SEX DIFFERENCES IN CARDIAC TOLERANCE TO OXYGEN DEPRIVATION – 40 YEARS OF CARDIOVASCULAR RESEARCH

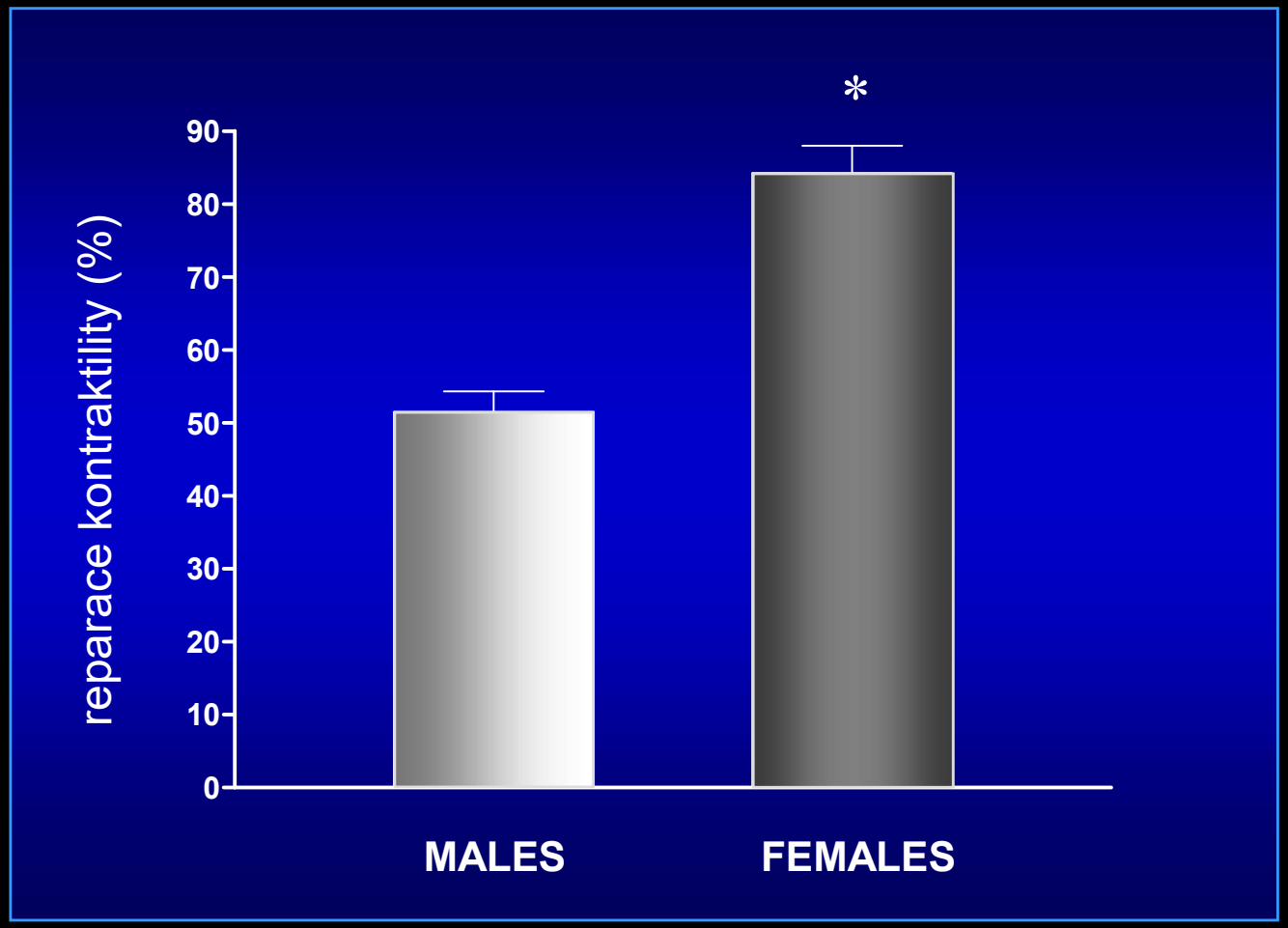
B. Ošťádal

Institute of Physiology, Czech Academy of Sciences, Prague

1984 – 2024

A FORTY-YEARS HISTORY OF ONE RESEARCH

SEX DIFFERENCES IN CARDIAC TOLERANCE TO OXYGEN DEPRIVATION

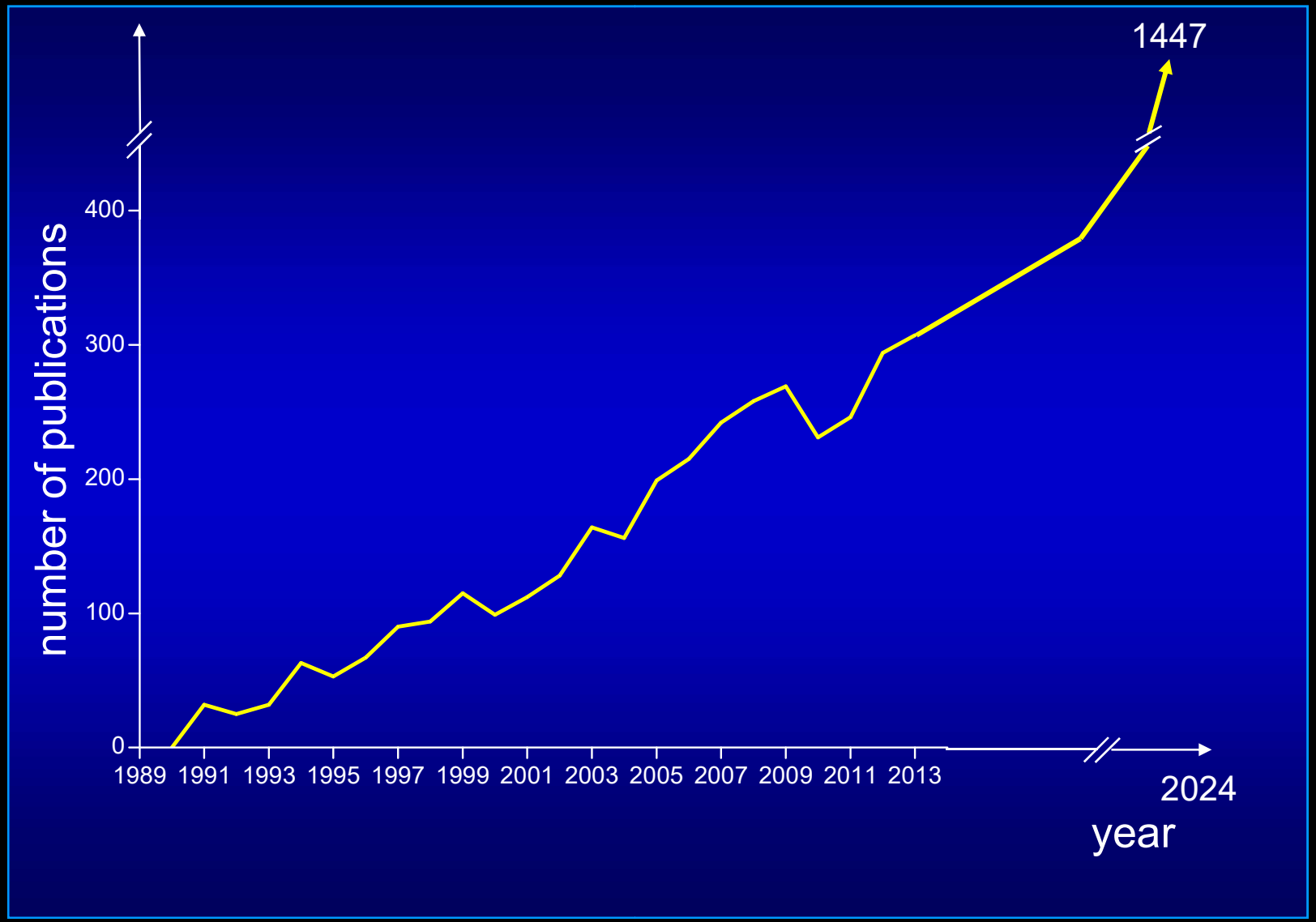


Ostadal et al.1984

„ ….study in the early 1980s (Ostadal et al. 1984) first described a gender dimorphism of myocardial resistance in female vs. male rats exposed to acute hypoxia….“

Ou et al.	*J Appl Physiol 1994*
Kolodgie et al.	*J Mol Cell Cardiol 1997*
Moolman	*Cardiovasc Res 2006*

SEX DIFFERENCES - HEART
Web of Science



THIS TREND IS OBVIOUSLY THE RESULT OF TWO FACTS:

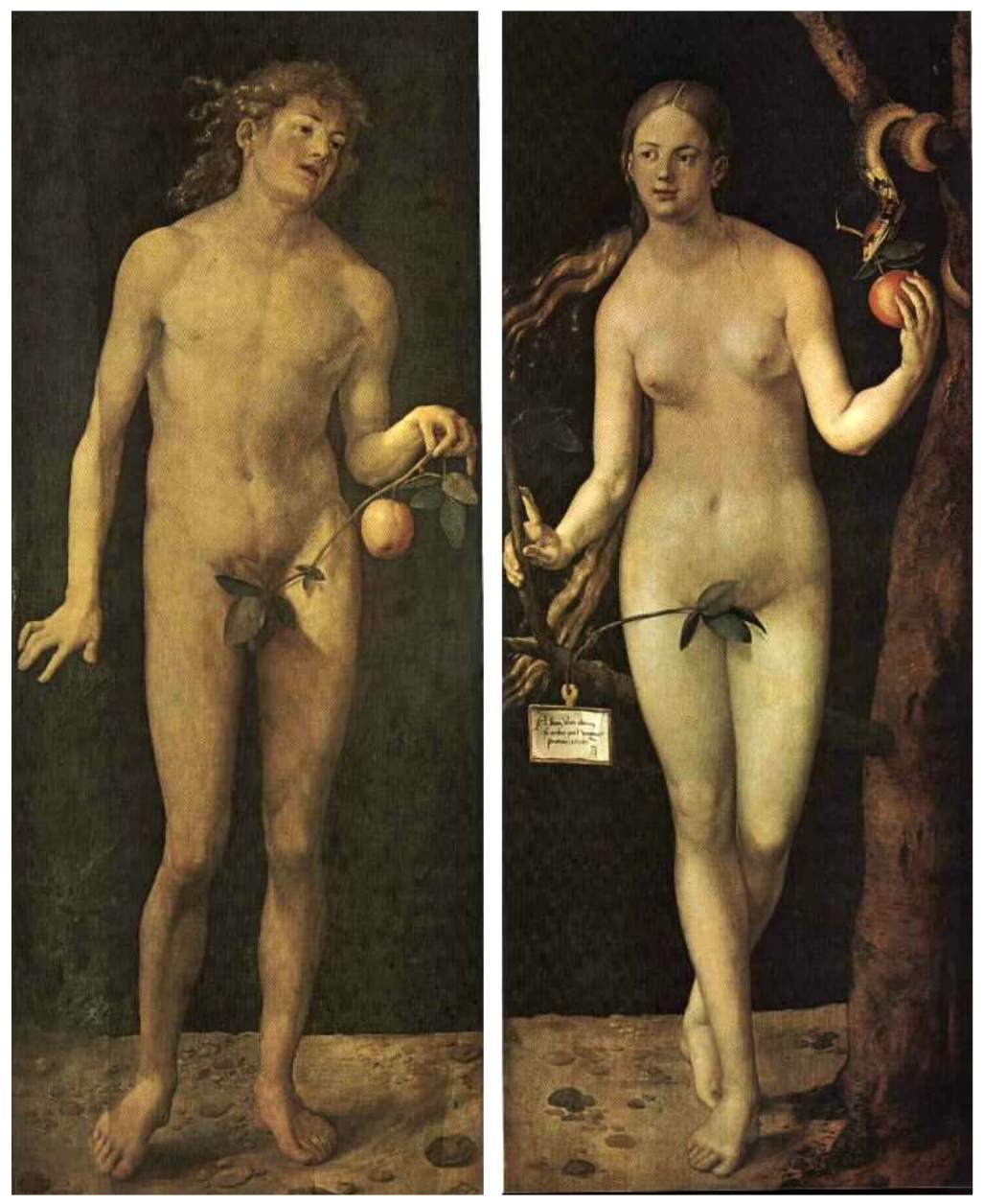
- the number of examples of sex differences under physiological and pathological conditions is steadily increasing

- controversial reports on the beneficial and adverse effects of hormonal replacement therapy (HRT) in women during menopause

SEX DIFFERENCES

NORMAL HEART

Why should the heart be the same....?

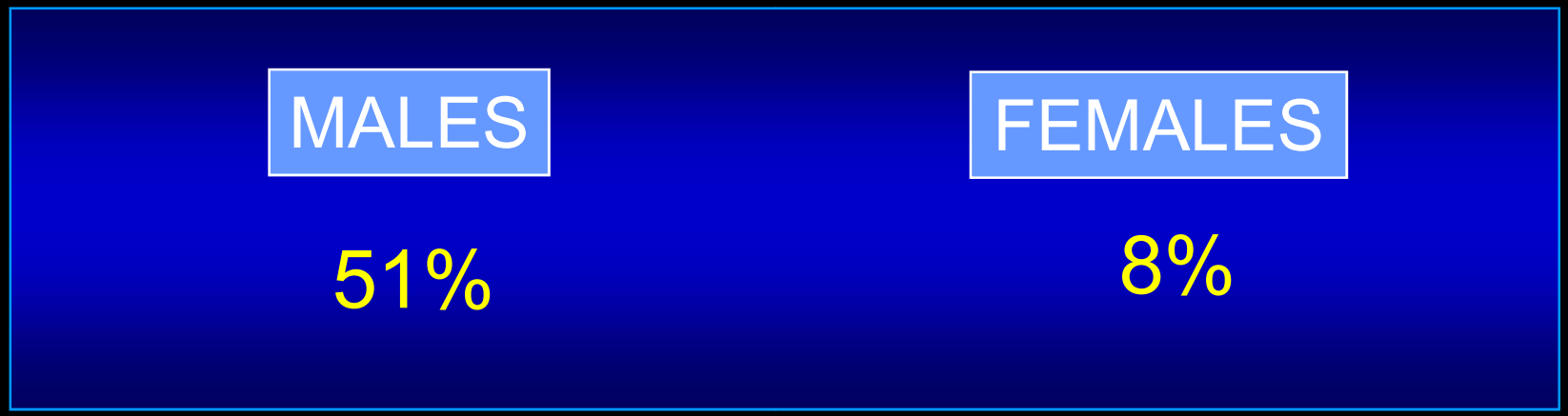


AGEING OF CARDIOMYOCYTES
age 20-90 years

MEN	WOMEN
LV – myocyte loss - 45mil/year	LV – number unchanged
RV – myocyte loss - 19mil/year	RV – number unchanged

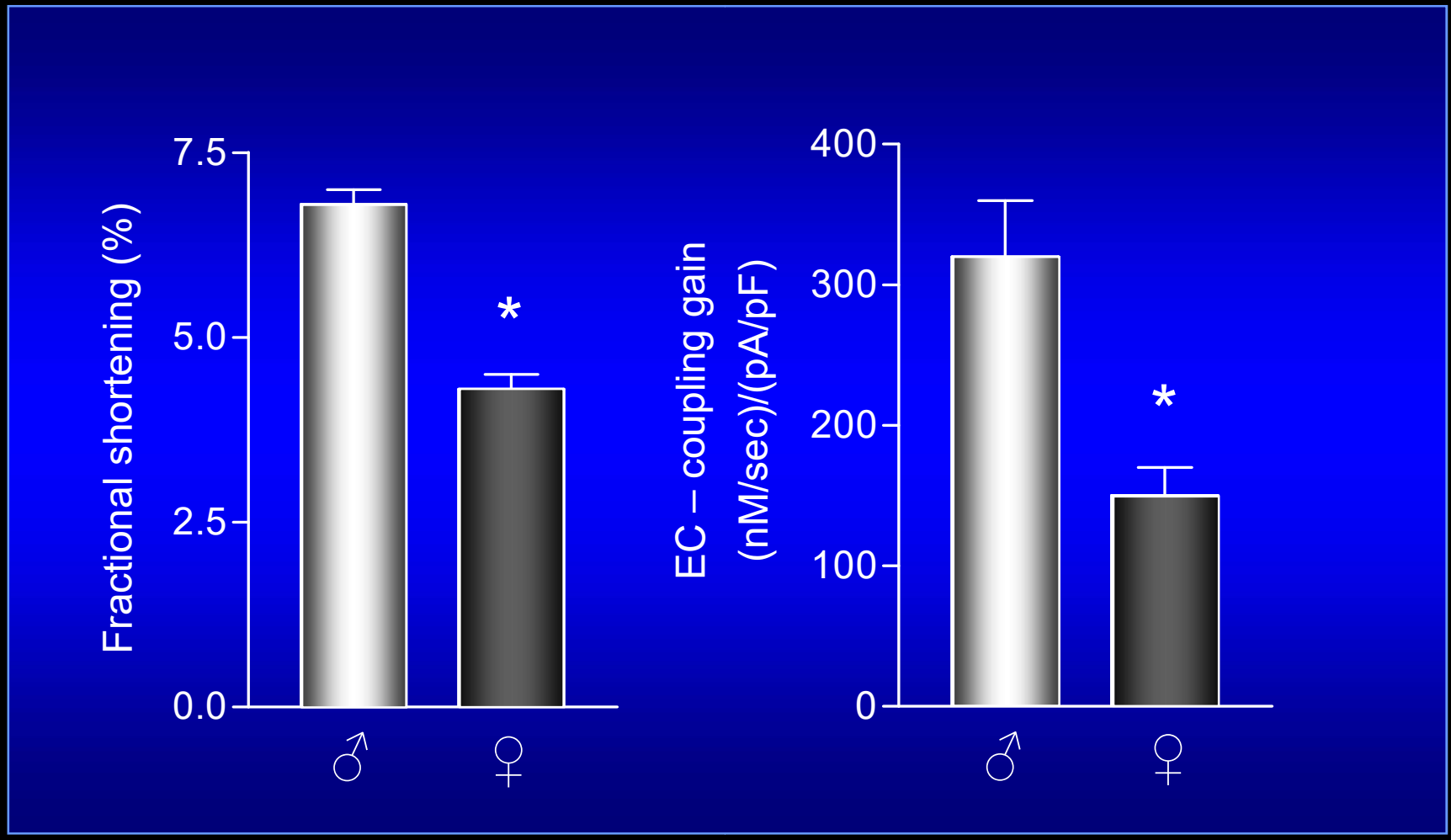
Anversa et al., 2005

MYOCYTE CROSS-SECTION AREA
increase during life (monkey)



