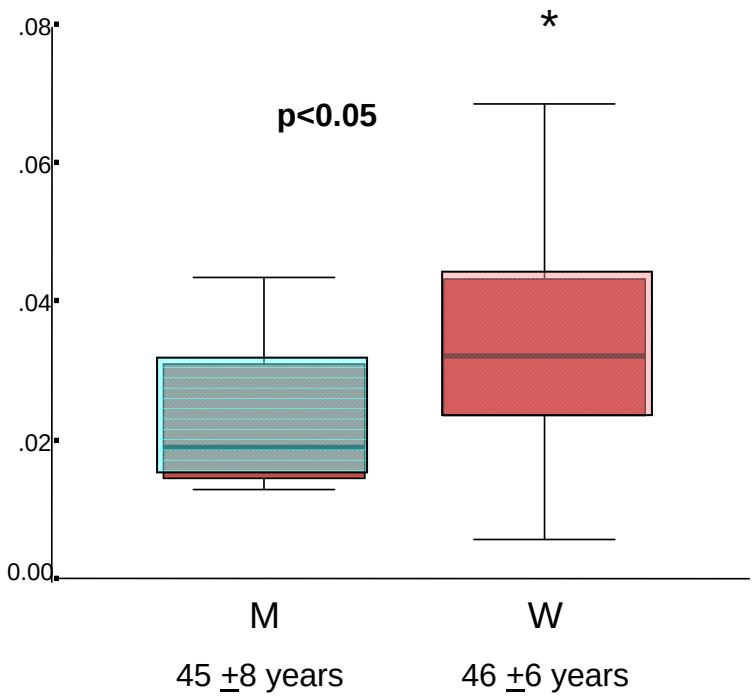
BNP elevated

Female hearts in controls and patients with HFPEF are smaller and stiffer than males

Pressure volume analysis in females and males



Ventricular stiffness

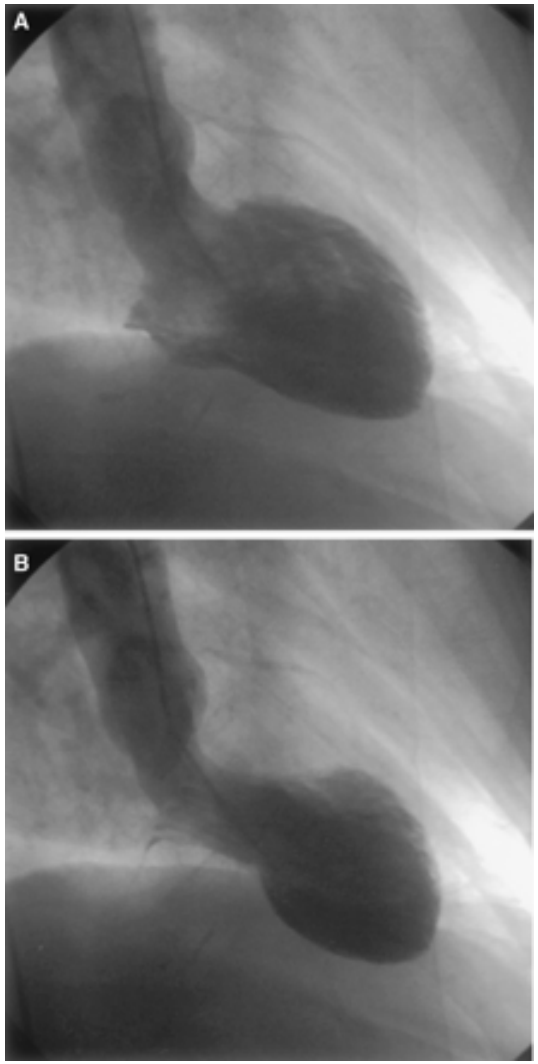


V Regitz-Zagrosek et al; Progress in Cardiovascular Disease, 2007

Some HF forms occur almost only in women - *Tako tsubo* cardiomyopathy

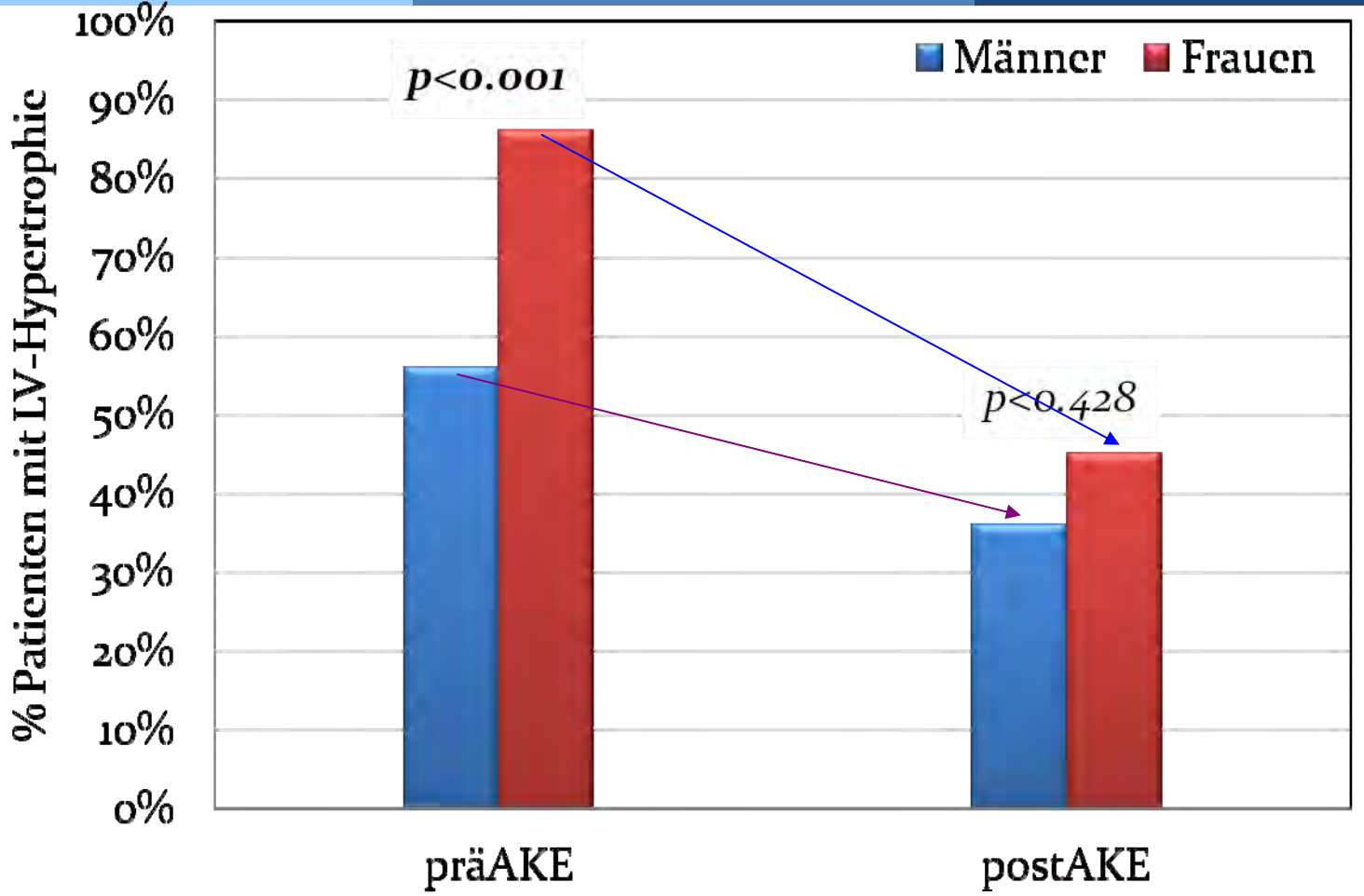
Mimics myocardial infarction
But normal coronary arteries
Severe disease
Triggered by massive psychological stress

Was believed to be extremly rare – German registry with more than 300 pts in 2 years



Sharkey, Circulation 2005

Sex differences in myocardial hypertrophy (MH): More (concentric) MH and faster regression after AVR in women



Schwellenwerte für LVH:
LVMM/BSA >125 g/m² bei Männern und >104 g/m² bei Frauen (nach MONICA, Augsburg)

Petrov et al, Circulation. 2009, 120(18): 821-822;