Zhang et al., 2007

SEX DIFFERENCES – EC COUPLING



Parks and Howlett, 2013

SEX DIFFERENCES
MOLECULAR LEVEL – FEMALE MYOCYTES

- ↓ L-type calcium channels
- ↓ calcium load of the SR
- ↑ Na/Ca exchange proteins
- ↓ mitochondrial calcium uptake
- ↓ content of cardiac mitochondria
- ↓ ROS
- ↓ density of beta-adrenergic receptors

Ostadal et al., 2009, Fazal et al., 2

The above mentioned sex differences, characteristic for the normal myocardium, create the logical presumption of the different reaction to various pathological conditions

SEX DIFFERENCES

ISCHEMIC HEART DISEASE

SEX DIFFERENCES
CARDIOVASCULAR DISEASES

- IHD
- atherosclerosis
- hypertension
- arrhytmias
- remodeling

SEX DIFFERENCES
ISCHEMIC HEART DISEASE

- premenopausal women

  the onset of IHD occurs 10 years later

  than in men, myocardial infarction

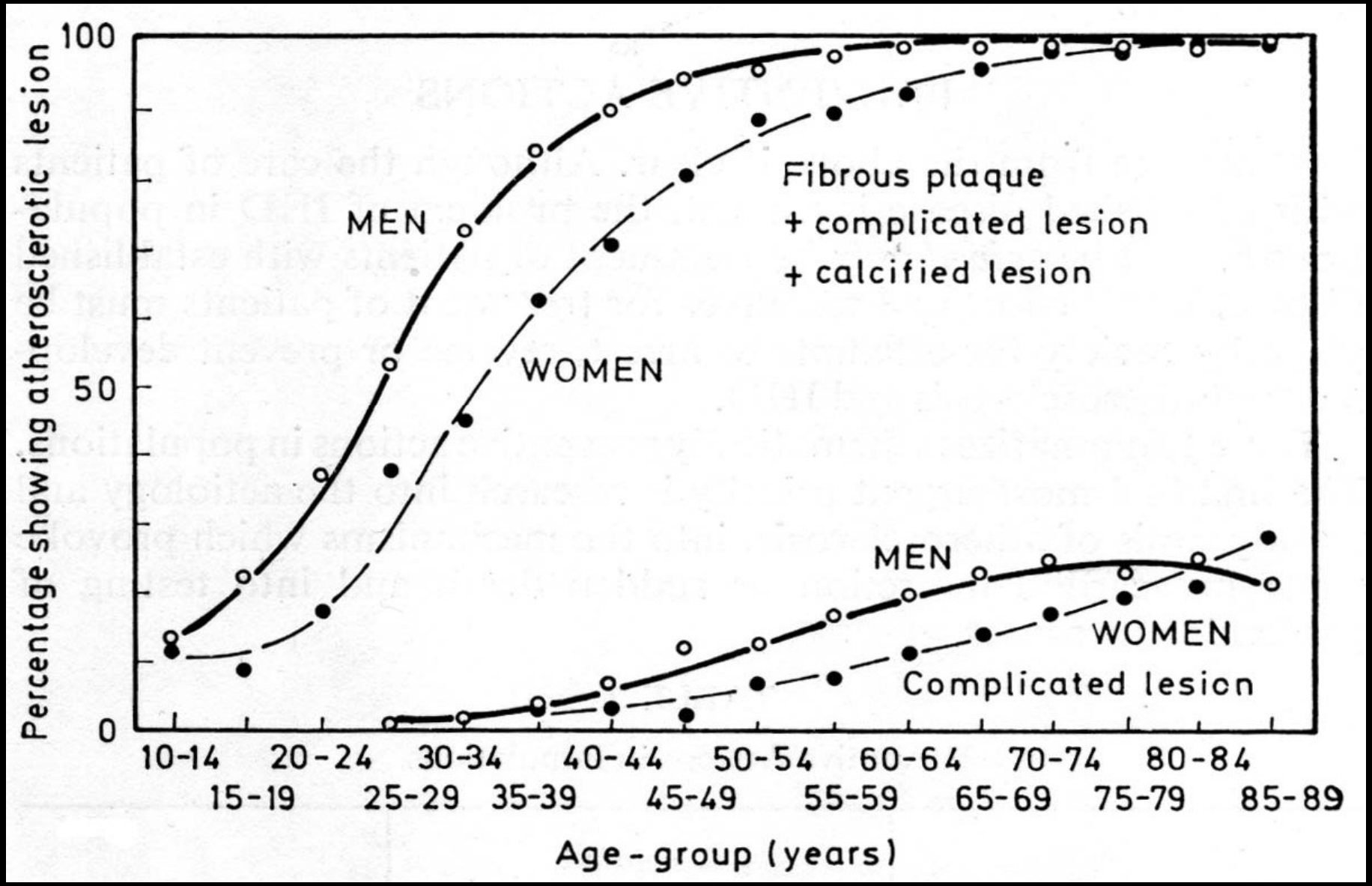
  even 20 years later

- after menopause

  10-fold increase of IHD (in men 4.5-fold)

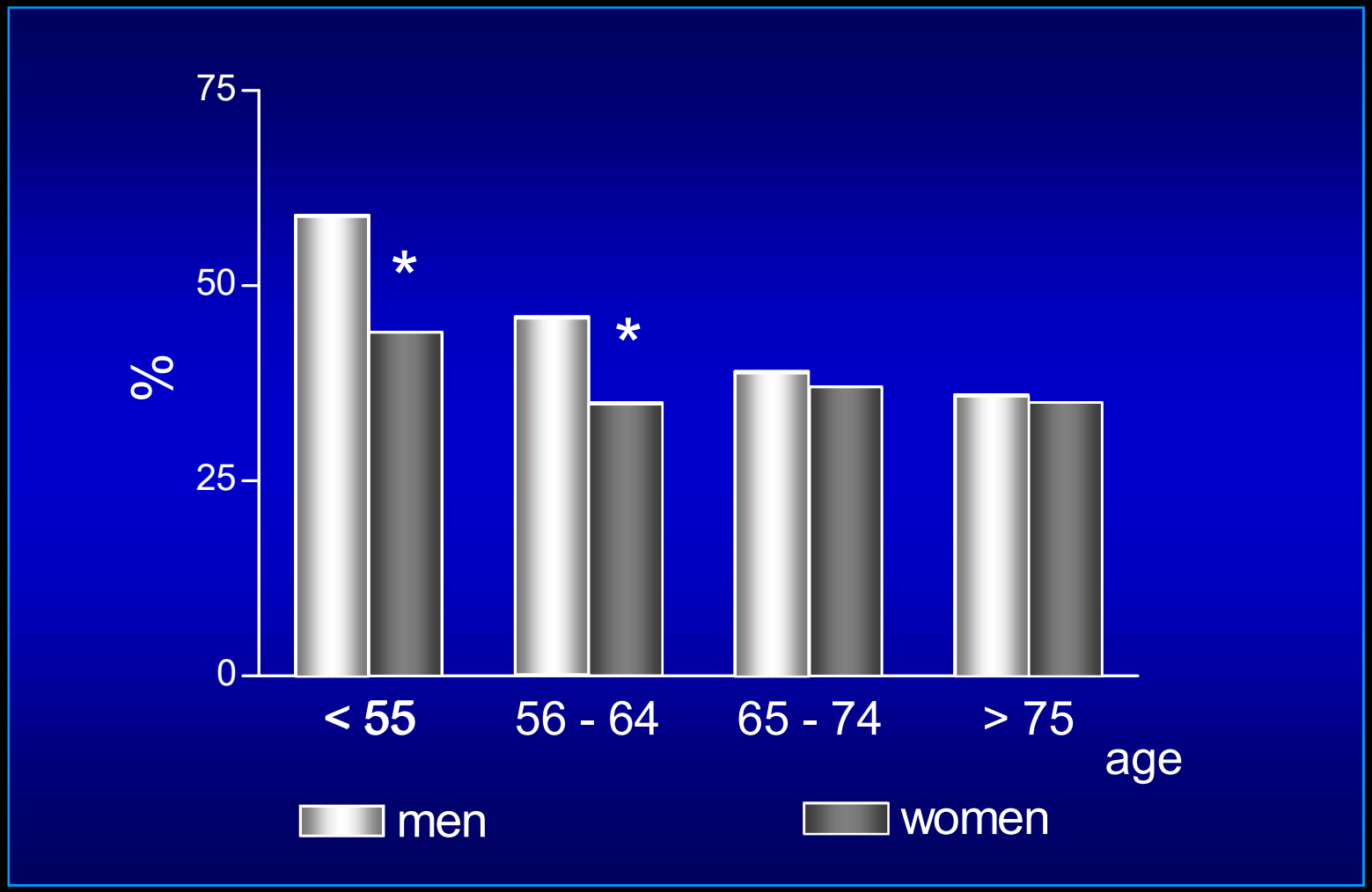
Duvall, 2003

SEX DIFFERENCES - ATHEROSCLEROTIC CHANGES



Fejfar, WHO Annual Report, 1972

SEX DIFFERENCES
acute coronary syndrome with ST elevation



Rosengren et al., 2004
(Euro Heart Survey)

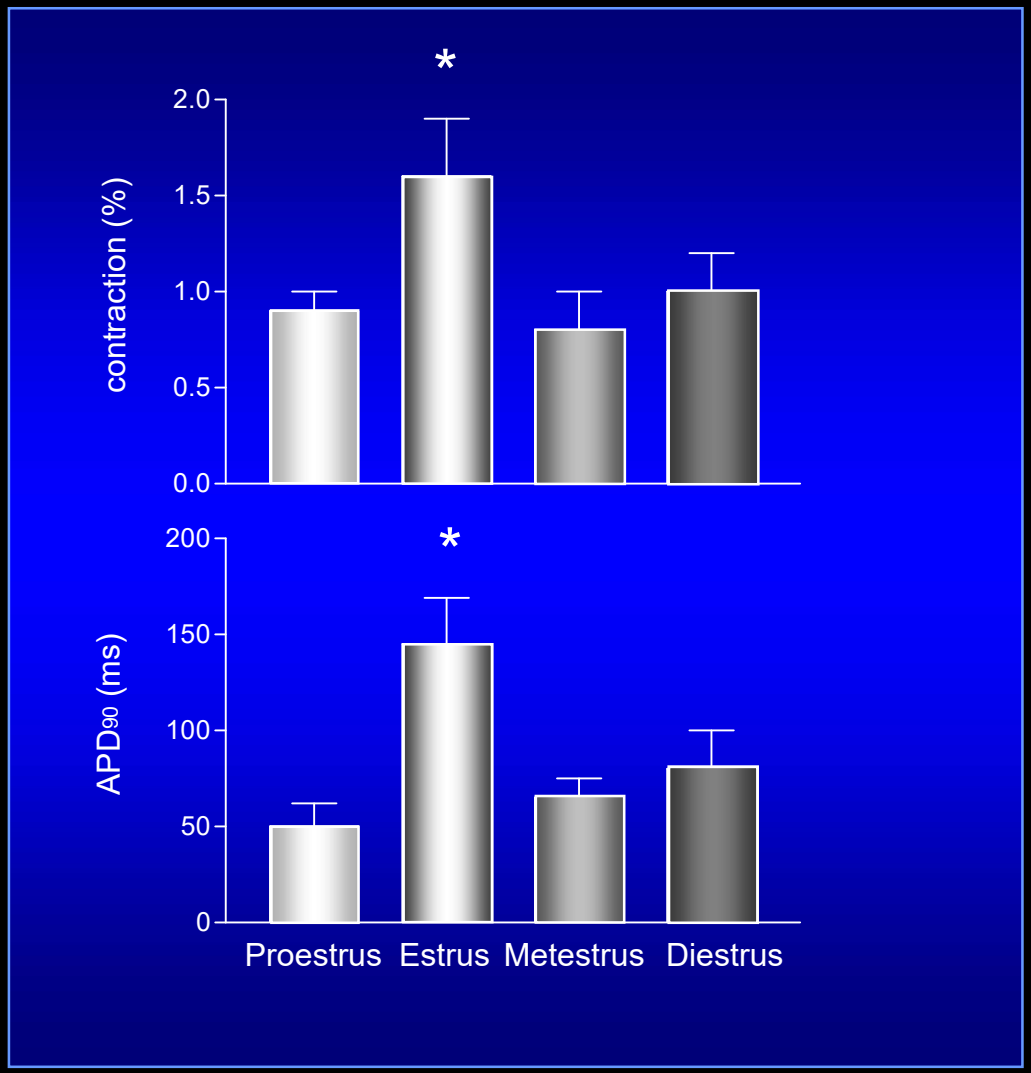
EXPERIMENTAL STUDIES

SEX DIFFERENCES
EXPERIMENTAL STUDIES
major problems

- *experiments are performed almost exclusively on males*
- *sex- studies are affected by the stage of estrus in cycling female animals*
- *rat females have no menopause*