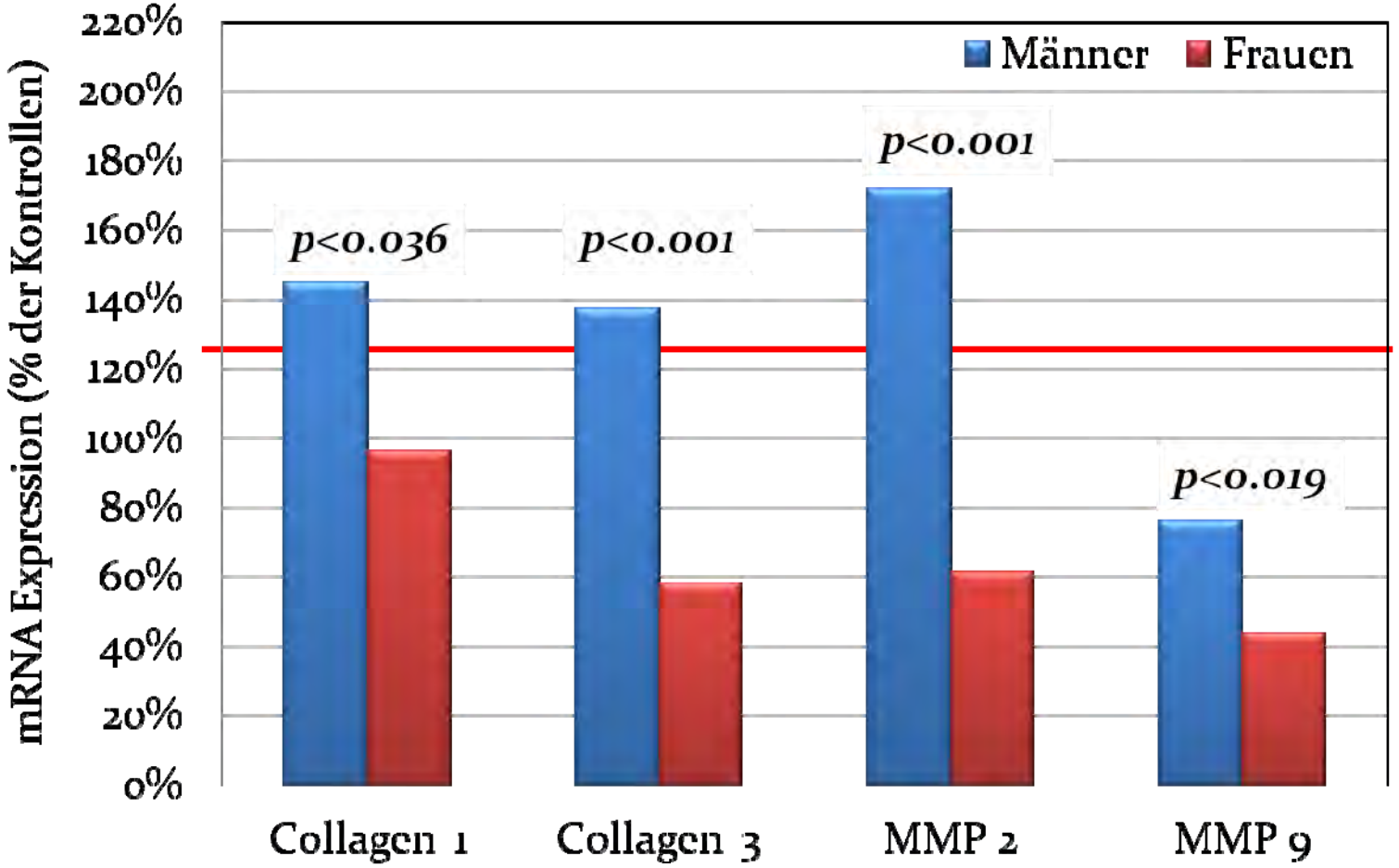
Reversibility of MH - Prospective clinical study

92 women and men with aortic stenosis undergoing aortic valve replacement in DHZB

	Frauen (N=53)	Männer (N=39)	*p*
N (%)	**53 (58%)**	**39 (42%)**	**N/A**
Alter [Jahre]	72 ± 9	67 ± 11	0.028
BMI [kg/m²]	**29.2 ± 6.2**	**27.9 ± 4.1**	**0.702**
BSA [m²]	1.84 ± 0.2	2.02 ± 0.2	0.001
GFR [ml/min]	68 ± 24	81 ± 23	0.006
Dyspnoe bei Belastung	**81 %**	**74 %**	**0.436**
Ruhedyspnoe	**19 %**	**5 %**	**0.053**
Synkope	**26 %**	**21 %**	**0.512**
NYHA II – III	**81 %**	**83 %**	**0.470**
Hypertonie	**81 %**	**77 %**	**0.622**
Diabetes mellitus	**25 %**	**26 %**	**0.903**
Hypercholesterinämie	**57 %**	**46 %**	**0.321**
Schilddrüsenerkrankungen	34 %	8 %	0.003

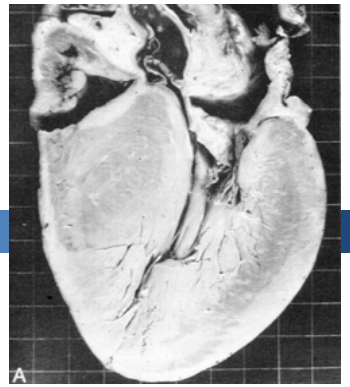
Petrov et al, Circulation. 2009, 120(18): 821-822;

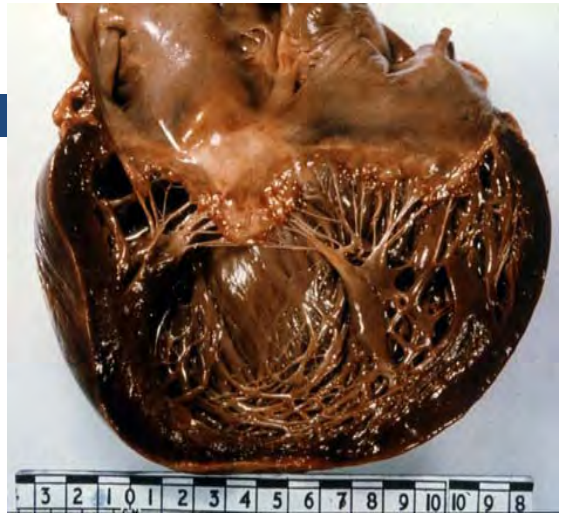
Greater profibrotic gene expression in men than in women with AS in surgical LV biopsies



Petrov et al, Circulation. 2009, 120(18): S821-822;

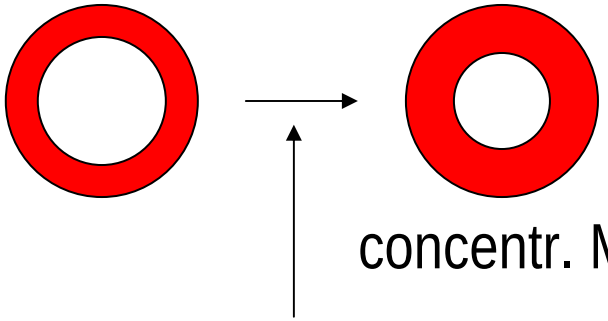
Manifestation of HF – Hypothesis based on HFPEF, AS





MH,
diast. Dysfunction
↓ distensibility

normal



concentr. MH

Pressure load
Hypertension
Aortic stenosis

Women?!

HF, syst.Dysfunction,
↓ Pump function

Men

No guidelines

Plenty of guidelines

Better
Reversibility?

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CME

Cardiac Resynchronization Therapy Is More Effective in Women Than in Men

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Trial

Aysha Arshad, MD,* Arthur J. Moss, MD,† Elyse Foster, MD,‡ Luigi Padeletti, MD,§ Alon Barsheshet, MD,† Ilan Goldenberg, MD,† Henry Greenberg, MD,* W. Jackson Hall, PHD,† Scott McNitt, MS,† Wojciech Zareba, MD, PHD,† Scott Solomon, MD,‖ Jonathan S. Steinberg, MD,* on behalf of the MADIT-CRT Executive Committee

New York and Rochester, New York; San Francisco, California; Florence, Italy; and Boston, Massachusetts

Resynchronization therapy leads to better survival in women than in men

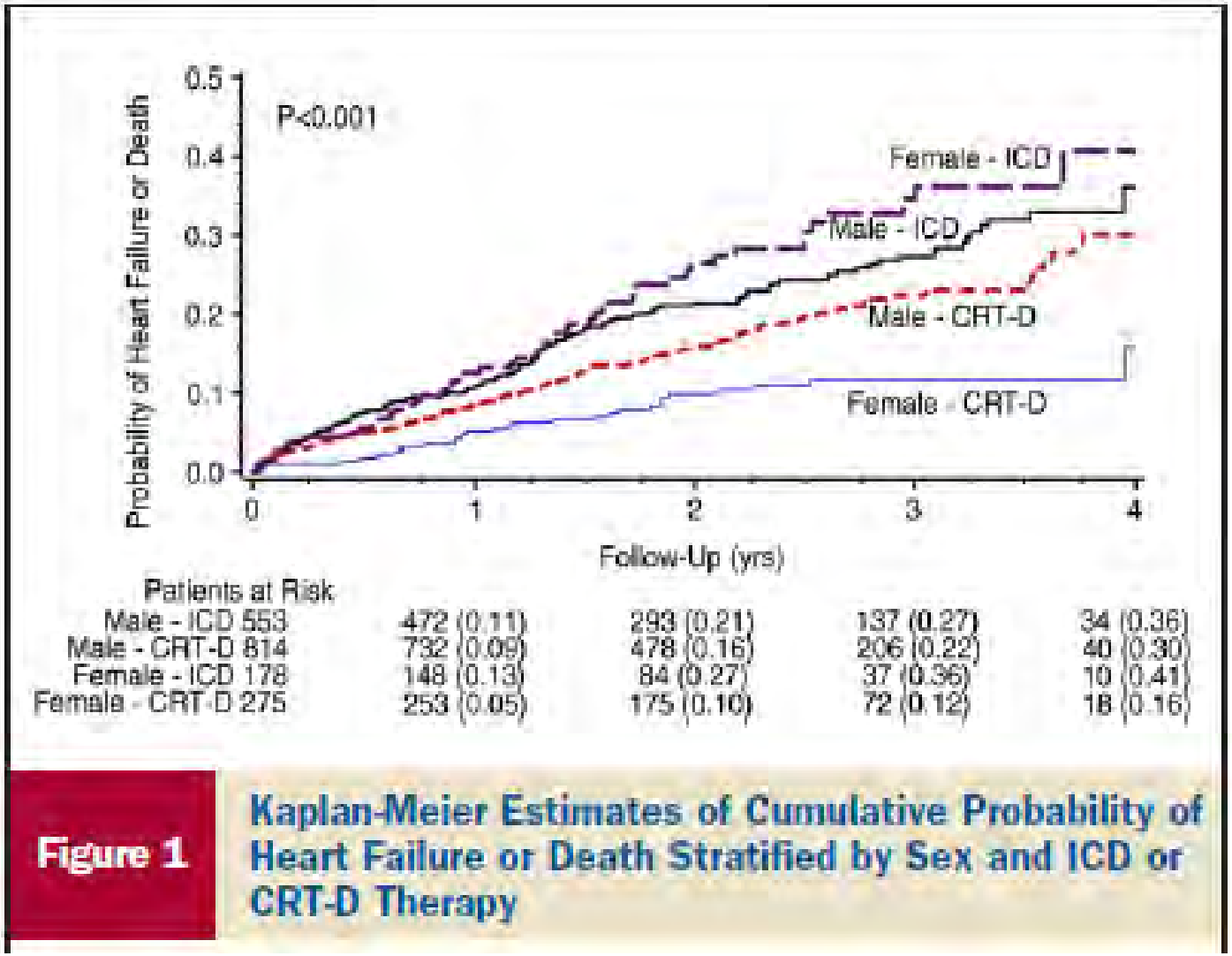
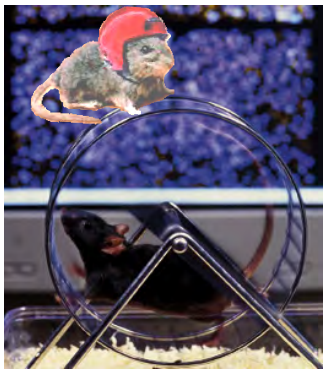
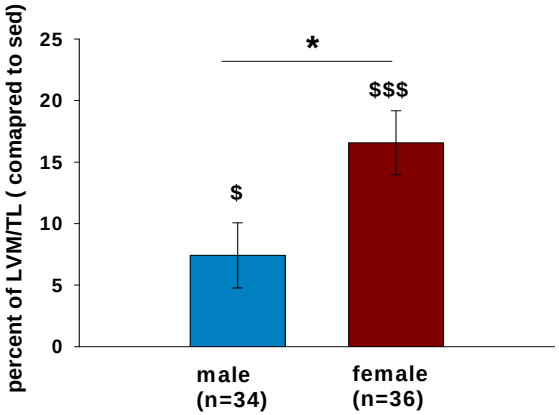


Figure 1 Kaplan-Meier Estimates of Cumulative Probability of Heart Failure or Death Stratified by Sex and ICD or CRT-D Therapy

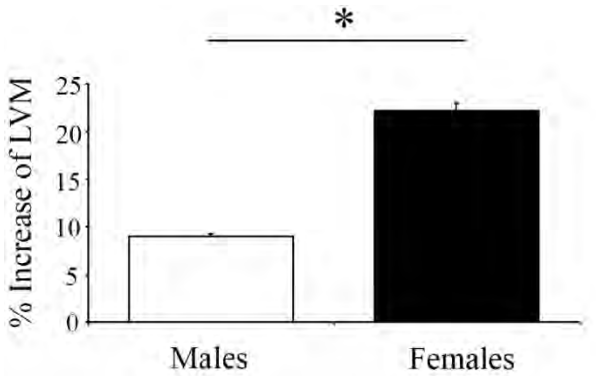
JACC 2011

Sex differences in physiological and pathological cardiac hypertrophy in animal models



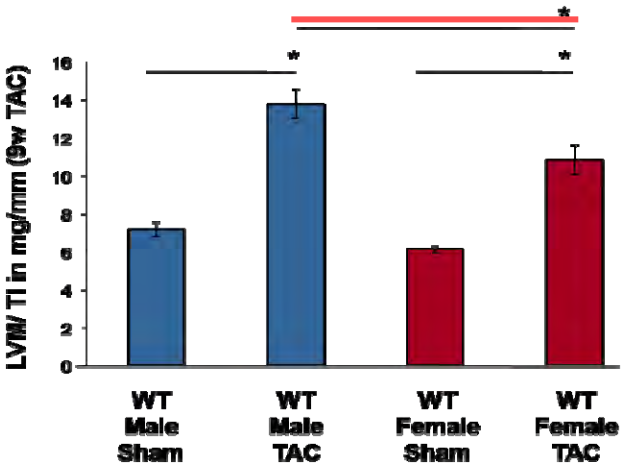


Greater cardiac hypertrophy in female mice after voluntary exercise



Greater cardiac hypertrophy in female mice after forced exercise

TAC
(transverse aortic constriction)

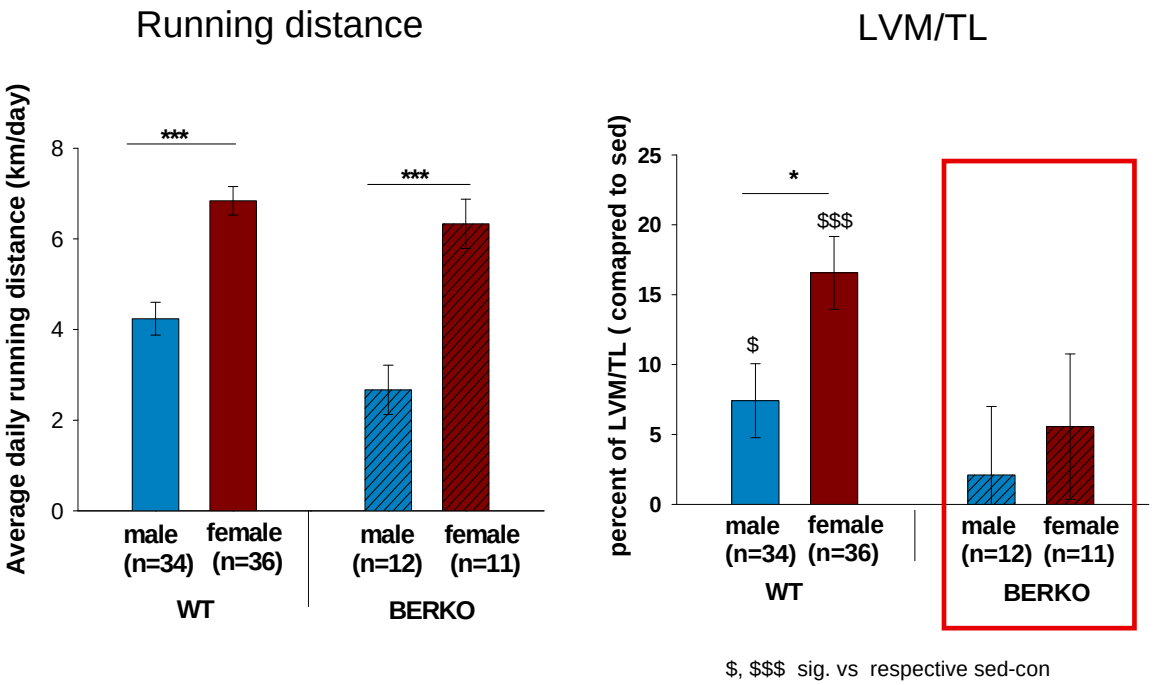


Females develop more physiological MH, males more pathological MH

Am J Physiol Heart Circ Physiol 2011 (in press), Am J Physiol 2010

Contribution of ER and AR to MH – physiological MH

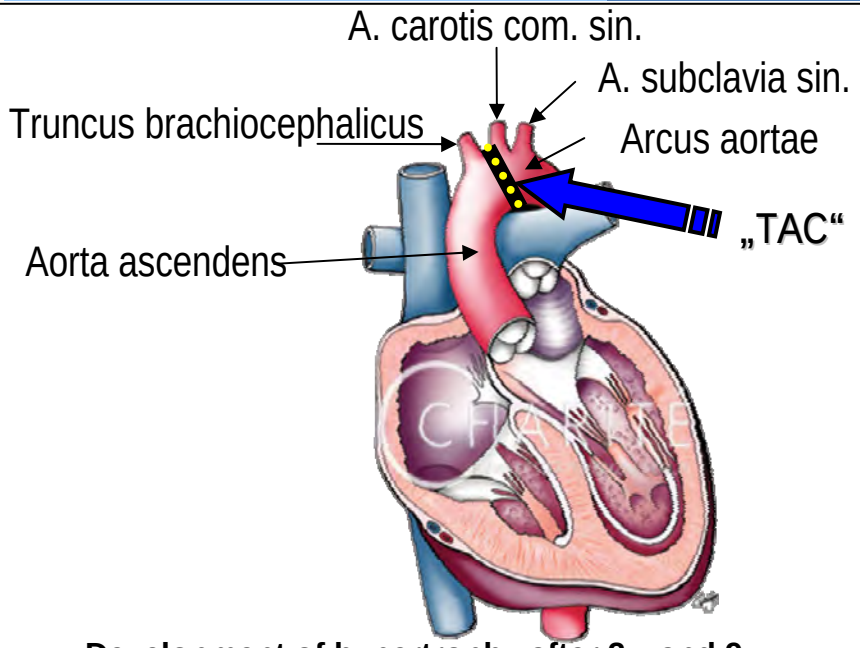
ER β-KO mice do not develop physiological MH at voluntary exercise (VCR)