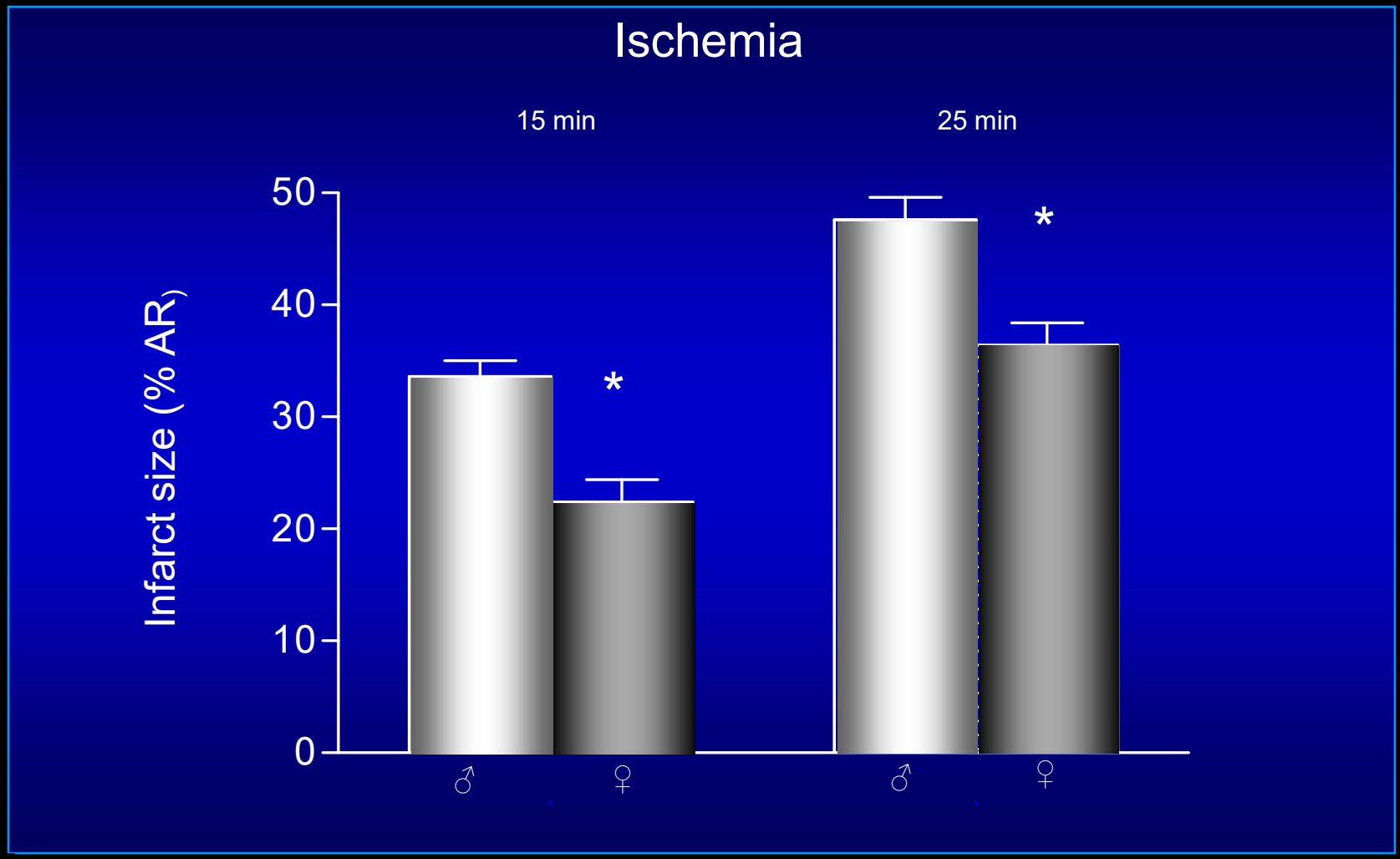
CONTRACTION AND ESTROUS CYCLE

mice



MacDonald et al., 2014

SEX DIFFERENCES – INFARCT SIZE
rat



Bae and Zhang, 2005

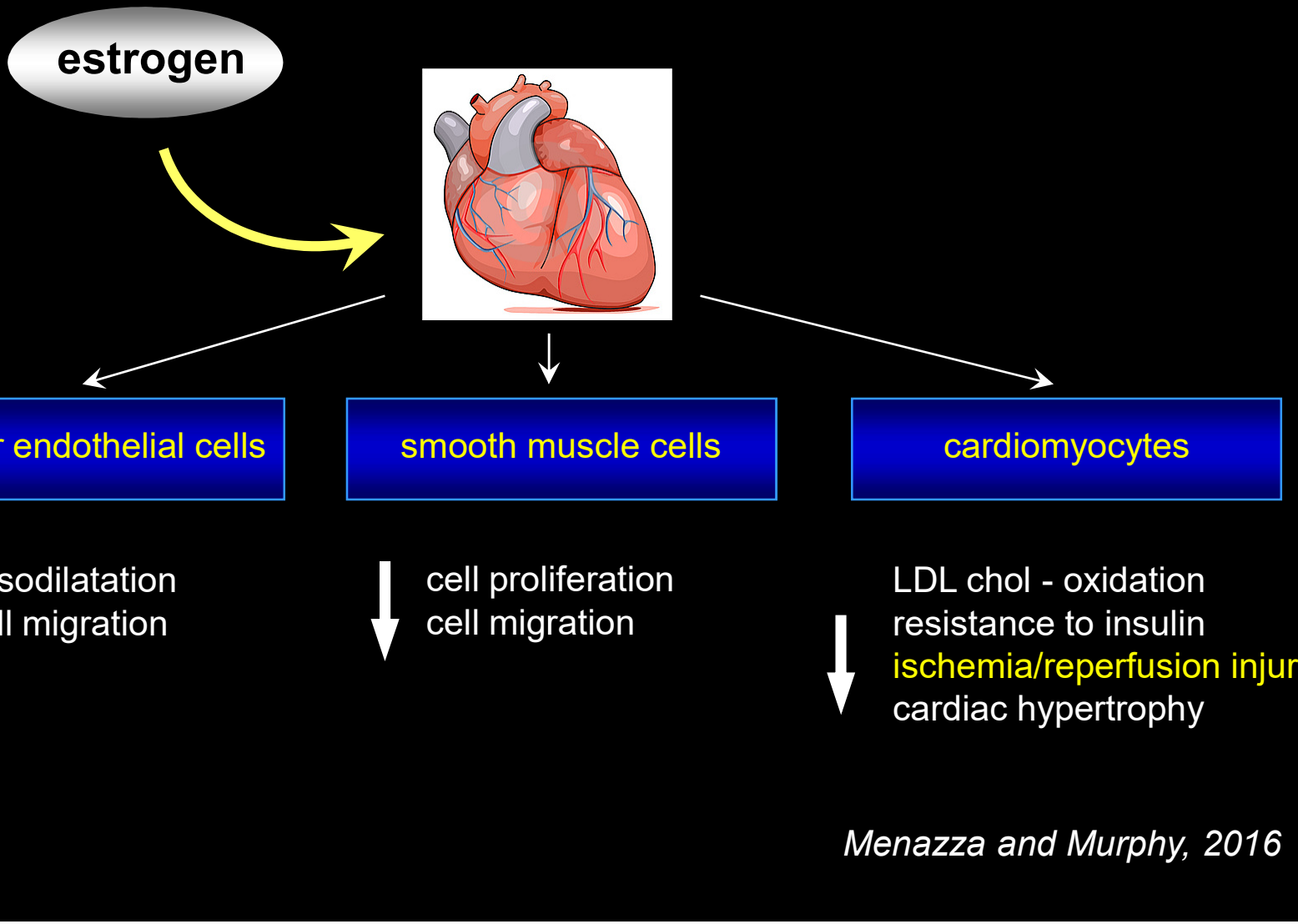
POSSIBLE MECHANISMS OF SEX DIFFERENCES

ESTROGENS AND CARDIOVASCULAR SYSTEM

- ovarian cycle
- pregnancy
- menopause
- oral contraceptives
- hormonal therapy (HRT)

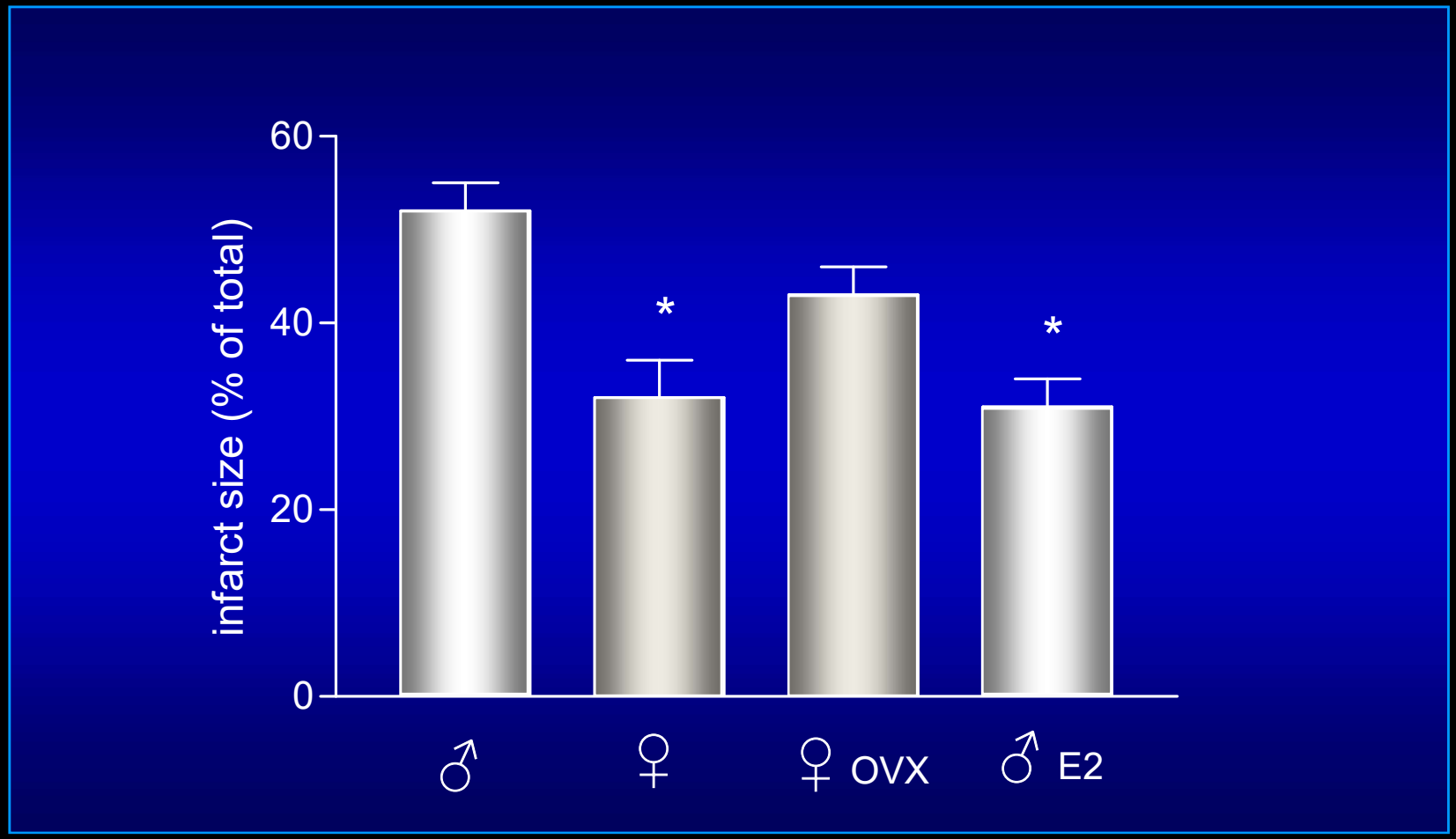
Dubey et al., 2002

HIGH TOLERANCE OF THE FEMALE HEART
effect of estrogen



Menazza and Murphy, 2016

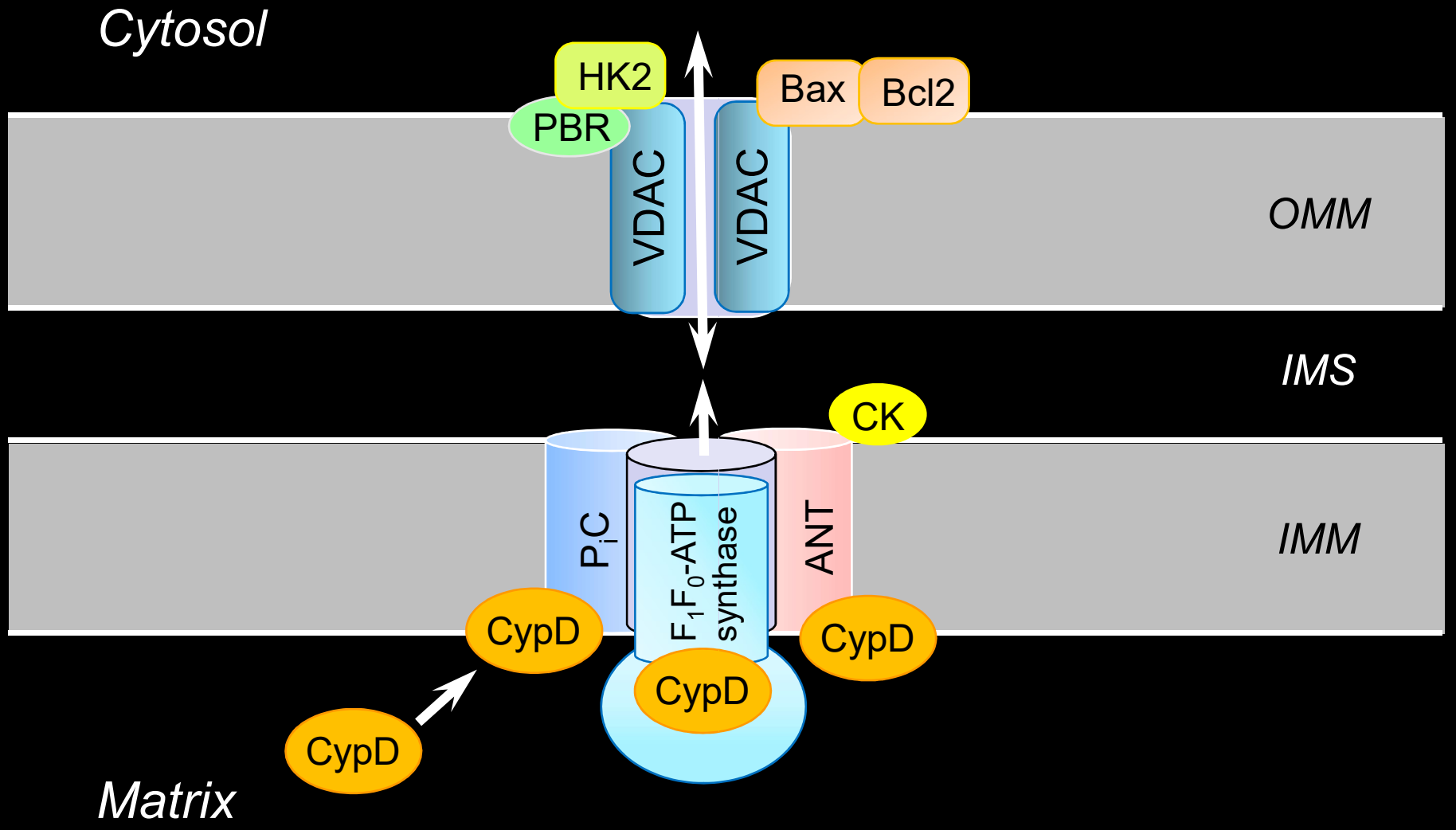
SEX DIFFERENCE – INFARCT SIZE
effect of ovariectomy - rat



Lagranha et al., 2010

POSSIBLE ROLE OF MITOCHONDRIA

PROPOSED MODEL OF THE MITOCHONDRIAL PTP COMPLEX



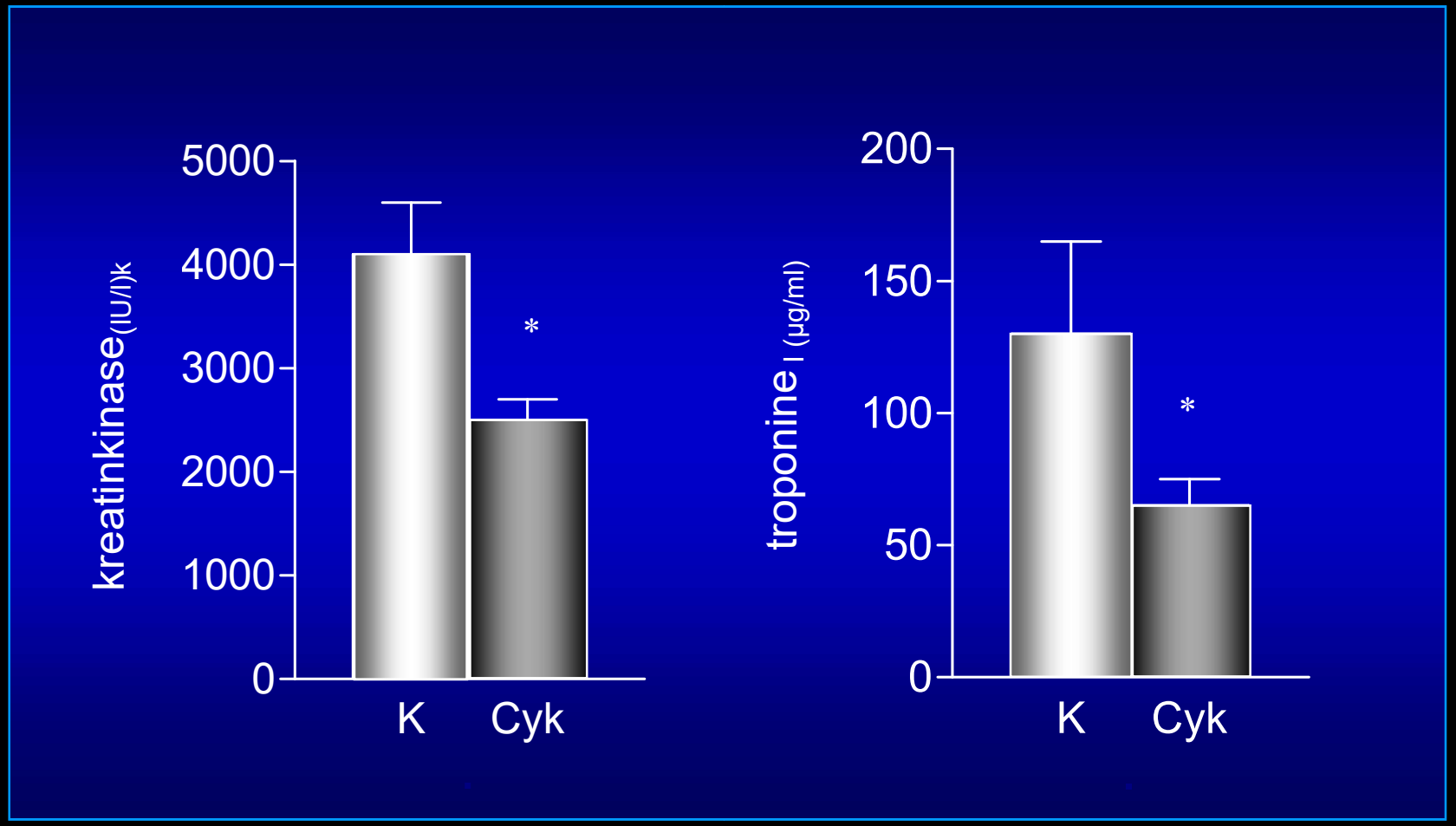
Javadov et al., 2017

OPENING OF THE MITOCHONDRIAL PORE
I/R injury

- collapse of MMP
- decrease of oxidative metabolism
- increase of oxidative stress
- swelling of mitochondria

  damage of the outer membrane
- removal of damaged mitochondria

BLOCKADE OF THE MPT PORE
(adult patients - cyclosporine)



Piot et al., 2008

CARDIAC MITOCHONDRIA
sex specificities

F < M

- mitochondrial content
- calcium uptake rate
- ROS production

F > M

- mitochondrial efficiency and differentiation
- glutamate/malate – stimulated respiration
- ADP / O ratio
- fatty acid utilization during exercise
- calcium retention capacity

F = M

- oxygen consumption rate (baseline)
- cardiolipin content
- other substrates – stimulated respiration

Ventura-Clapier et al., 2017

ESTROGEN AND MITOCHONDRIAL PERMEABILITY TRANSITION PORE

OPENING

- I/R injury
- ovariectomy

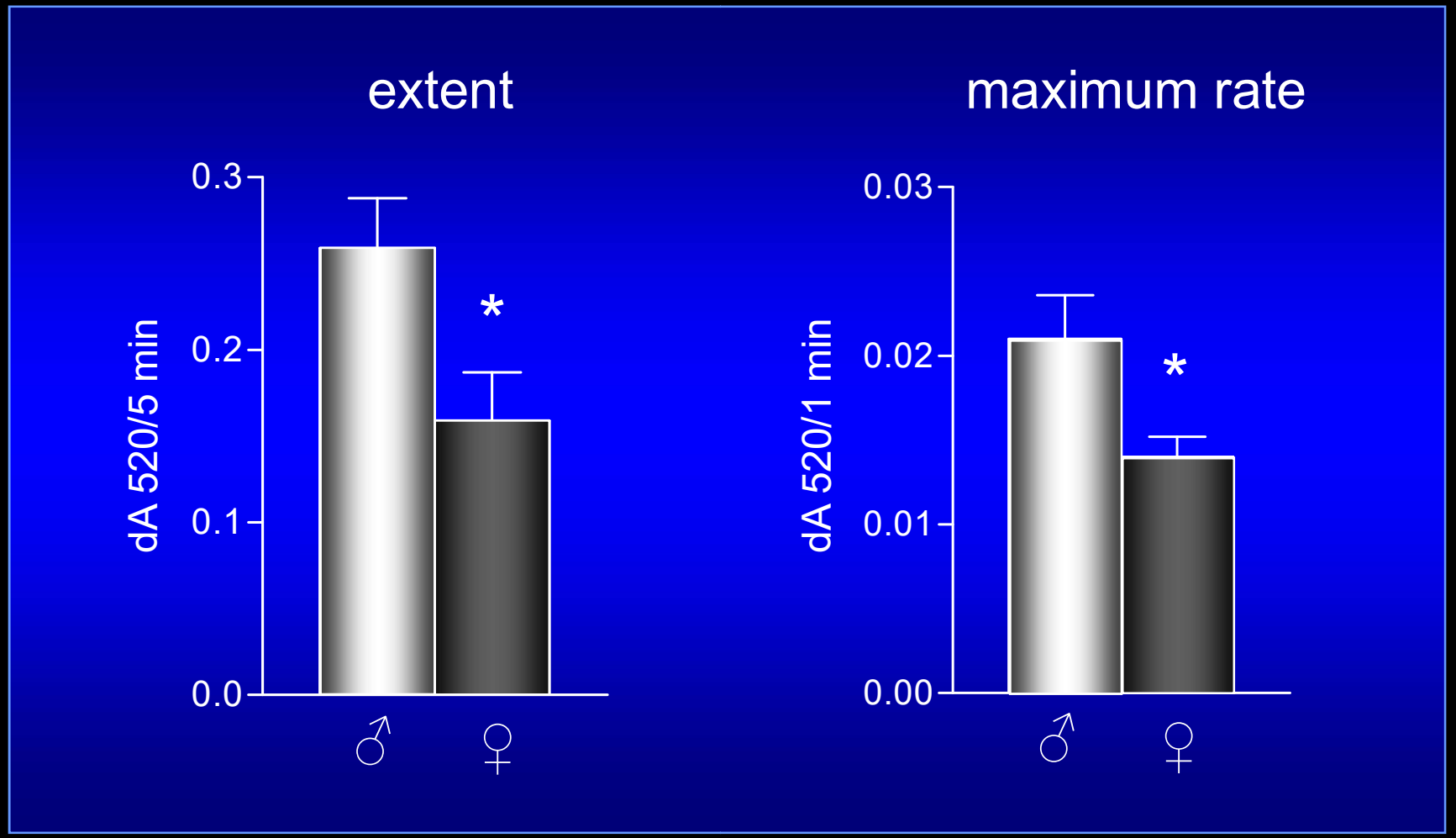
CLOSURE

- cyclosporin
- estrogen

Pavón et al., 2012

SEX DIFFERENCES

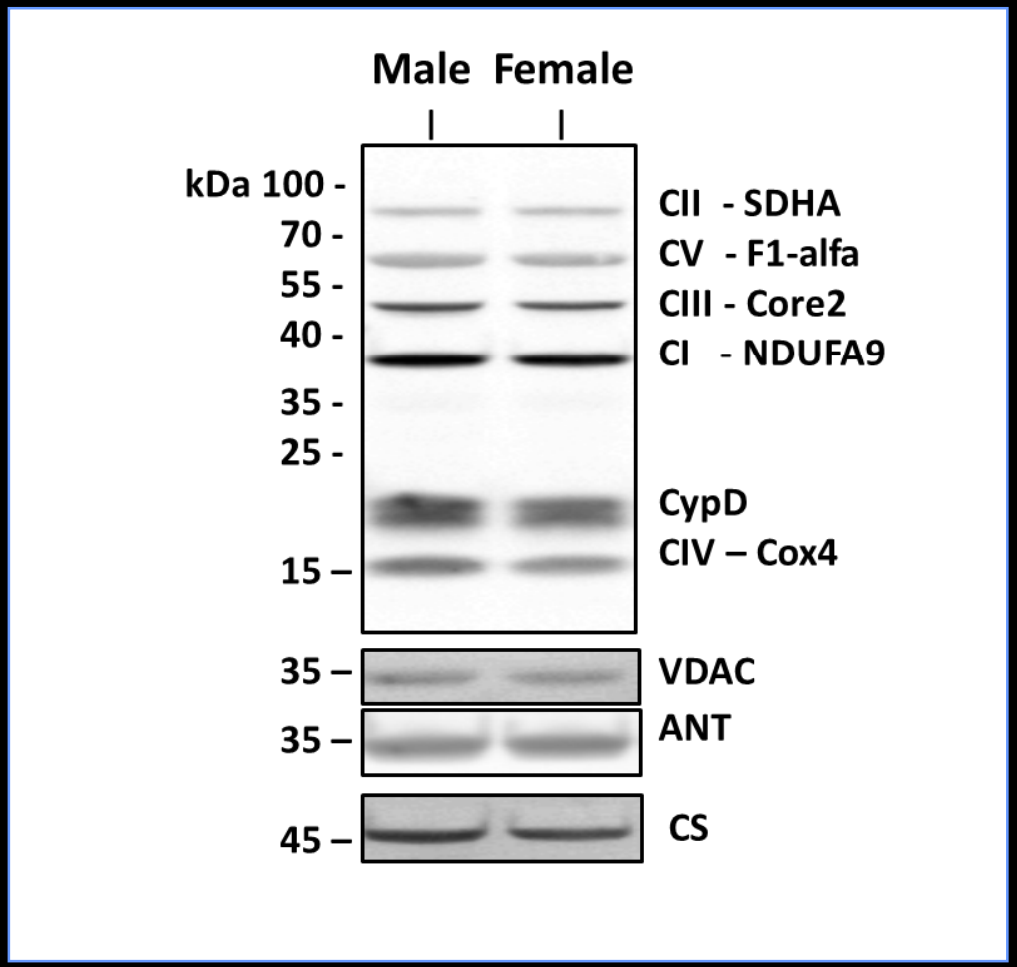
swelling of cardiac mitochondria (200 μM $CaCl_2$)



Milerova et al., 2016

Can be possible sex related changes in MPTP components involved in this process?

CARDIAC MITOCHONDRIA
proteins of MPT pore



Milerova et al., 2016, Ostadal et al., 2019

AGE AND SEX DIFFERENCES
CARDIAC MITOCHONDRIA

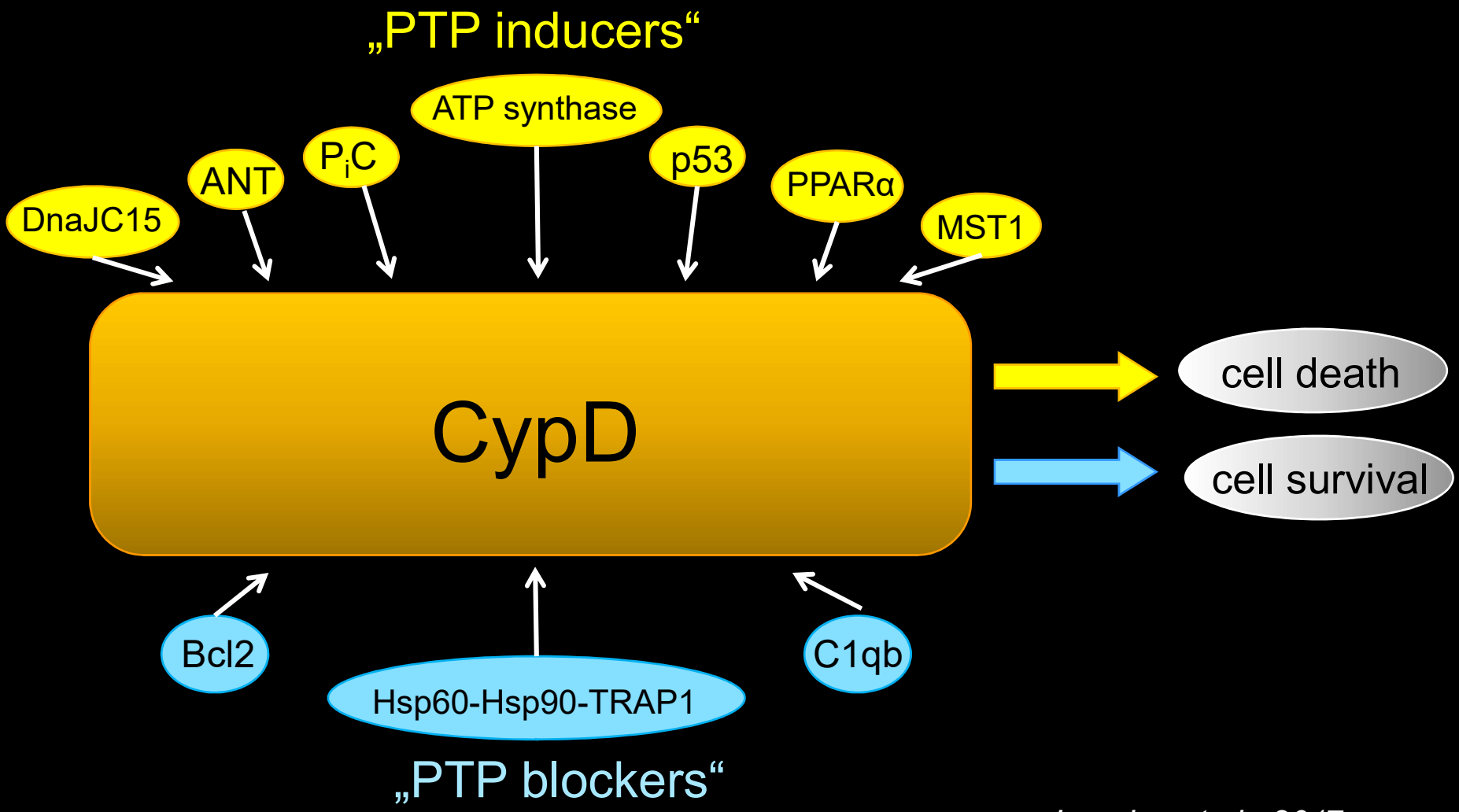
Differences in the sensitivity to calcium load thus cannot be explained by changes in components of MPTP and rather reflect regulation of MPTP function, e.g.

calcium interaction with CyP-D

calcium transport to mitochondria

SEX DIFFERENCES ?

INTERACTION OF CypD WITH MITOCHONDRIAL PROTEINS



Javadov et al., 2017

SEX DIFFERENCES - MITOCHONDRIA

Changes in mitochondrial function could participate on sex differences in cardiac tolerance to oxygen deprivation

SEX DIFFERENCES AND ISCHEMIC HEART DISEASE

SITUATION IN 2024

SEX DIFFERENCES AND THE HEART
international institutions

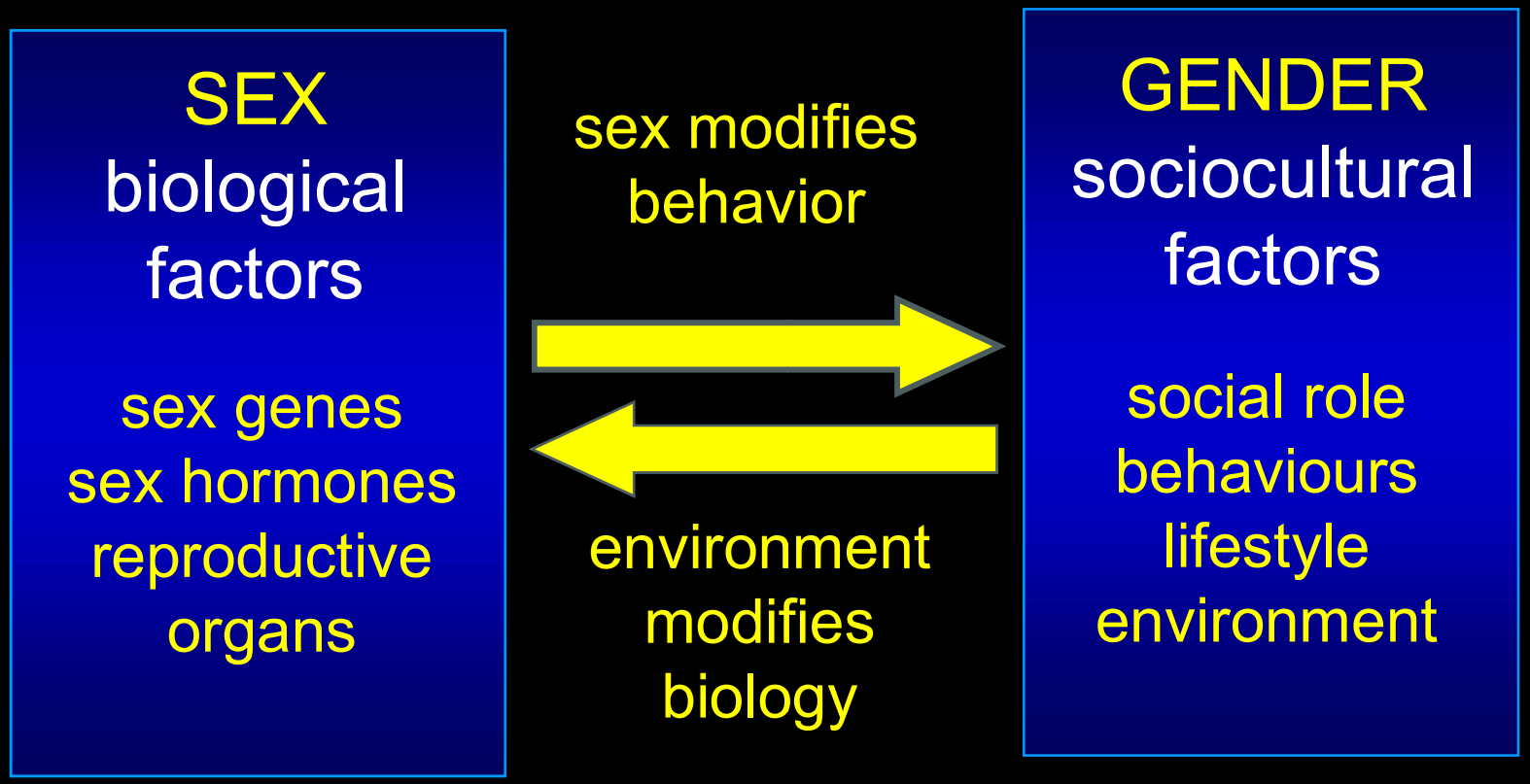
- Organization for Study of Sex Differences (2006 – USA)
- International Society for Gender Medicine (2007 – Germany)
- The Lancet Women and Cardiovascular Disease Comission (2021)

SEX DIFFERENCES AND THE HEART
clinical studies

- the representation of women in clinical trials is still insufficient
- only 2% of studies report data on sex-specific risk factors

Hassan et al., 2022

CONCEPT OF SEX AND GENDER IN CARDIOLOGY



Regitz-Zagrosek, Nature, 2023

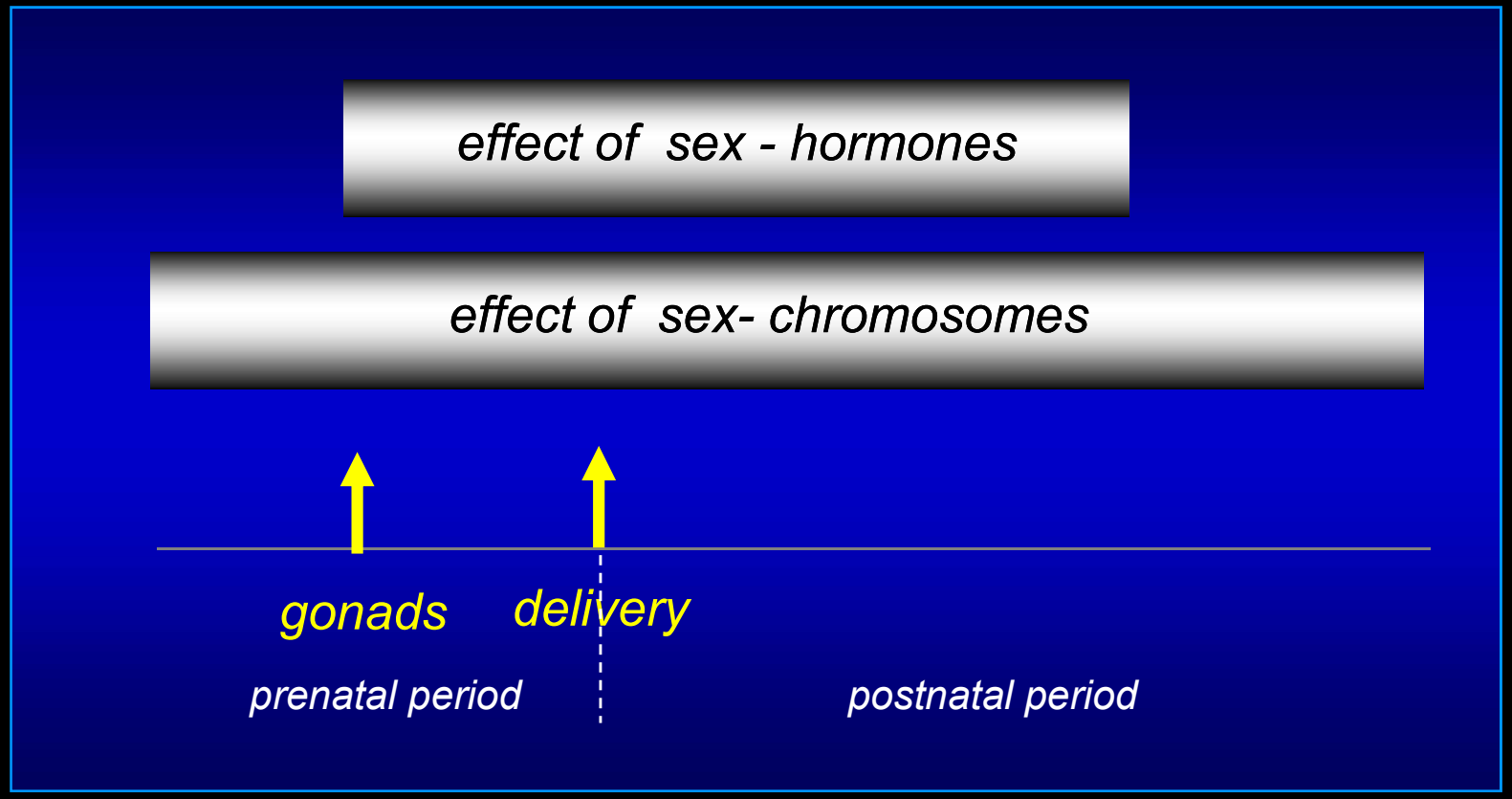
SEX DIFFERENCES AND ISCHEMIC HEART DISEASE

Despite the growing amount of evidence, the differential contribution of biological (sex) and a sociocultural (gender) factors to the onset and course of ischemic heart disease is not yet known

Regitz-Zagrosek, Nature, 2023

SEX DIFFERENCES AND THE HEART

when do they arise ?



already before the development of gonads !