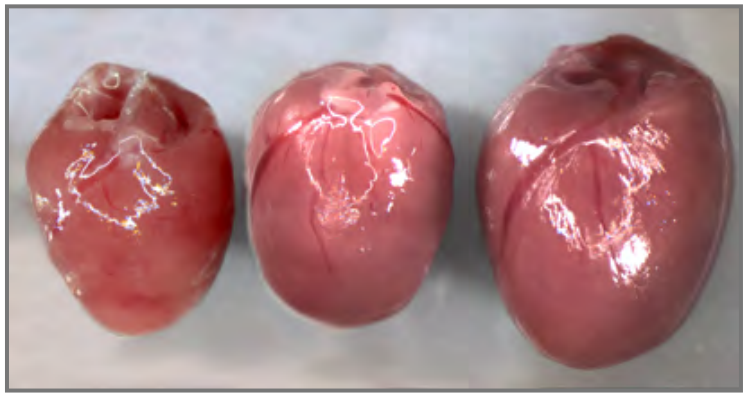
$, $$$ sig. vs respective sed-con

ER β deletion inhibits physiological MH in male and female mice

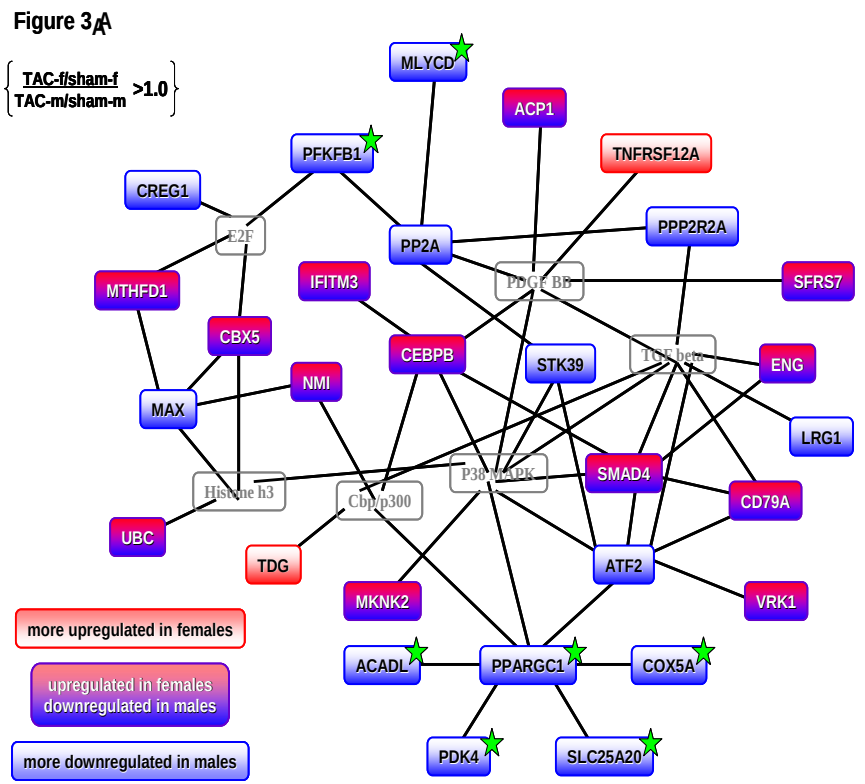
Sex differences in an animal model for pressure overload



Development of hypertrophy after 2w and 9w



Sham 2W TAC 9W TAC



Female TAC hearts have less downregulation of metabolic genes

D. Fliegner, Am J Physiol 2009

Sex differences in gene expression pathways after pressure overload

	Biological Process	Cellular Compartment	Kegg -Pathway	Gene
F/WT/TAC	Regulation metab. process Regulation cell metabolism Electron transport Oxidative phosphorylation	Mitochondria Inner mitoch. membrane Mitochondrial membrane	Oxidative Phosphorylation	Ndufs4/5 Cox7A Cox10 Atp5k
M/WT/TAC	Regulation cell metabolism Regulation cell proliferation Extracellular matrix Fibroblast growth	Intracellular Cytoplasm Cytoskeleton Nucleus	MAPK-Pathway Adhärens junction Fibroblast growth	Mapk6 Filamin Actin Catenin
F/ERβ$^{-/-}$/TAC	Biopolymer metabolism Regulation cellular process Metabolism nucleic acids Regulation transcription	Intracellular Cytoplasm Cytoskeleton Nucleus	WNT-Pathway p53- Pathway	Mapk8 Wnt IF Creb
M/ERβ$^{-/-}$/TAC	Biopolymer metabolism Regulation prog. cell death Cell cycle Cell death	Intracellular Cytoplasm Membran bound organelle Nucleus	DRPLA (Apoptosis) CML-Pathway	Aip Kaspase 7/9 BCL-family TGF

D. Fliegner, Am J Physiol 2009

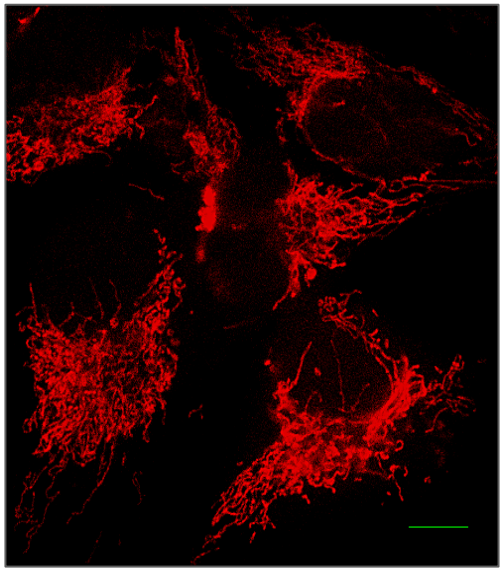
Estrogen receptor α in mitochondria

ERα has been detected so far in mitochondria

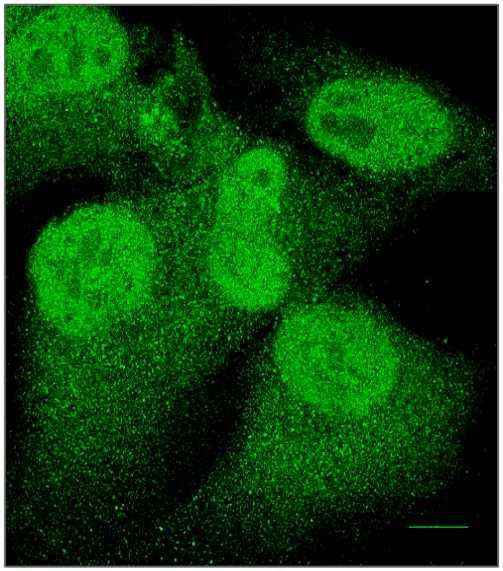
in few tissues:

- rabbit uterus, rat heart; rat cerebral vessels;
- brain endothelial cells (reviewed in Chen et al., 2008)

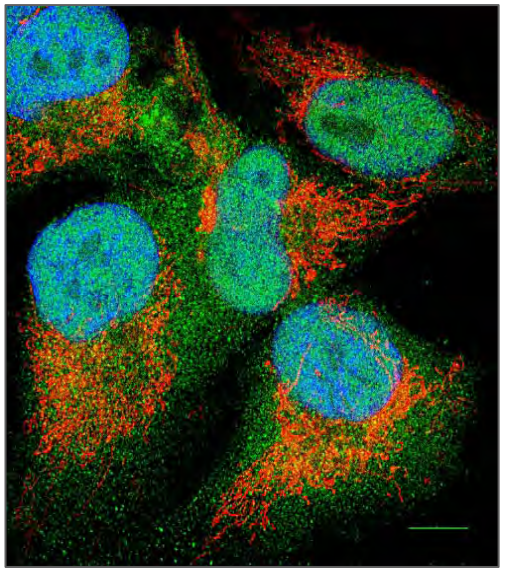
MitoTracker



ERα

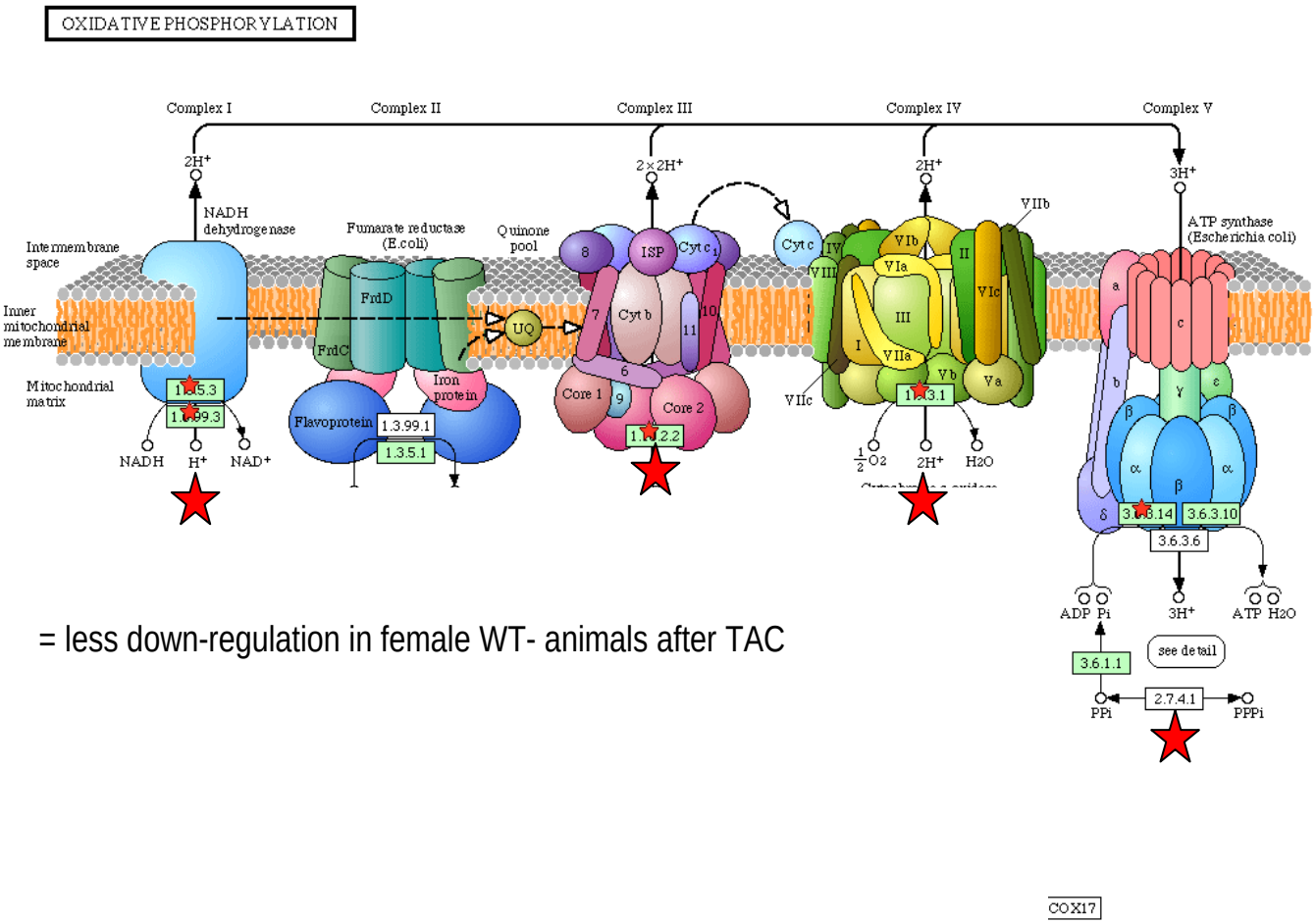


Merged+ Dapi



AC16 cells, S. Mahmoodzadeh (data unpublished)

Sex-specific expression of respiratory chain genes -less down-regulation in females after TAC

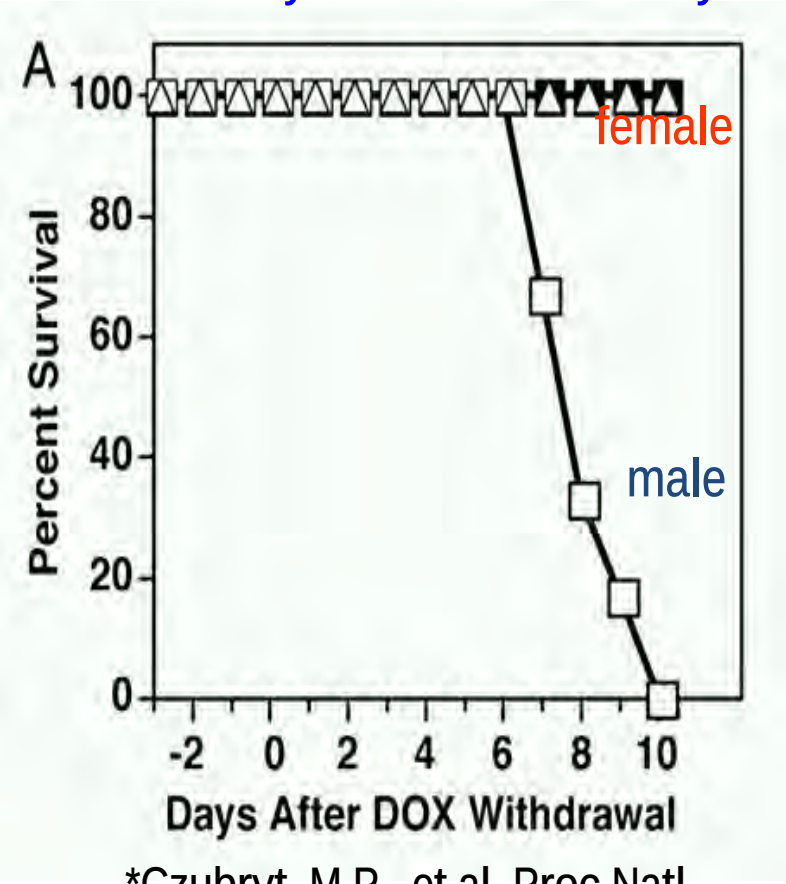


★ = less down-regulation in female WT- animals after TAC

D. Fliegner, Am J Physiol 2009

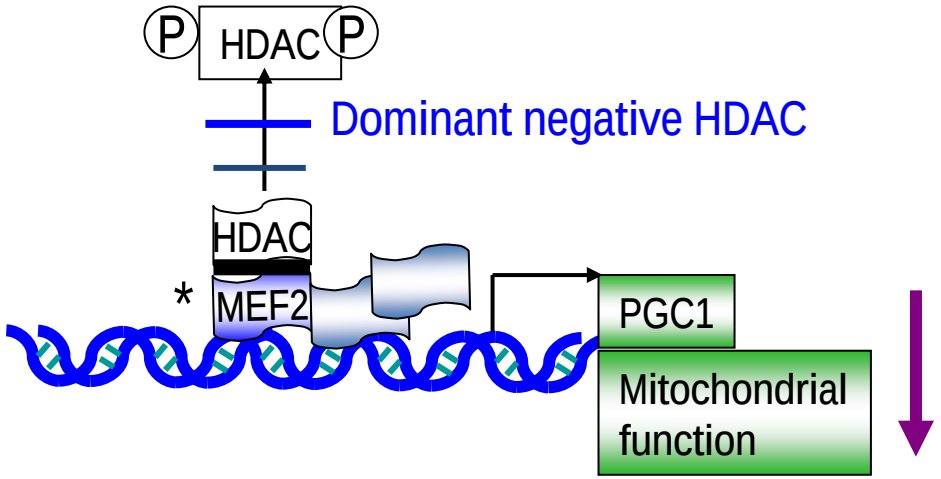
Sex differences in transgenic animals with permanent MEF2 repression - mitochondria

In an animal model with permanent MEF2 inhibition and subsequent mitochondrial dysfunction only male mice die early.



*Czubryt, M P. et al. Proc Natl Acad Sci USA, 2003

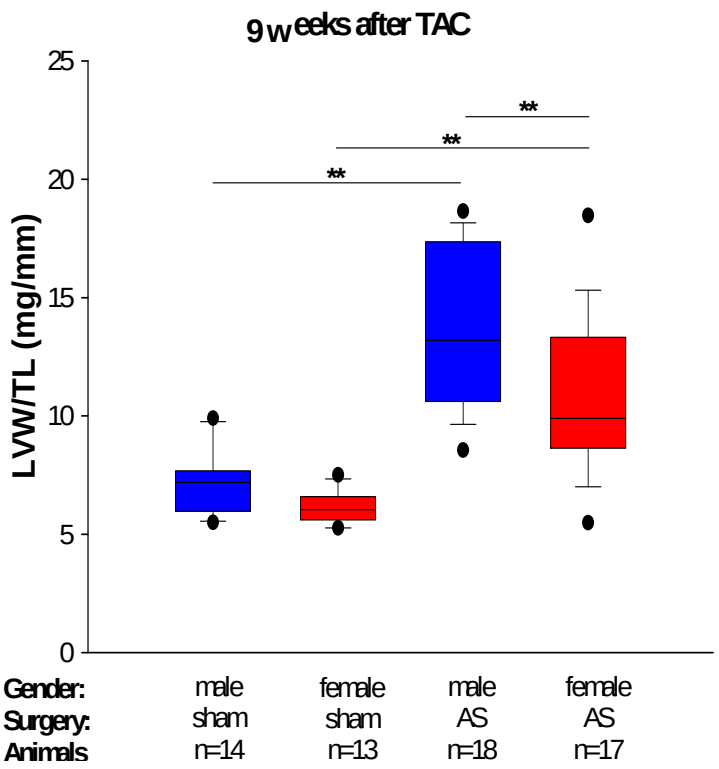
Permanent MEF inhibition leads to mictochondrial dysfunction