Deegan et al.,2021

SEX DIFFERENCES AND THE HE ART
unresolved theoretical questions

- interaction of different sex hormones
- interaction of hormones and genes during development
- molecular basis of different function of mitochondria

Deegan et al.,2021

SEX DIFFERENCES
CONCLUSIONS

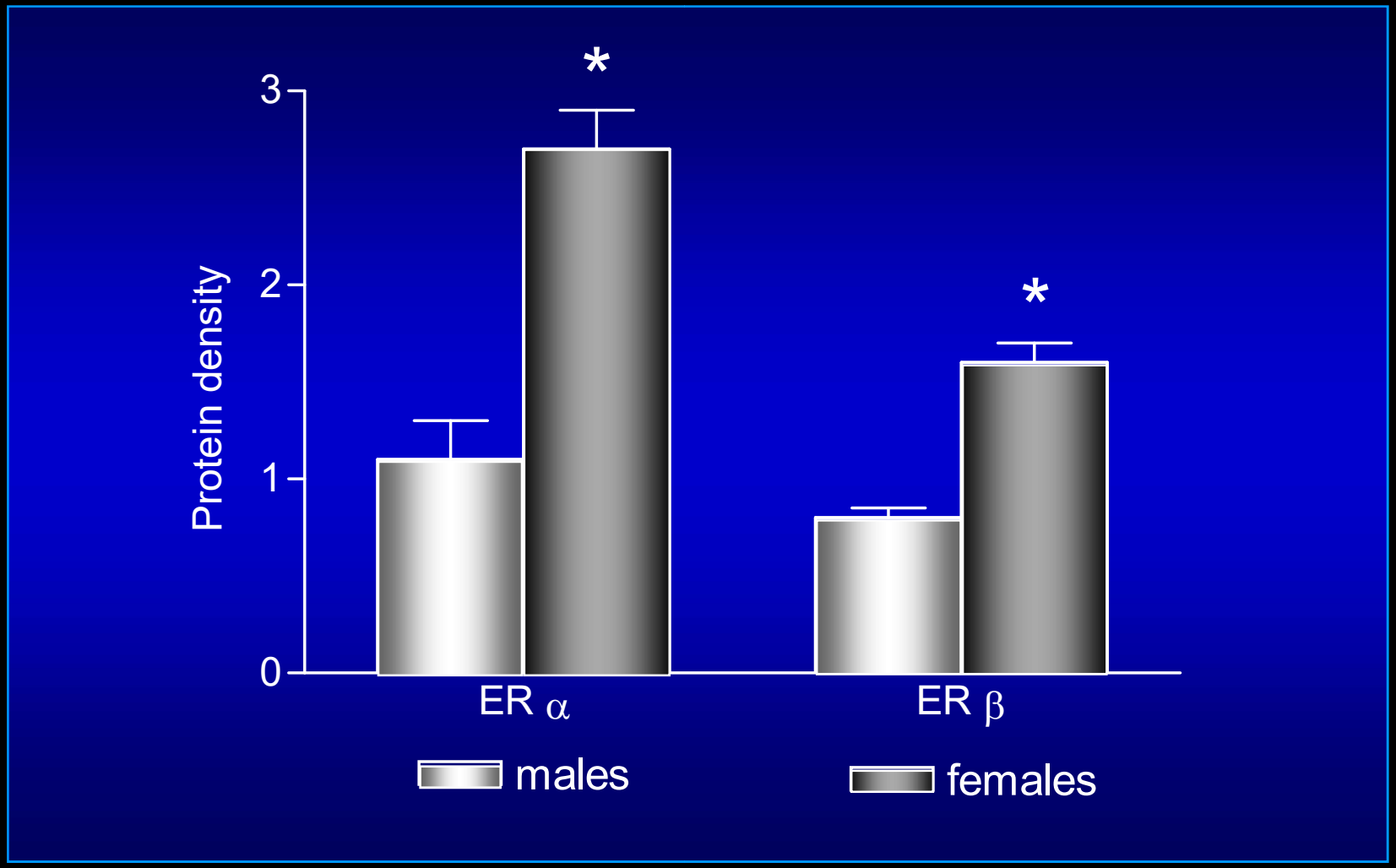
- male and female hearts differ in many parameters under physiologic and pathologic conditions
- detailed mechanisms of these differences are still unknown
- sex differences should be considered in clinical practice

WE ARE DIFFERENT ! PLEASE RESPECT !

Keith Haring

Drahota Z.
Houštěk J.
Hlaváčková M.
Charvátová Z.
Kolář F.
Milerová M.
Neckář J.
Netuka I.
Ošťádal P.
Ošťádalová I.
Pirk J.
Szarszoi O.
Škarka L.

SEX DIFFERENCES
estrogen receptors in the fetal heart



Patterson et al., 2010

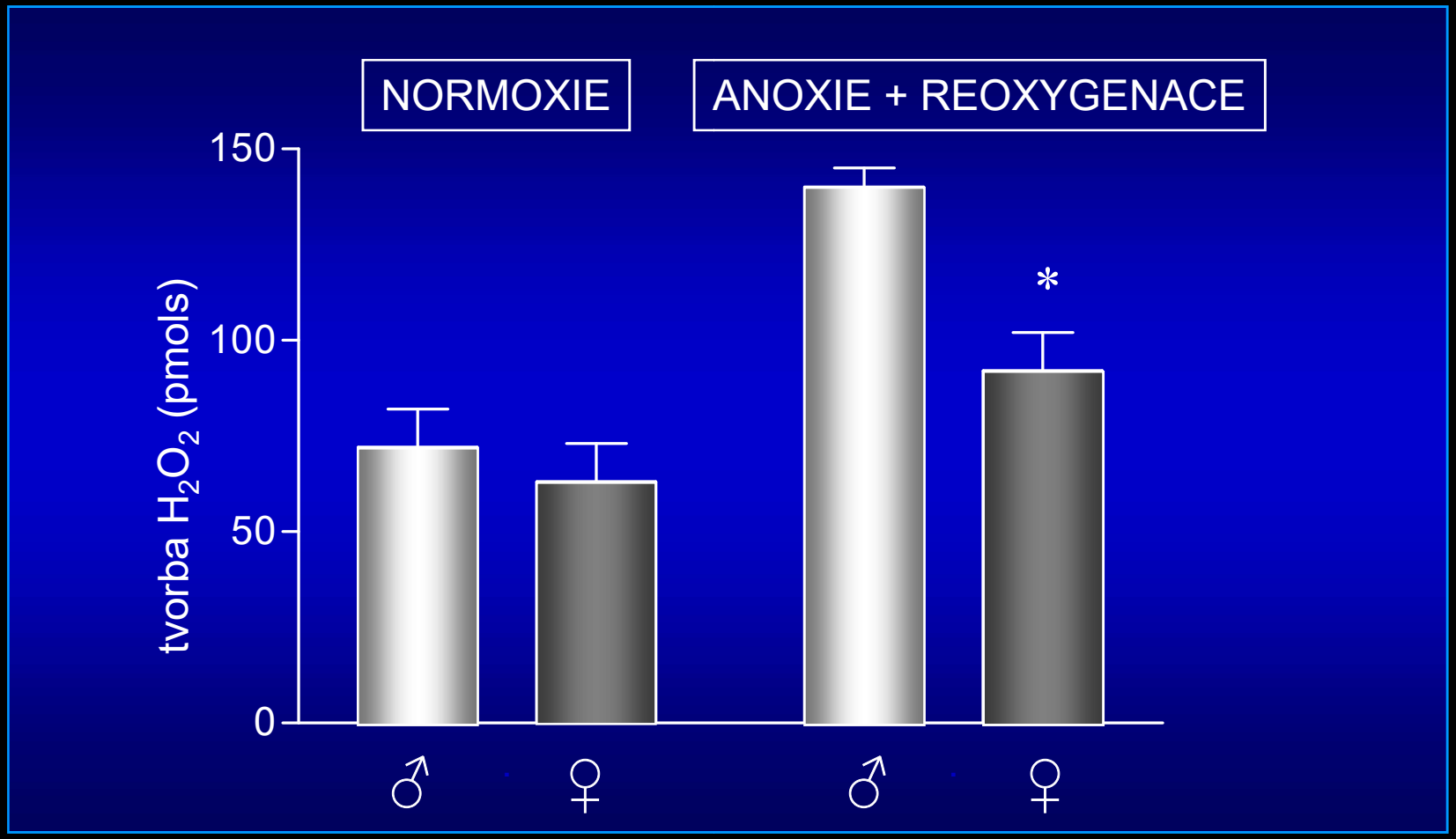
POHLAVNÍ ROZDÍLY – SRDEČNÍ MITOCHONDRIE

Různá citlivost ke kalciu nemůže být proto vysvětlena rozdíly ve složení MPTP póru – je spíše důsledkem rozdílů v regulaci MPTP funkce, např.

interakce vápníku s cyklofilinem - D

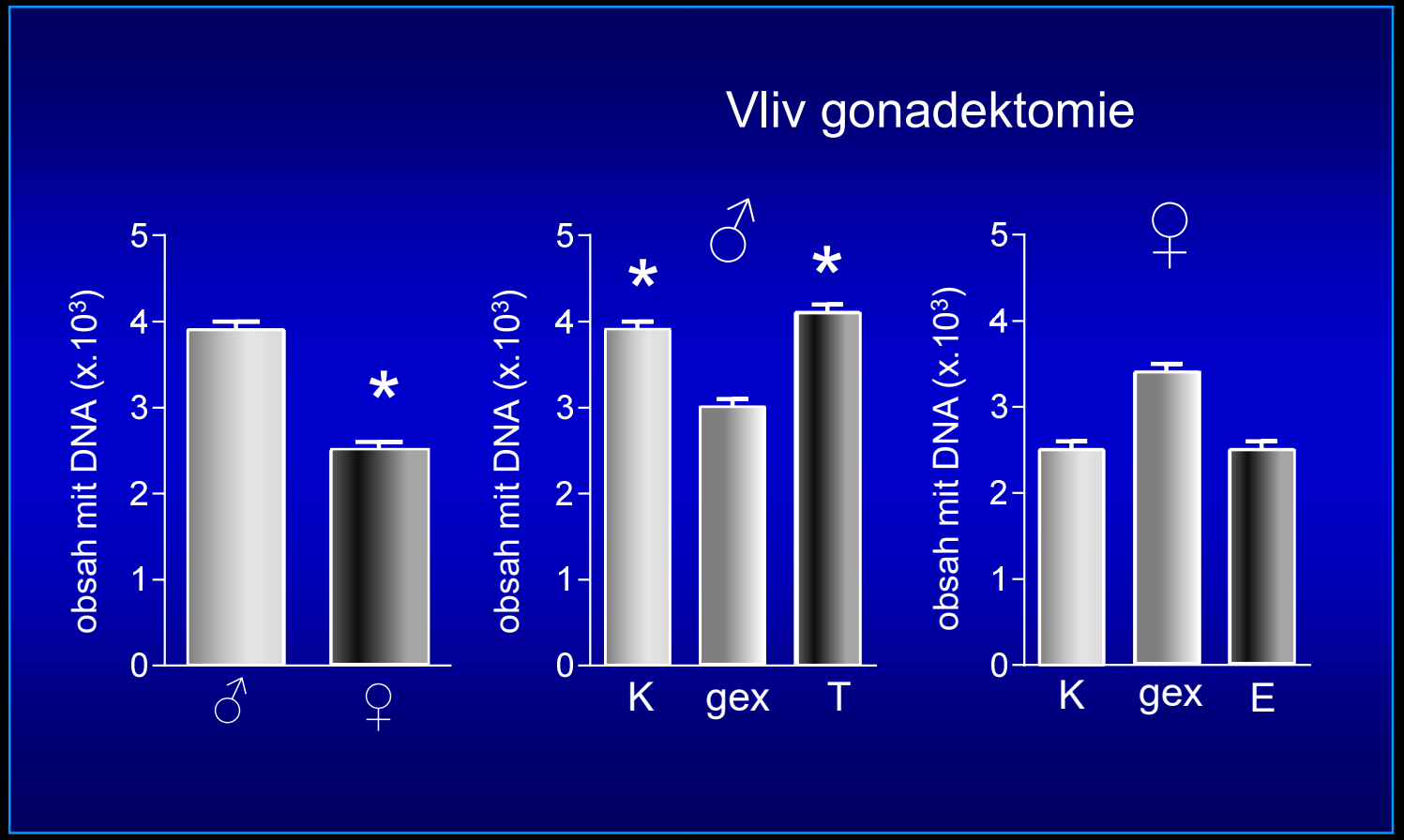
transport vápníku do mitochondrií

POHLAVNÍ ROZDÍLY – SRDEČNÍ MITOCHONDRIE
tvorba H_2O_2



Lagranha a spol. 2010

POHLAVNÍ ROZDÍLY A SRDCE
obsah mitochondriální DNA

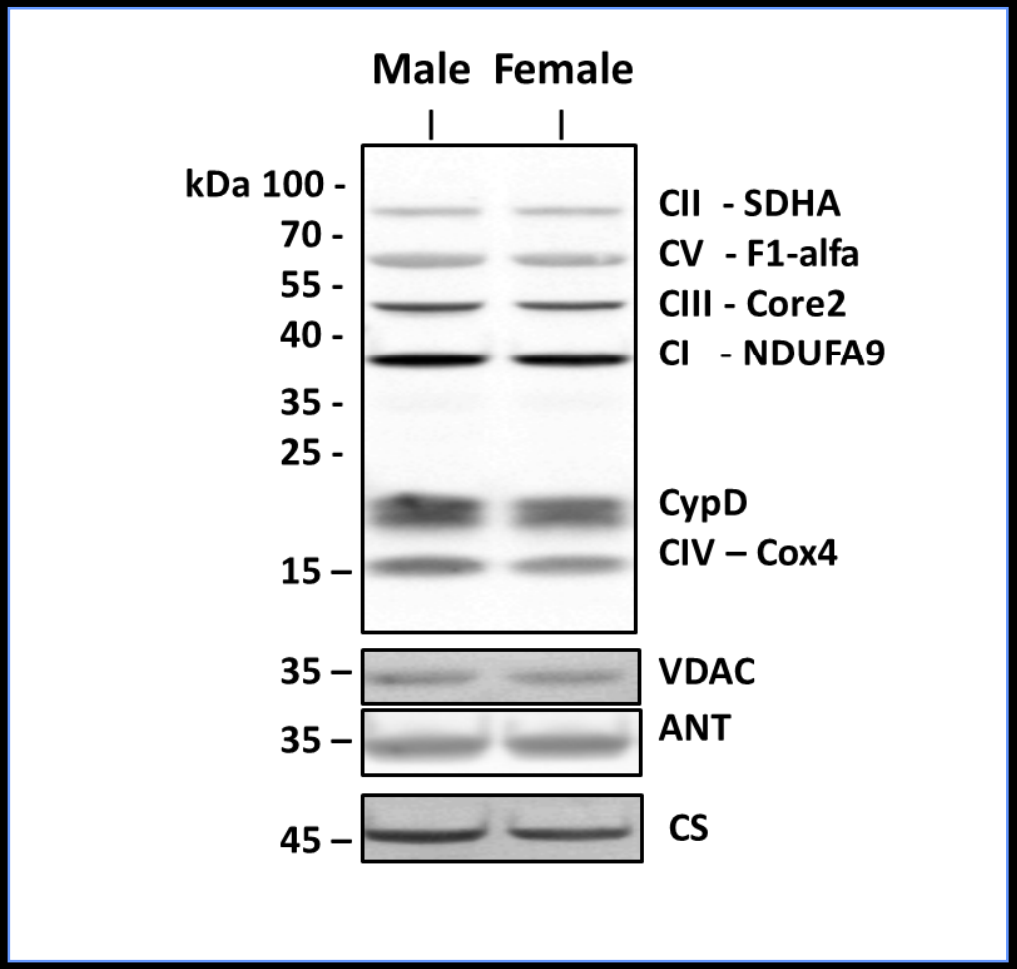


Cao a spol. 2022 - Nature

AGE AND SEX DIFFERENCES
CARDIAC MITOCHONDRIA

Differences in the sensitivity to calcium load thus cannot be explained by changes in components of MPTP and rather reflect regulation of MPTP function

POHLAVNÍ ROZDÍLY – SRDEČNÍ MITOCHONDRIE
proteiny MPT póru



Milerova et al. 2016

ZÁVĚR

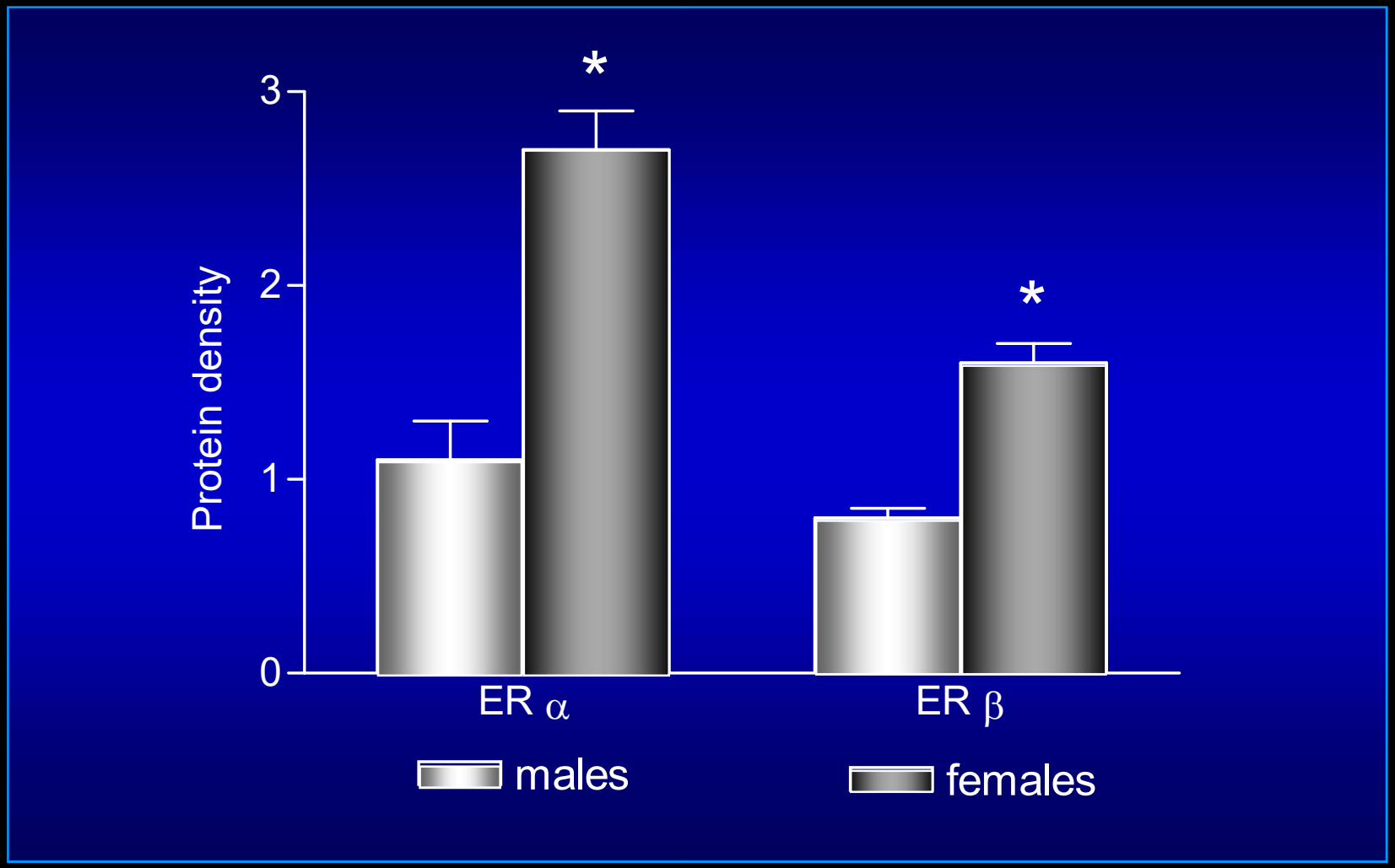
- mužské a ženské srdce se významě liší v řadě parametrů, a to jak za fyziologických tak patologických podmínek
- detailní mechanismy těchto rozdílů na své vysvětlení však dosud čekají
- pohlavní rozdíly by měly být brány v úvahu v experimentální i klinické kardiologii