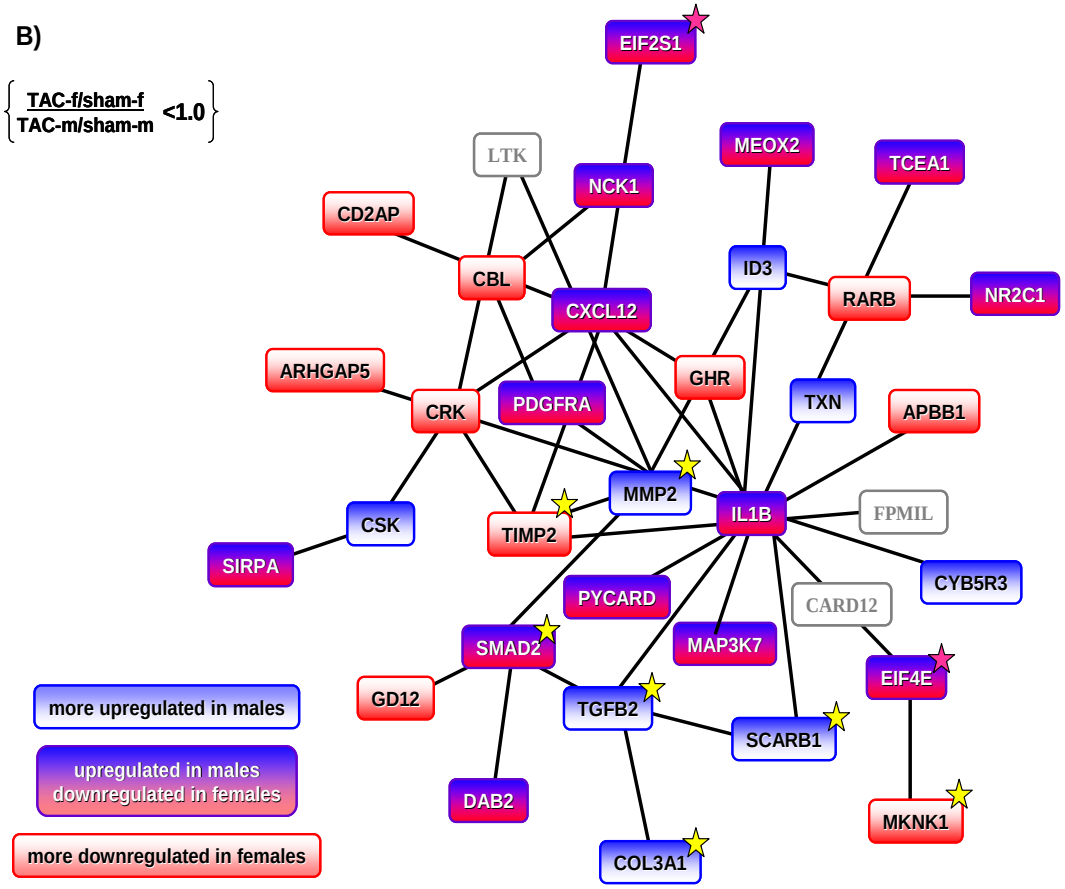


The better survival of the female animals is not discussed in detail. They maintained mito structure

Different adaptation to load in male and female mice after TAC

Males develop more excentric LVH and matrix gene upregulation

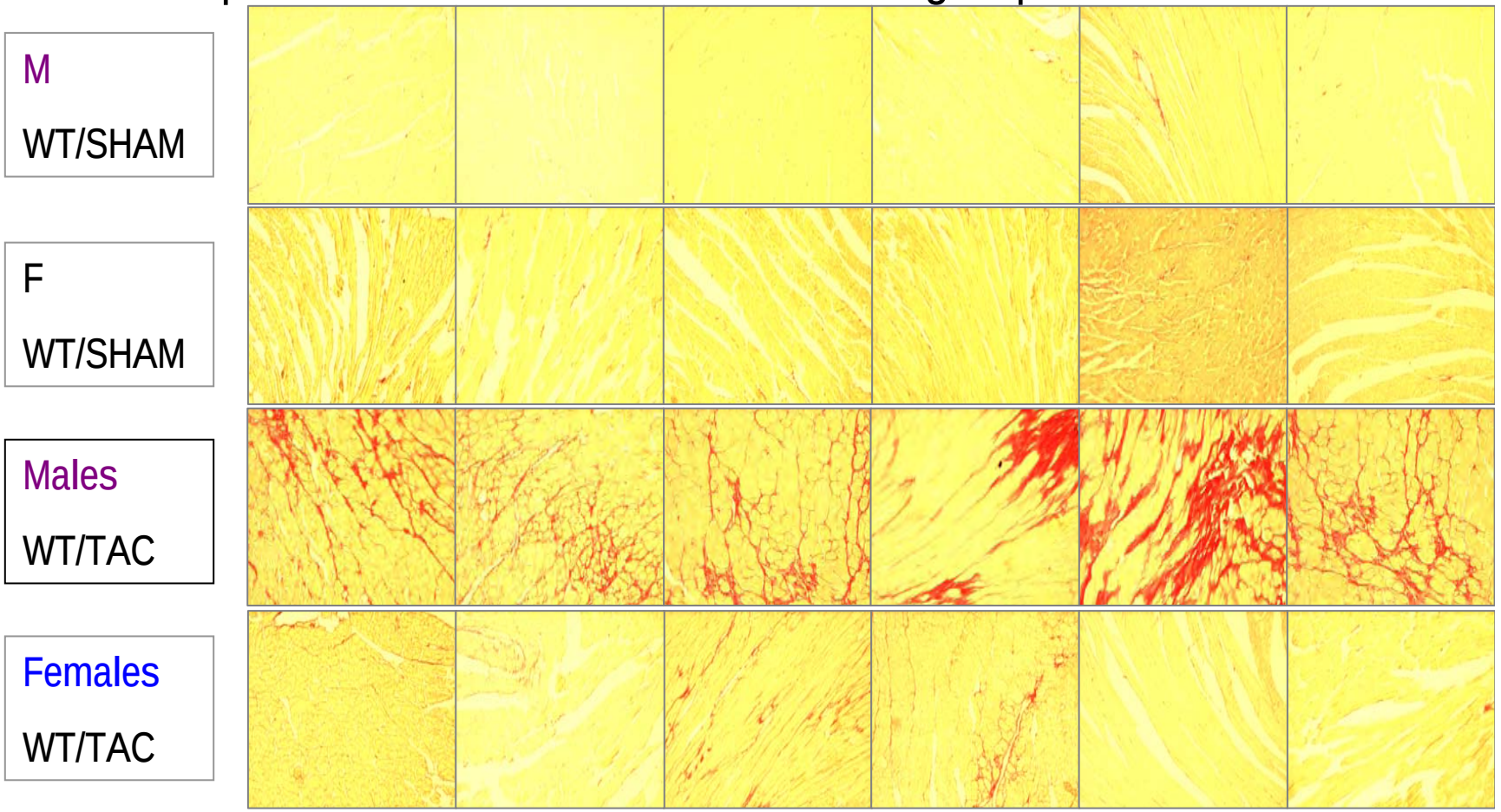




Altered by estrogen receptor modulation!

Stronger increase in fibrosis in male mice with aortic constriction (TAC) than in female mice

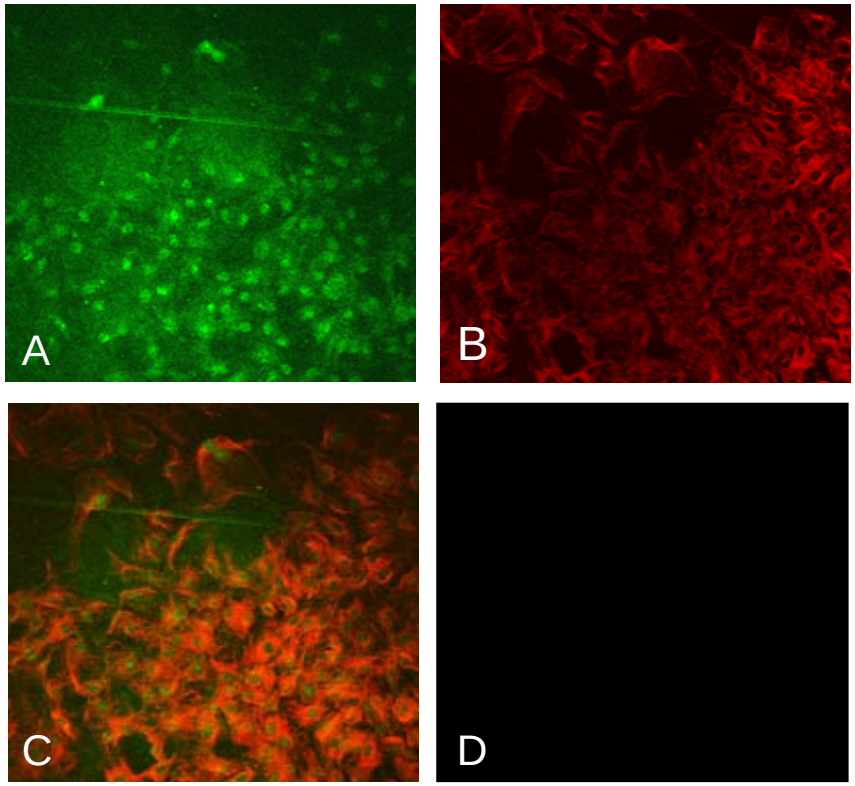
Representative slides from 6 animals/group



D Fliegner et al, Am J Physiol 2009

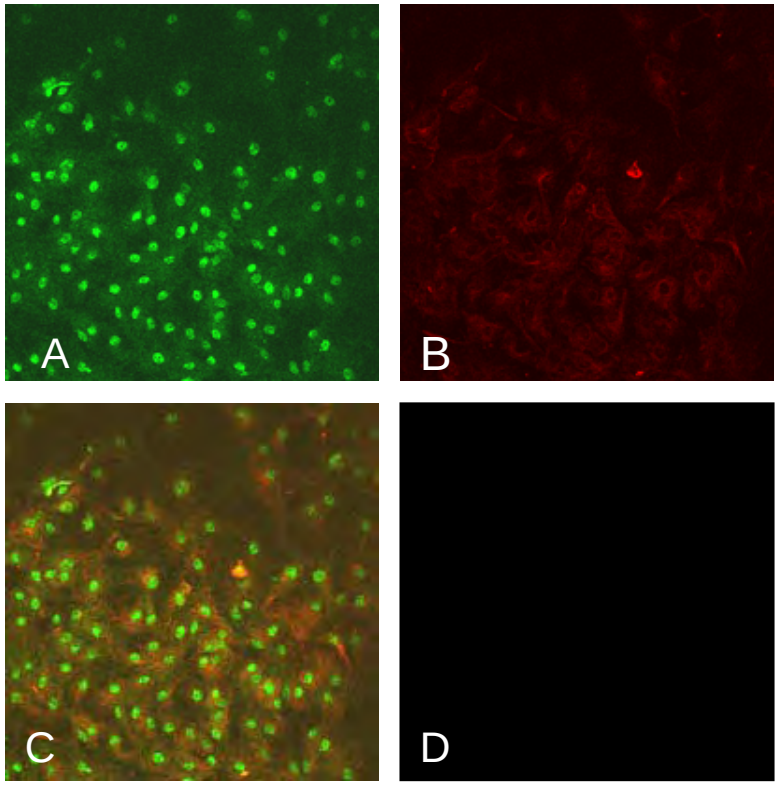
ERα in Rat Cardiac Fibroblasts

ERα is localized in cytosol and nuclei of cardiac rat fibroblasts



- E2

A: ERα staining (FITC-green)
B: Vimentin staining (CY3-red)
C: Merged image of A and B
D: Negative control: primary antibodies omitted. Magnification 20x