CO JE PŘÍČINOU SELHÁNÍ SUBSTITUČNÍ THERAPIE ?
hypotézy

- načasování
- protekce se snižuje s věkem
  - ↓ tetrahydrobiopterin – kofaktor eNOS
  - změny hladiny a aktivity ER
  - ↑ aterosklerosa
  - ↑ 27 – hydroxycholesterol → antagonizuje vliv estrogenu (eNOS) ↓

Murphy, 2011

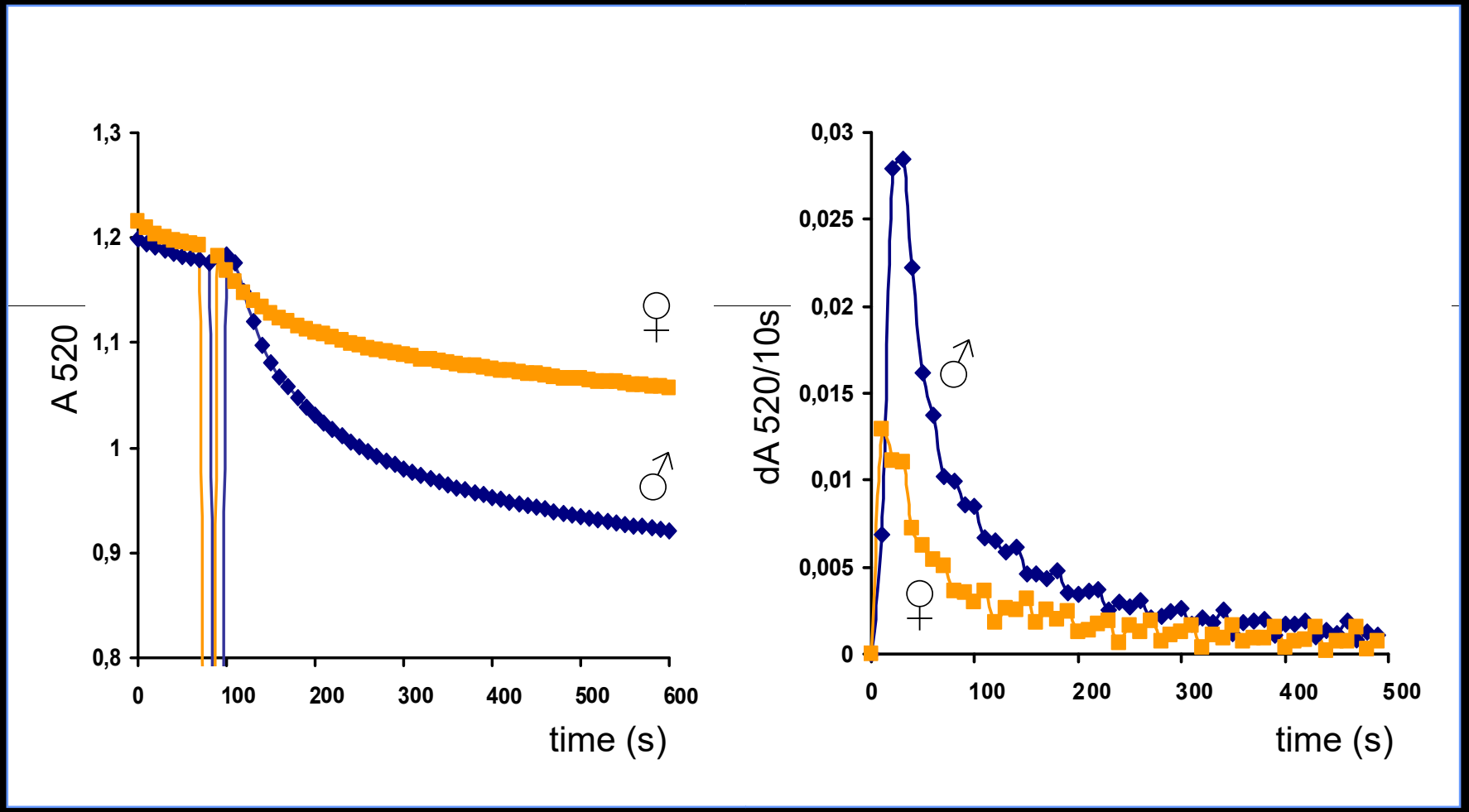
POHLAVNÍ ROZDÍLY A SRDCE
estrogenové receptory ve fetálním srdci



Patterson a spol. 2010

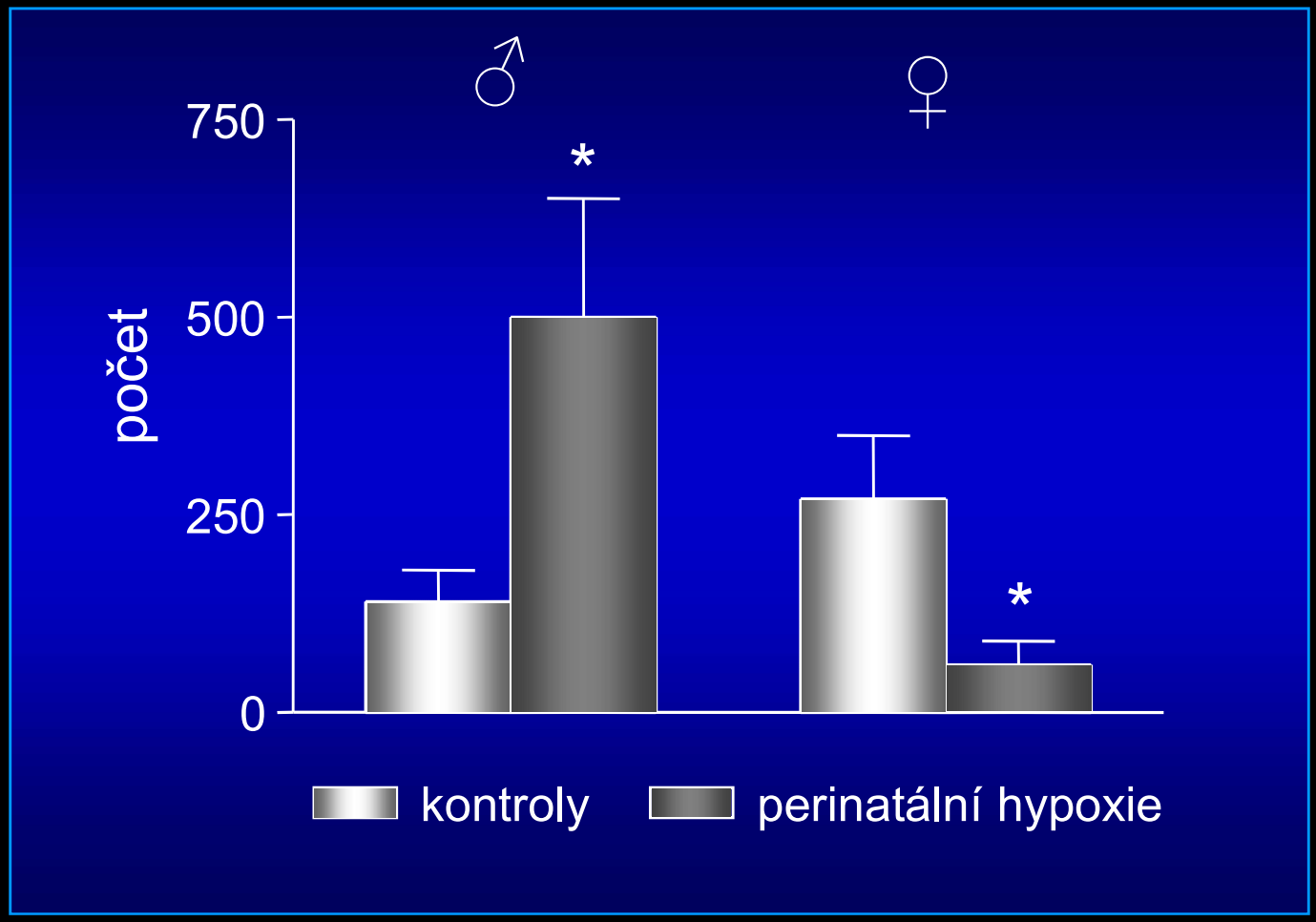
SEX DIFFERENCES

swelling of cardiac mitochondria (200 μM $CaCl_2$)



Milerova et al., 2016

POZDNÍ DŮSLEDKY - POHLAVNÍ ROZDÍLY
odolnost srdce k ischemii – arytmie



Netuka et al. 2006

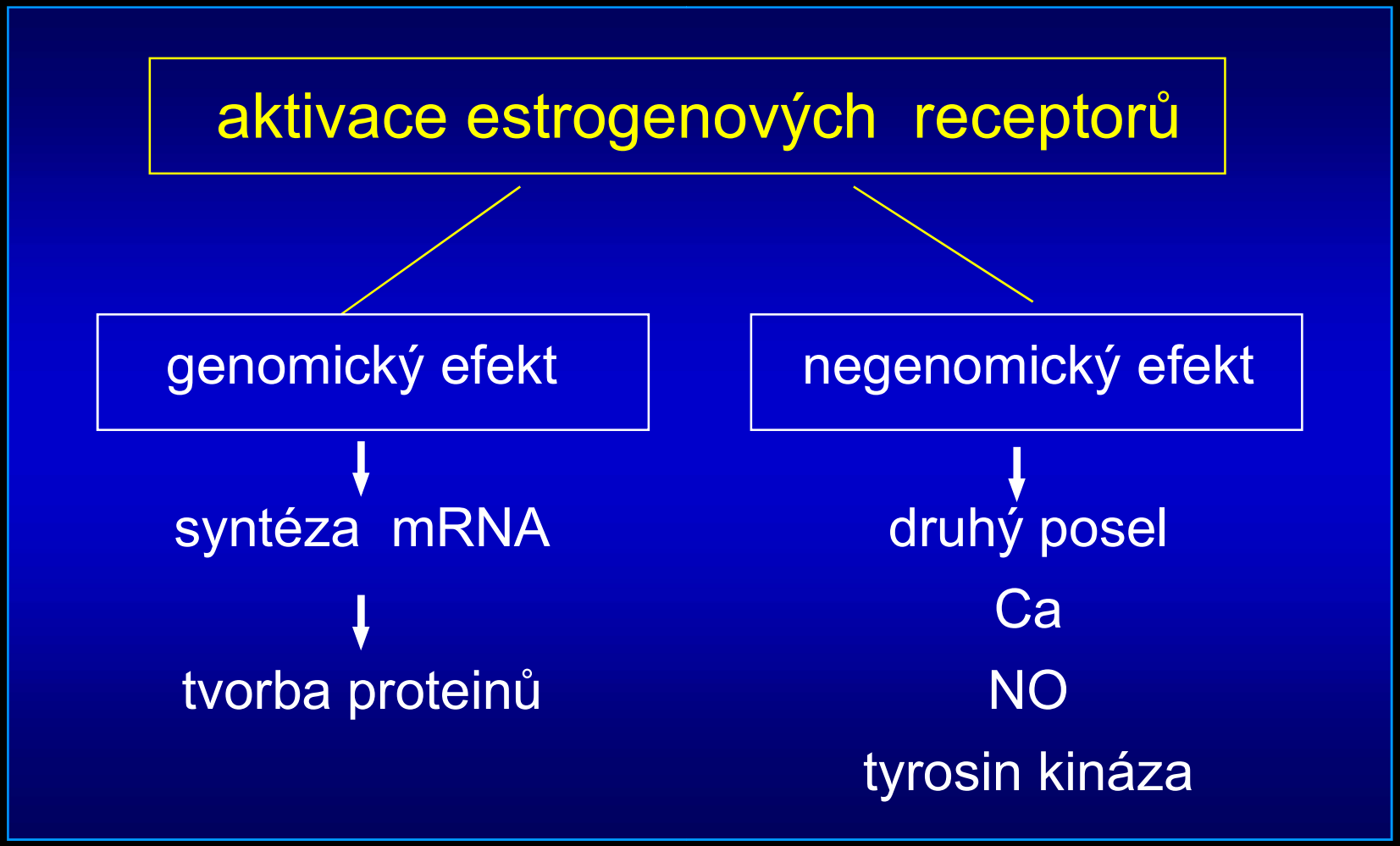
Pohlavní rozdíly ve funkci mitochondrií se mohou podílet na rozdílech v citlivosti srdečního svalu k nedostatku kyslíku

POHLAVNÍ ROZDÍLY
MITOCHONDRIÁLNÍ GENY (670)
srdce potkana

- fatty acid metabolism ↑♂
- pyruvate dehydrogenase complex ↑♂
- oxidative phosphorylation =
- apoptotic genes ↑♂

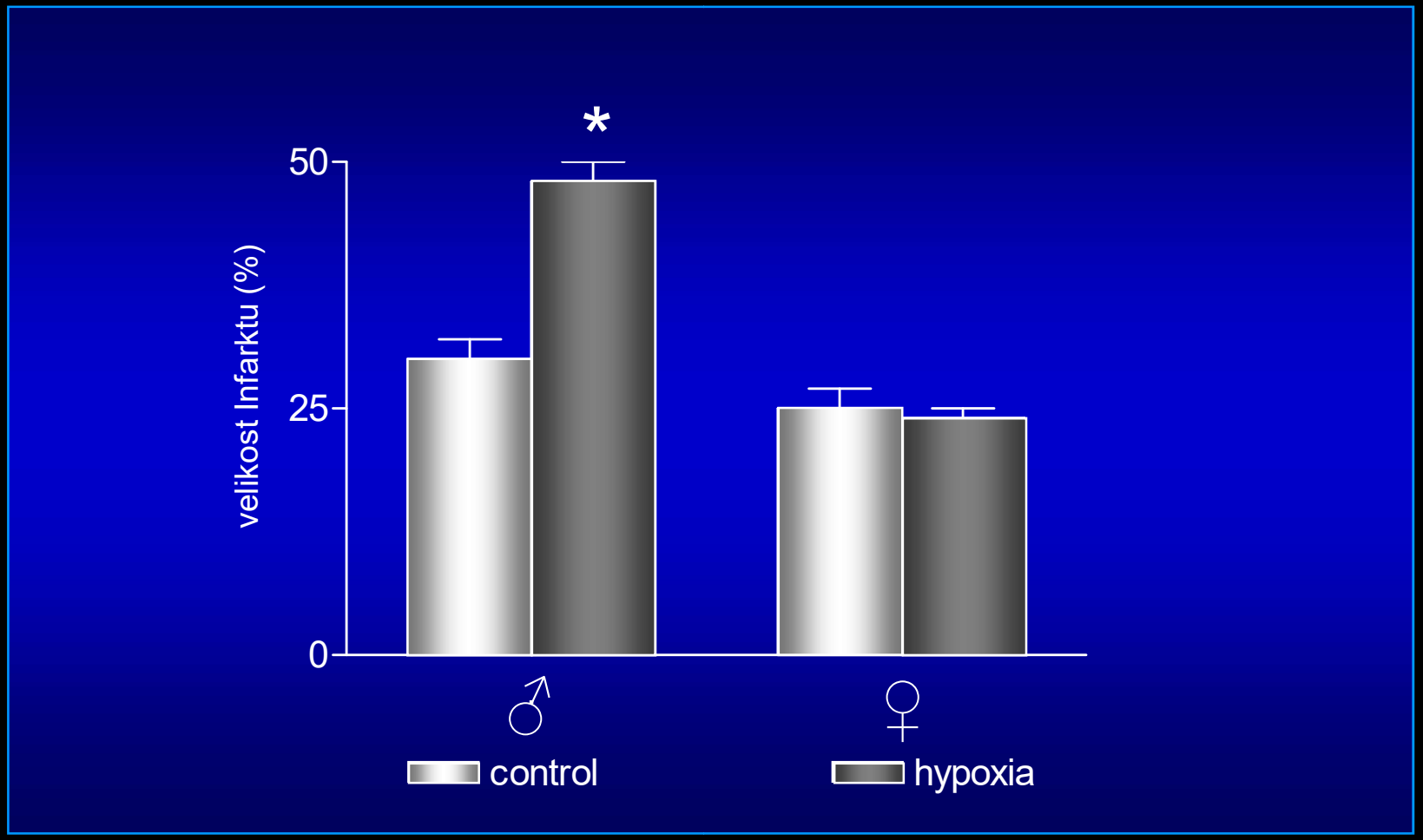
Vijay et al. 2015

VLIV ESTROGENŮ



Baker a spol. 2003

POZDNÍ DŮSLEDKY – POHLAVNÍ ROZDÍLY
velikost infarktu – dospělí samci a samice lab.potkana



Xue and Zhang., 2009

POHLAVNÍ ROZDÍLY - SRDCE
mitochondrie

F < M

- obsah mitochondrií
- vychytávání vápníku
- tvorba ROS

F > M

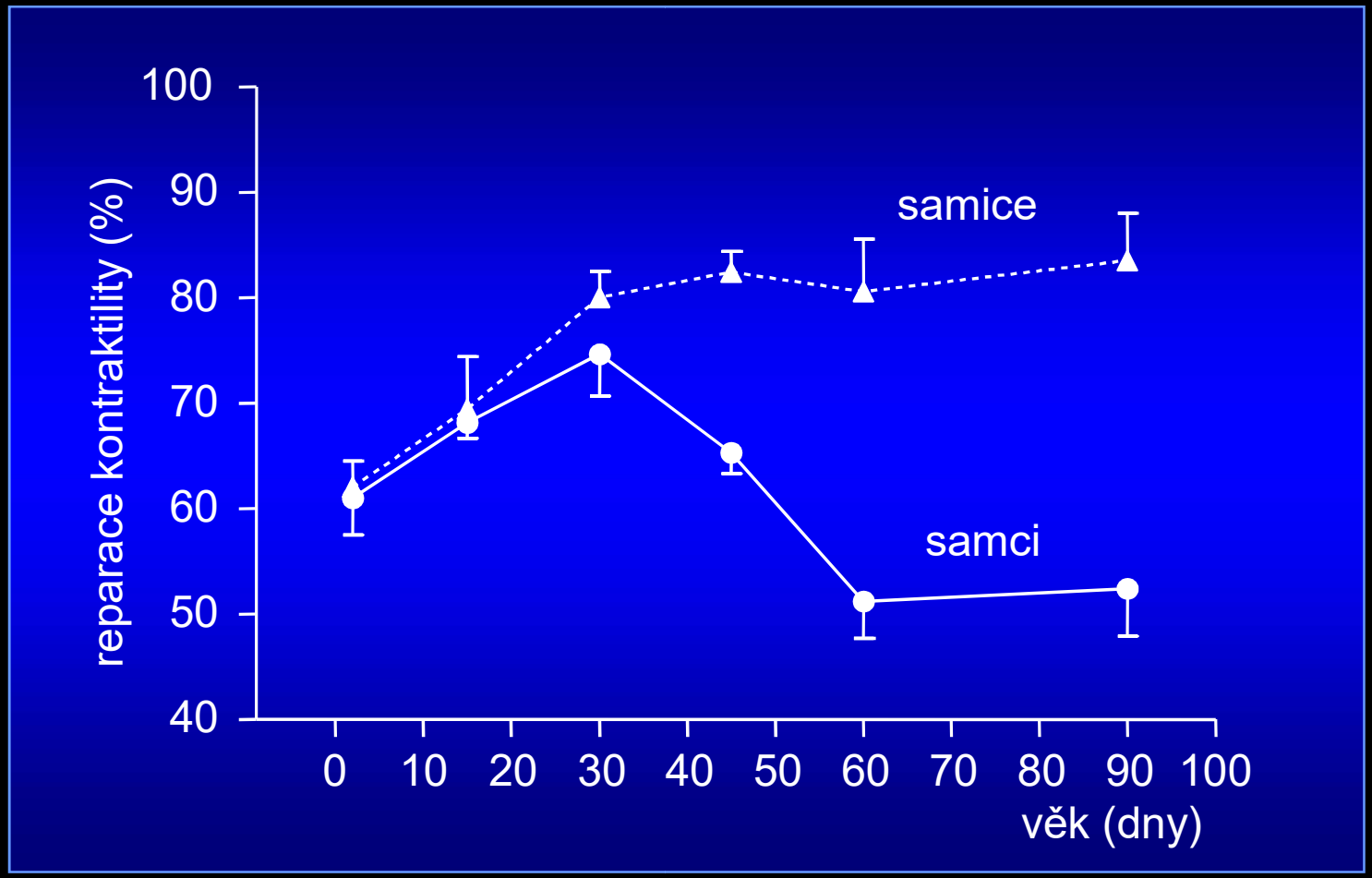
- mitochondriální výkonnost a differenciace
- glutamát/malát – stimulovaná respirace
- ADP / O ratio
- utilizace mastných kyselin při námaze
- retenční kapacita pro vápník

F = M

- bazální spotřeba kyslíku
- obsah kardiolipinu
- stimulace respirace jinými substráty

Ventura-Clapier et al., 2017

VĚK A POHLAVNÍ ROZDÍLY
ODOLNOST SRDCE K AKUTNÍ HYPOXII
ontogenetický vývoj - potkan



Ošťádal a spol. 1999

POHLAVNÍ ROZDÍLY A SRDCE

♀

♀

- ↓ velikost srdce
- ↓ minutový objem
- ↑ ejekční frakce
- ↑ kontraktilita
- ↓ krevní tlak
- ↑ počet myocytů
- ↑ frekvence

Pierre a spol. 2022

BIOLOGICKÝ VÝZNAM ODLIŠNOSTI ŽENSKÉHO SRDCE

zajištění zvýšené zátěže související s reprodukční funkcí

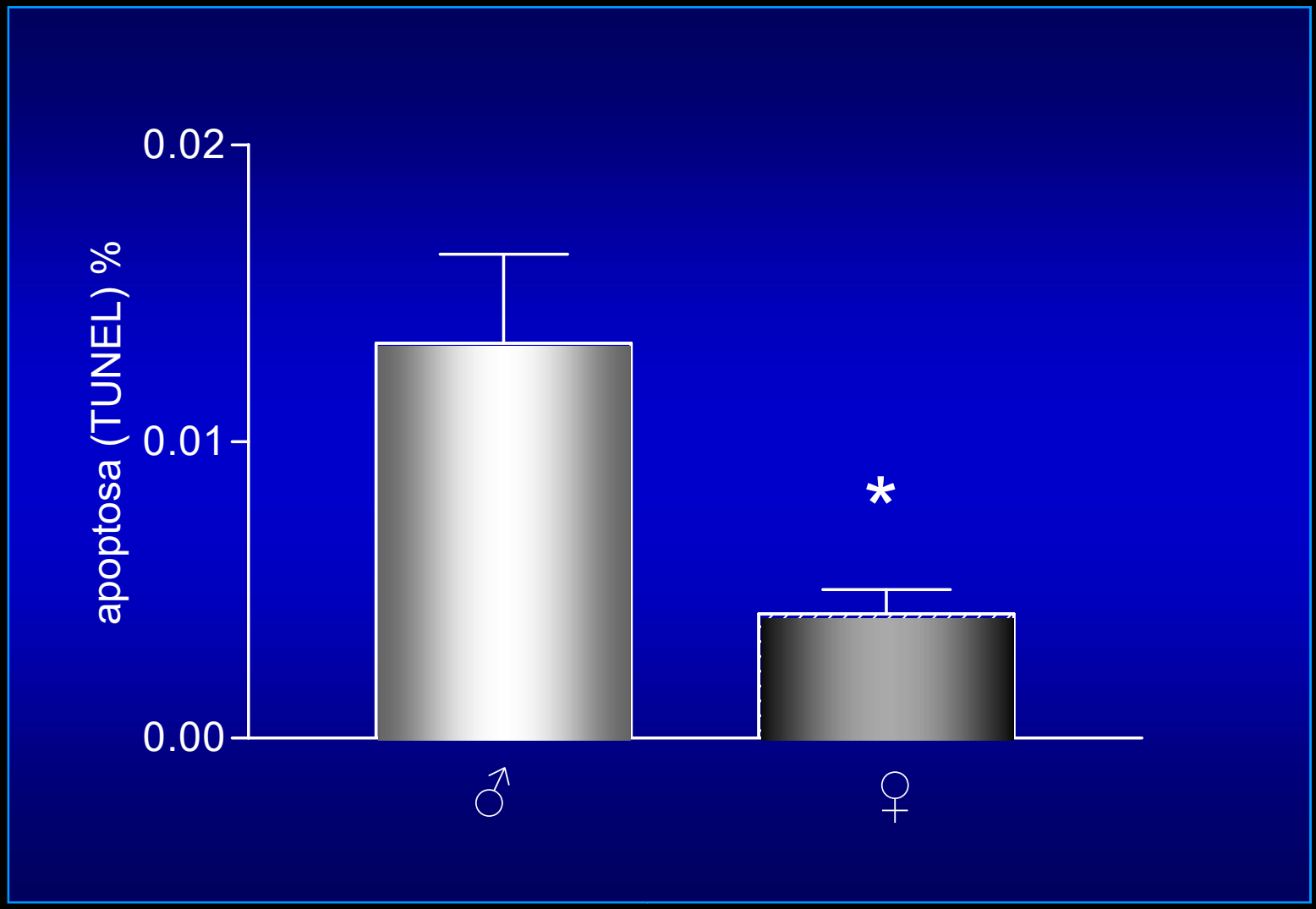
- TĚHOTENSTVÍ
- PORODY

OBECNÝ BIOLOGICKÝ FENOMÉN

zvýšit odolnost vysoce resistentního myokardu není možné

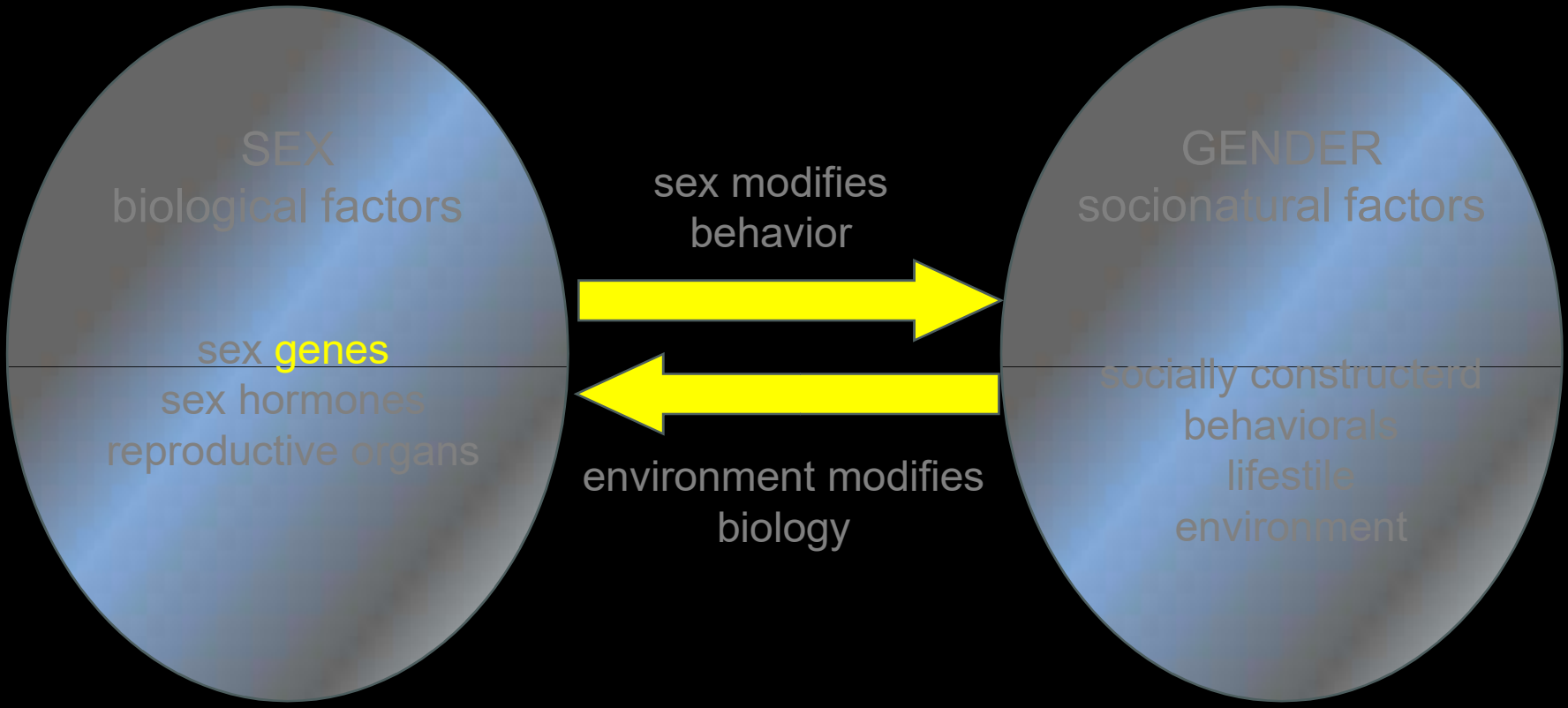
- studenokrevní
- novorozenci
- mladé samice

POHLAVNÍ ROZDĹY – SRDCE
apoptosa v normálním lidském srdci (21 – 93 let)



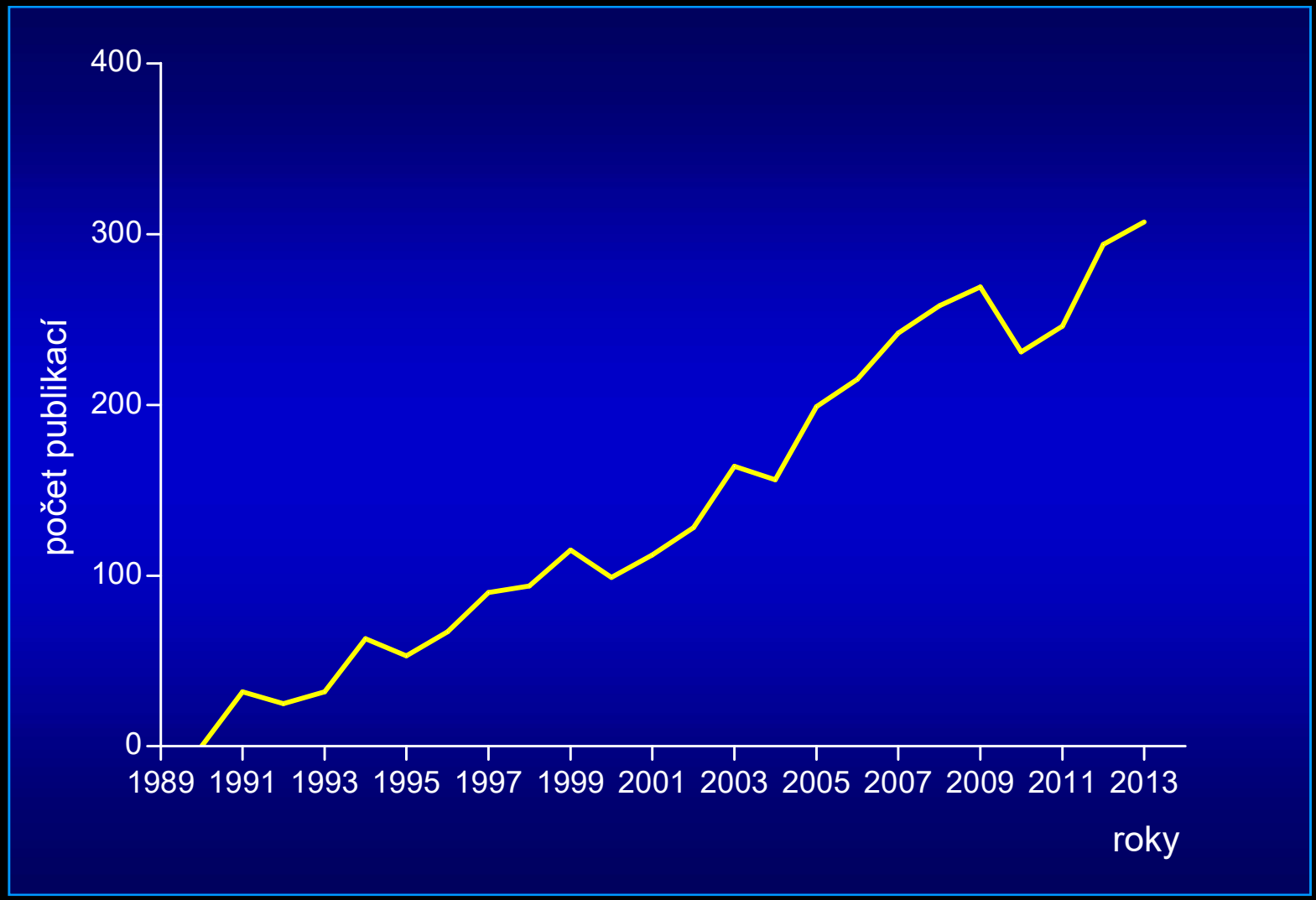
Mallat a spol. 2001

GENDER MEDICINE



Regitz-Zagrosek, Natural, 2023

POHLAVNÍ ROZDÍLY – SRDCE
Web of Science

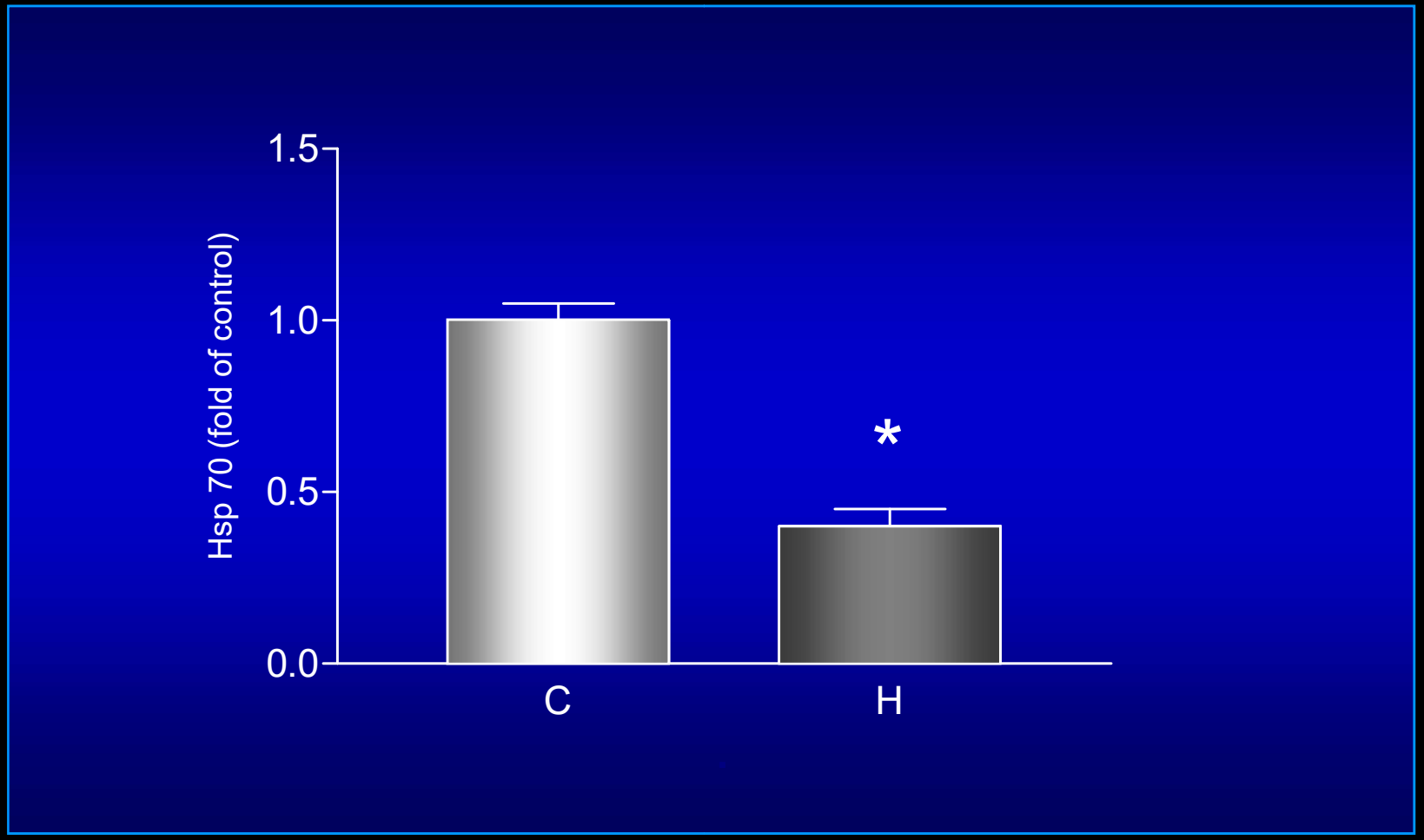


POHLAVNÍ ROZDÍLY A SRDCE
buněčné typy a rizika ICHS

	MYOCYTY	CÉVNÍ STĚNA	FIBROBLASTY
♀	↓ mortalita (do menopauzy)	↑ ruptura plátu (po menopauze)	↓ remodelace (do menopauzy)
♂	↑ mortalita	↑ arterioskleróza	↑ fibróza