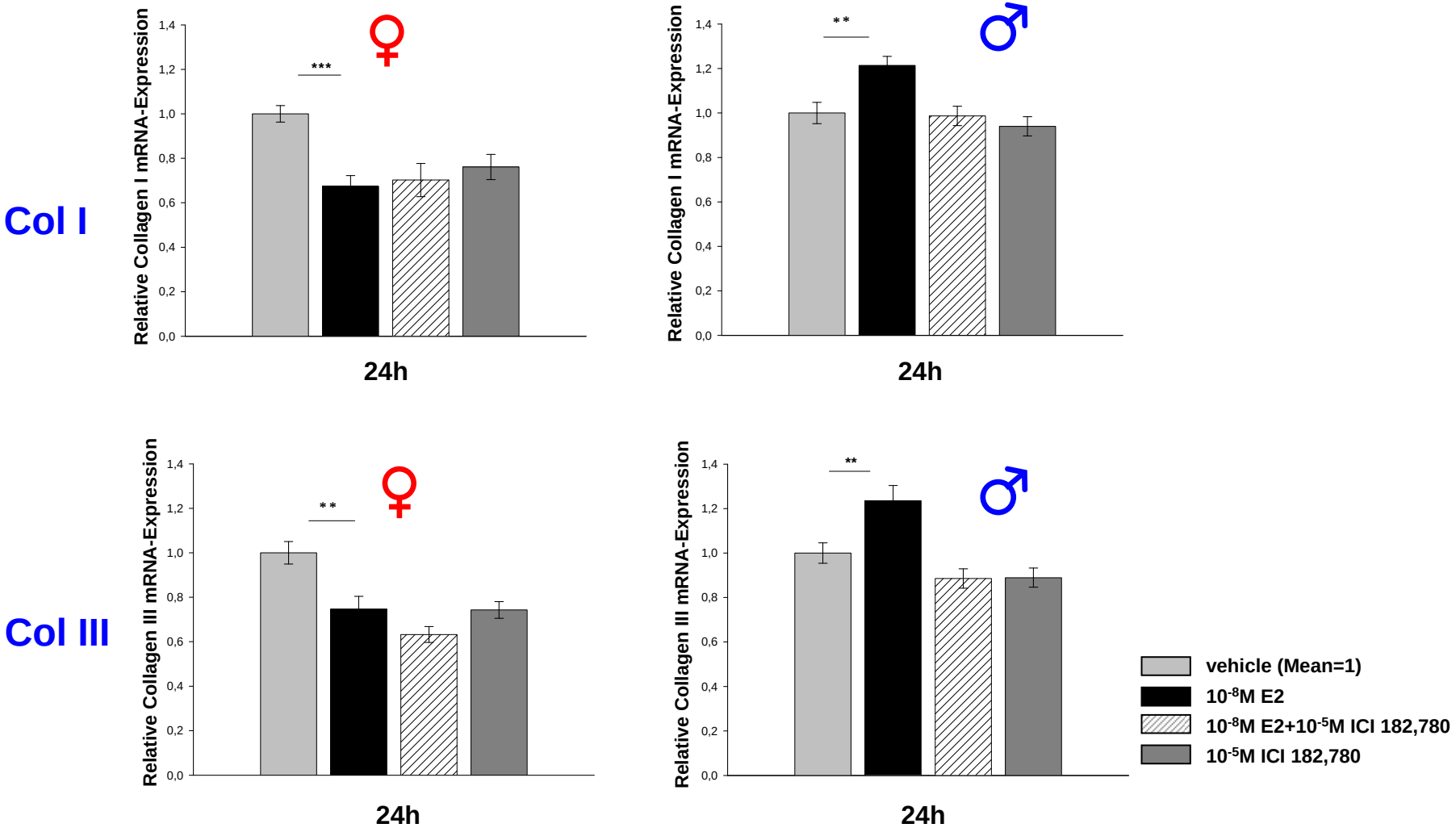


+10^{-8}M E2 (24h)

A: ERα staining (FITC-green)
B: Vimentin staining (CY3-red)
C: Merged image of A and B
D: Negative control: primary antibodies omitted. Magnification 20x

Dworatzek et al, unpubl

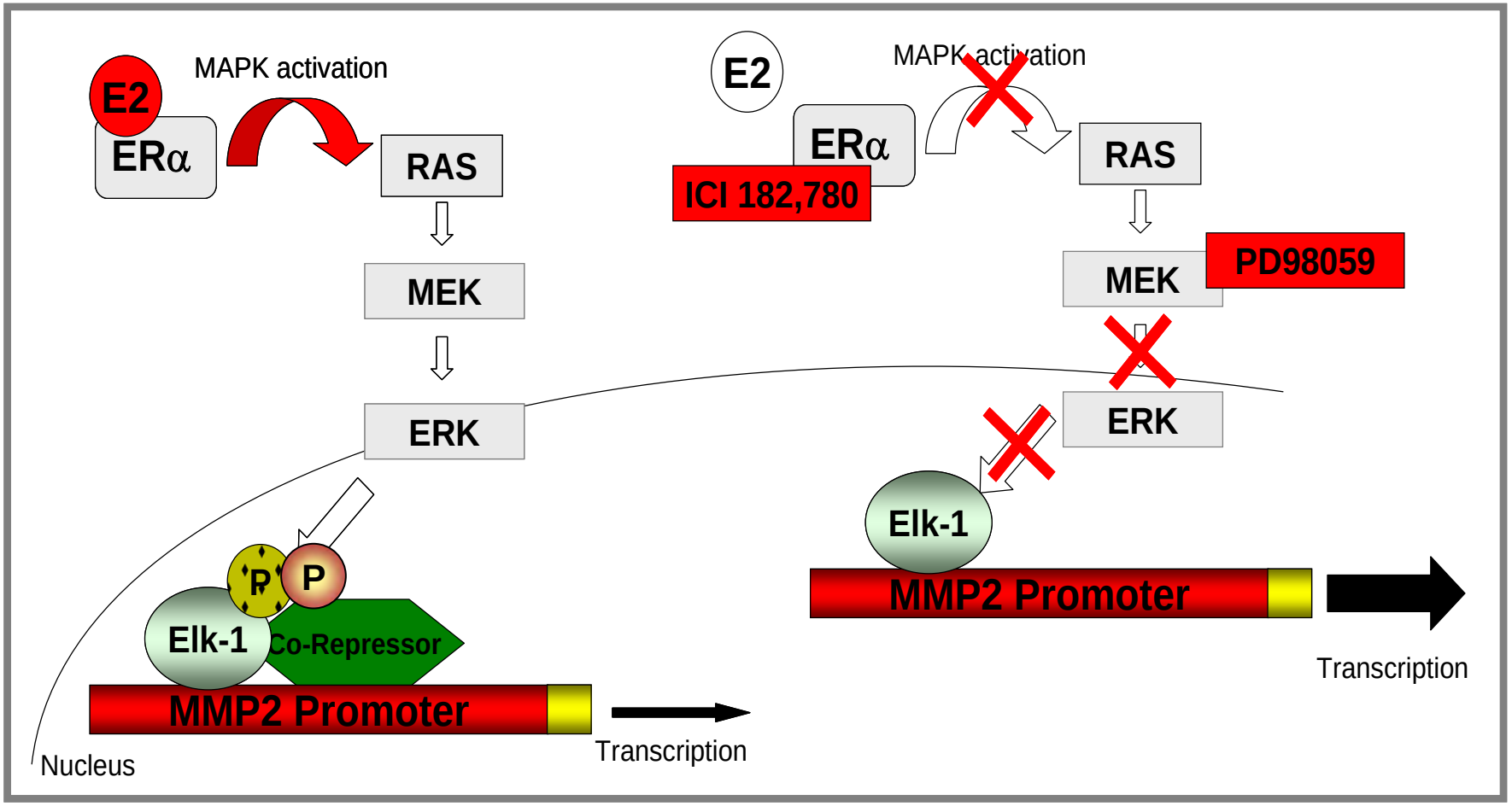
E2 mediates sex-specific regulation of Collagen I and III mRNA in rat cardiac fibroblasts



Mean ± SEM (n≥3); related to HPRT mRNA-Expression; ***p≤0,001; **p≤0,01; *p≤0,05

Petrov, Dworatzek et al., Circ 2010

Model for E2-dependent regulation of human MMP2 promoter activity



Dworatzek et al CVR 2010

Sex differences in numerous transgenic mouse models for cardiovascular disease

18 transgenic animal models show more severe phenotype and earlier death in males; only 2 in females.

	males	females
PLB inhibition	DCM at 6 Mo	Normal EF
TNF a over-expression	DCM	Hypertrophy ,
PPAR a (-/-) LPL	Die at 4 months	alive
PPAR a (-/-) + FA	100 % die early	25 % die early
Relaxin (-/-)	DCM	No pheno-ptype
FKPB12 (-/-)	Hypertrophy	No hyper-trophy

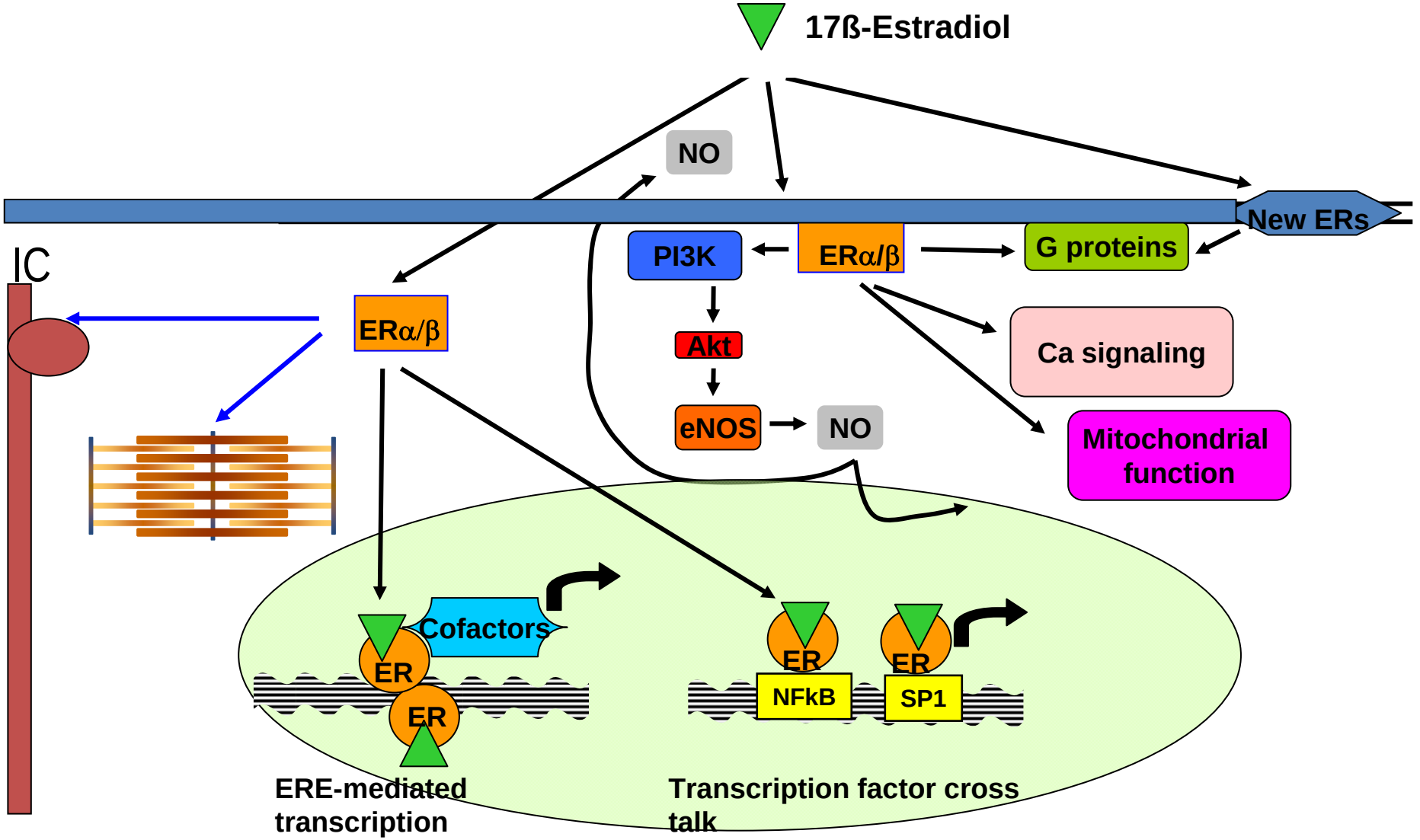
Rescued by estrogen

Female sex or E2 must interfere with a large number of pathways

Identification of these protective pathways could offer novel therapeutic aspects

Leinwand et al. CVR

Sex and ER a influence heart function: mitochondria, fibroblasts, cytoskeletal and contractile proteins

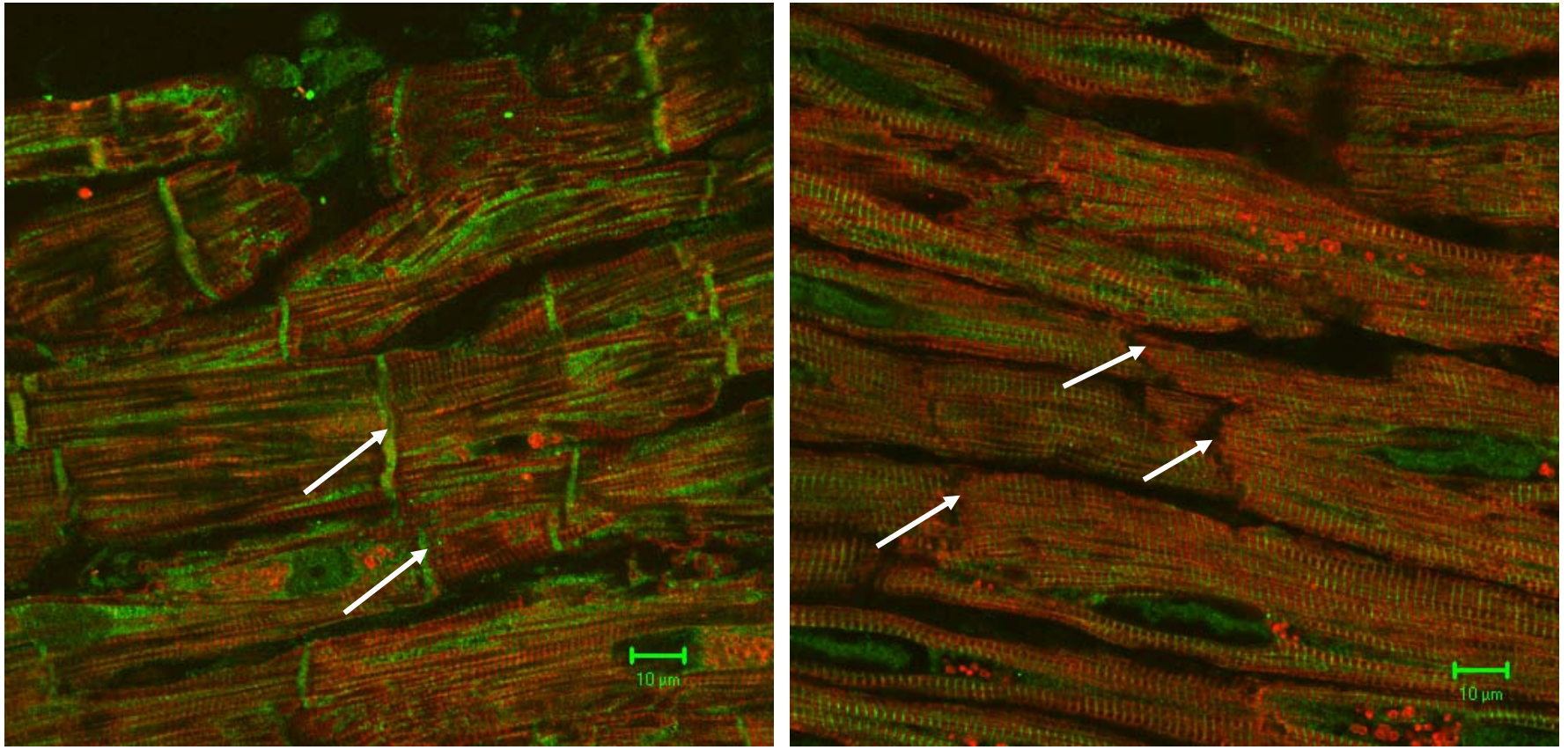


VRZ et al, Current Opinin Pharm 2007

Disease dependent changes of localization of ER α in the human heart

Controls (n= 14)

AS>/DCM (n= 13)



Estrogen receptor α

Troponin T

Mahmoodzadeth et al, Faseb J, 2006

Summary and conclusions

- Women and men differ in HF manifestations
- Women with pressure induced myocardial hypertrophy have a bettter adaptation of myocardial energy metabolism than men
- Men with pressure overload develop more fibrosis – unfavorable remodeling and slower reversibility of MH than in women
- Drugs should be developed in animals of both sexes and interventional therapy should be validated for both

Considering gender is a quality issue in medical research

nature

www.nature.com/nature

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Putting gender on the agenda

Biomedical research continues to use many more male subjects than females in both animal studies and human clinical trials. The unintended effect is to short-change women's health care.

Differences in the physiology of males and females, and in their response to disease, have been recognized for decades in many species — not least *Homo sapiens*. The literature on these differences now encompasses everything from variations in gene expression between male and female mice, to a higher susceptibility to adverse drug reactions in women compared with men. Moreover, hormones made by the ovaries are known to influence symptoms in human diseases ranging from multiple sclerosis to epilepsy.

And yet, despite the obvious relevance of these sex differences to experimental outcomes, three articles in this issue (see pages 688–690) document that male research subjects continue to dominate biomedical studies. Some 5.5 male animal models are used for every female in neuroscience, for example. And apart from a few large, whether to require the inclusion of such information. Funding agencies should demand that researchers justify sex inequities in grant proposals and, other factors being equal, should favour studies that are more equitable.

Funding agencies and researchers alike should also start thinking seriously about how to deal with the most fundamental sex difference: pregnancy. Pregnant women get ill, and sick women get pregnant. They need therapies, too, even though they are carrying a highly vulnerable fetus and their bodies are undergoing massive changes in hormonal balance, immune function

"Medicine as it is currently applied to women is less evidence-based than that being applied to men."

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