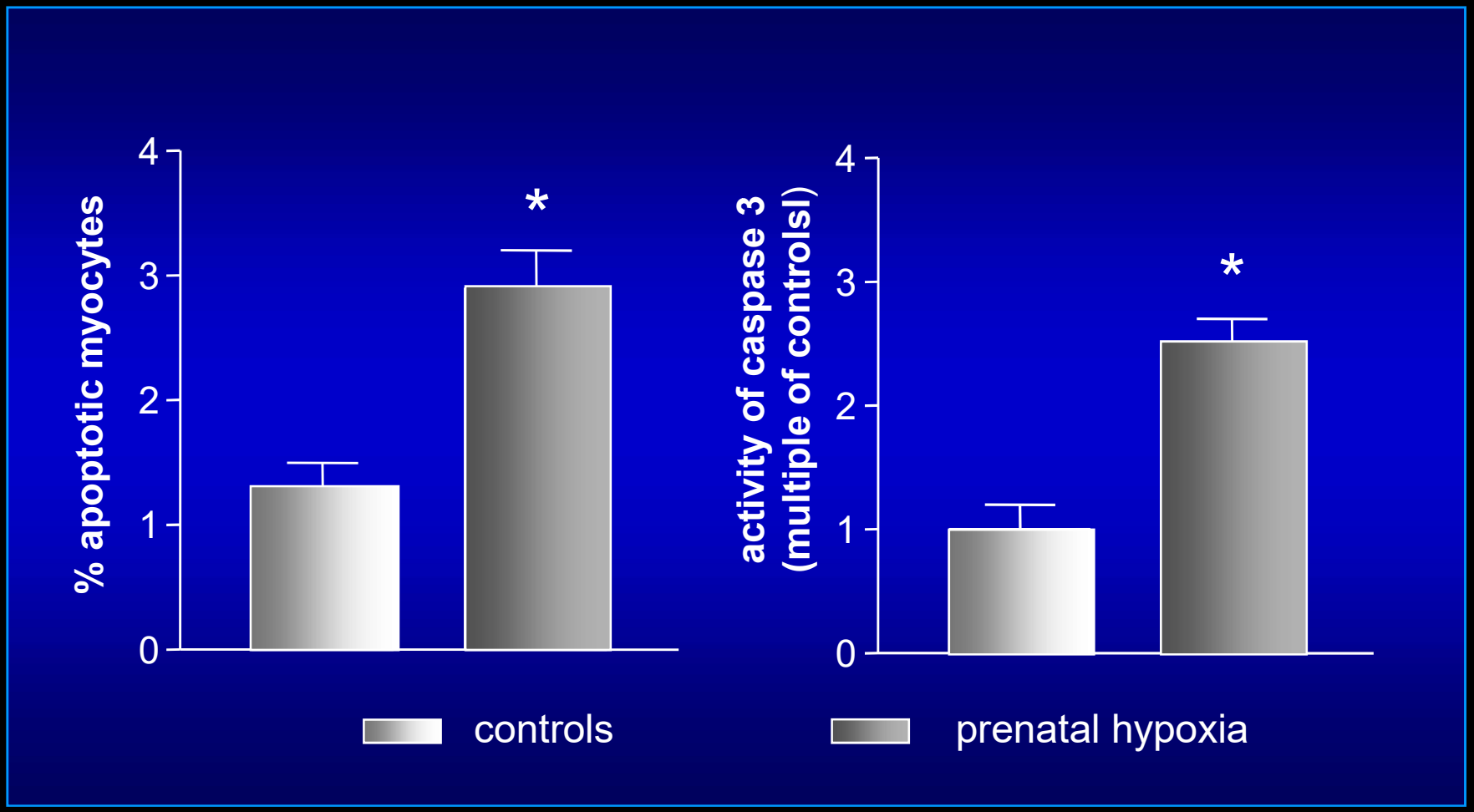
Walker a spol. 2021

EFFECT OF PRENATAL HYPOXIA
heat shock proteins 70 in fetal rat hearts



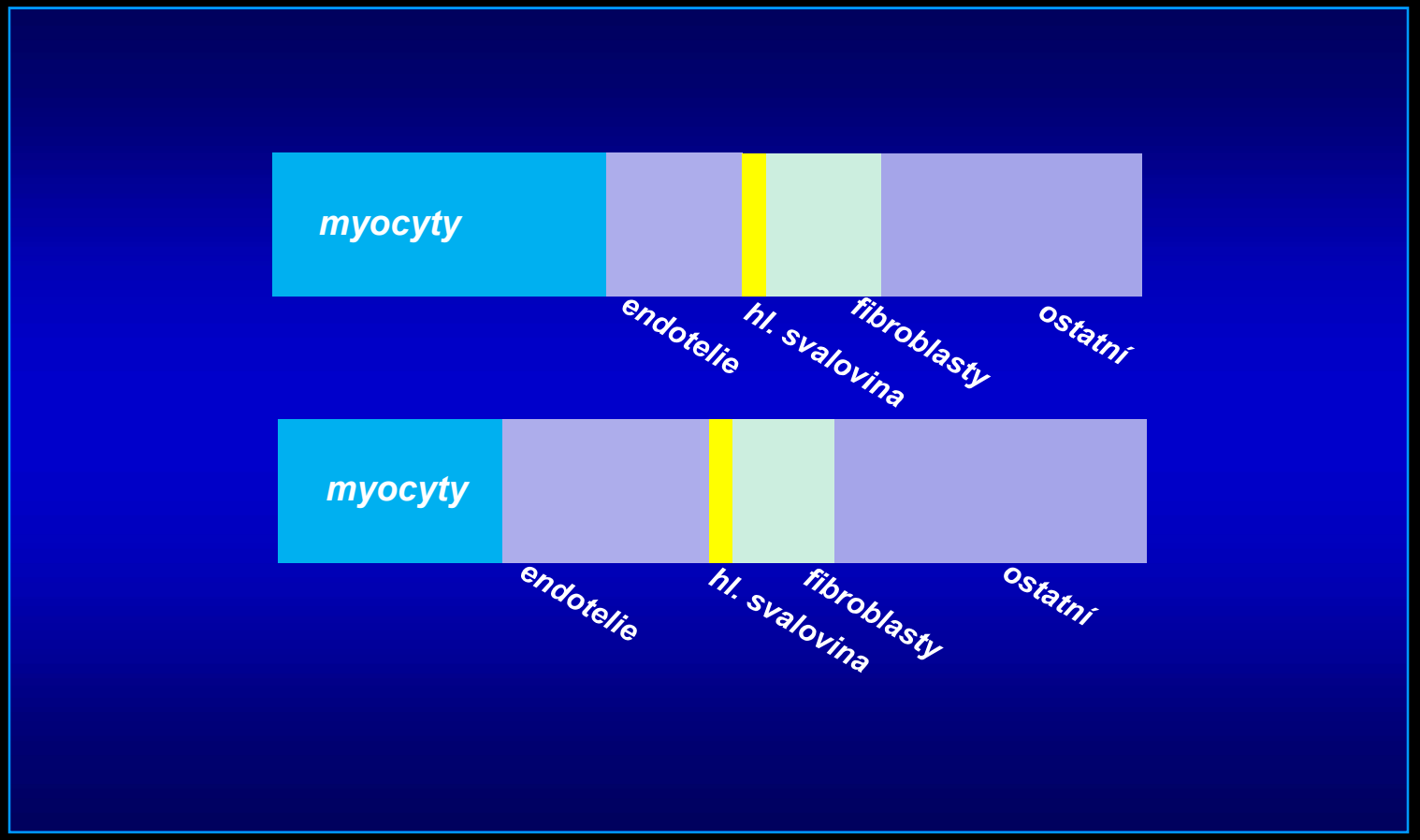
Bae et al., 2003

EFFECT OF CHRONIC PRENATAL HYPOXIA
apoptosis in fetal rat heart



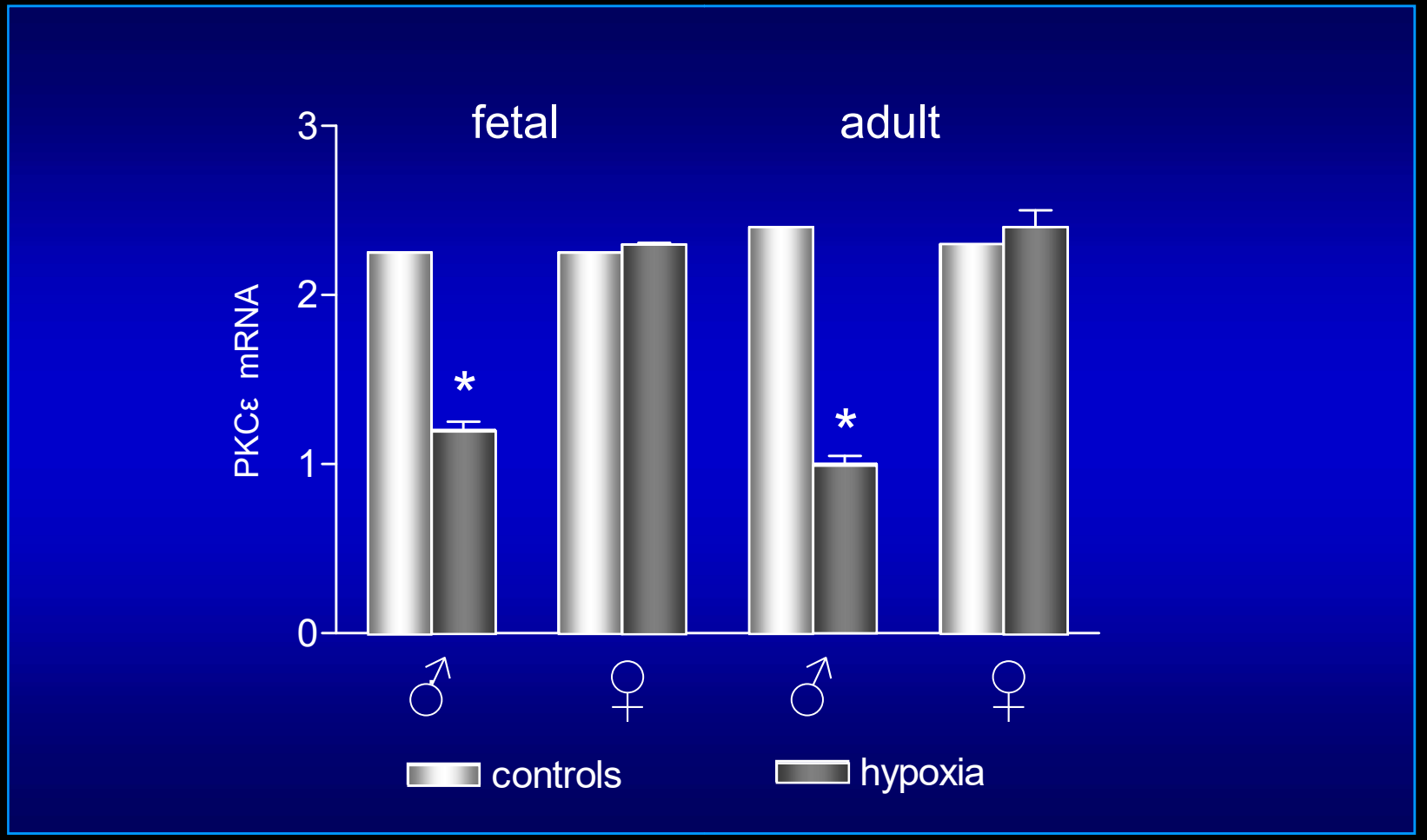
Bae et al. 2003

POHLAVNÍ ROZDÍLY - SRDCE
zastoupení buněčných typů u člověka



Walker a spol. 2021

SEX-DEPENDENT LATE EFFECTS
PKCε mRNA in fetal and adult rat hearts



Patterson et al., 2010

POHLAVNÍ ROZDÍLY - SRDCE
mitochondrie

F < M

- obsah mitochondrií
- vychytávání vápníku
- tvorba ROS

F > M

- mitochondriální výkonnost a differenciace
- glutamát/malát – stimulovaná respirace
- ADP / O ratio
- utilizace mastných kyselin při námaze
- retenční kapacita pro vápník

F = M

- bazální spotřeba kyslíku
- obsah kardiolipinu
- stimulace respirace jinými substráty

Ventura-Clapier et al., 2017

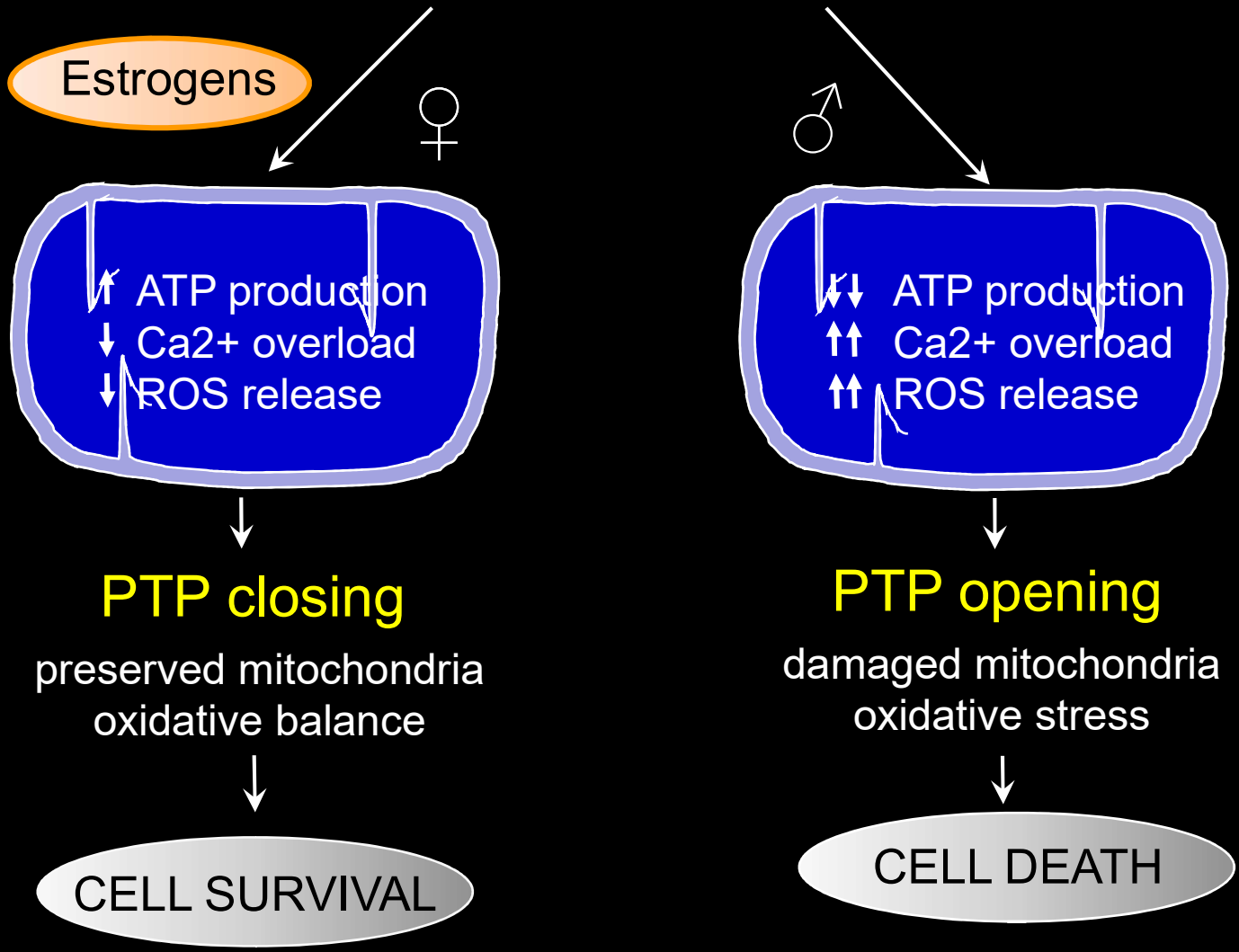
PROGESTERON A PROTEKCE MYOKARDU
možnosti

zmenšuje rozsah infarktu myokardu pouze u samic; možné mechanizmy

- ↓ zánět
- ↓ oxidativní stres
- ↓ apoptosa

Vipin et al., 2007

SEX AND BLOCKADE OF THE MPT PORE
I/R injury



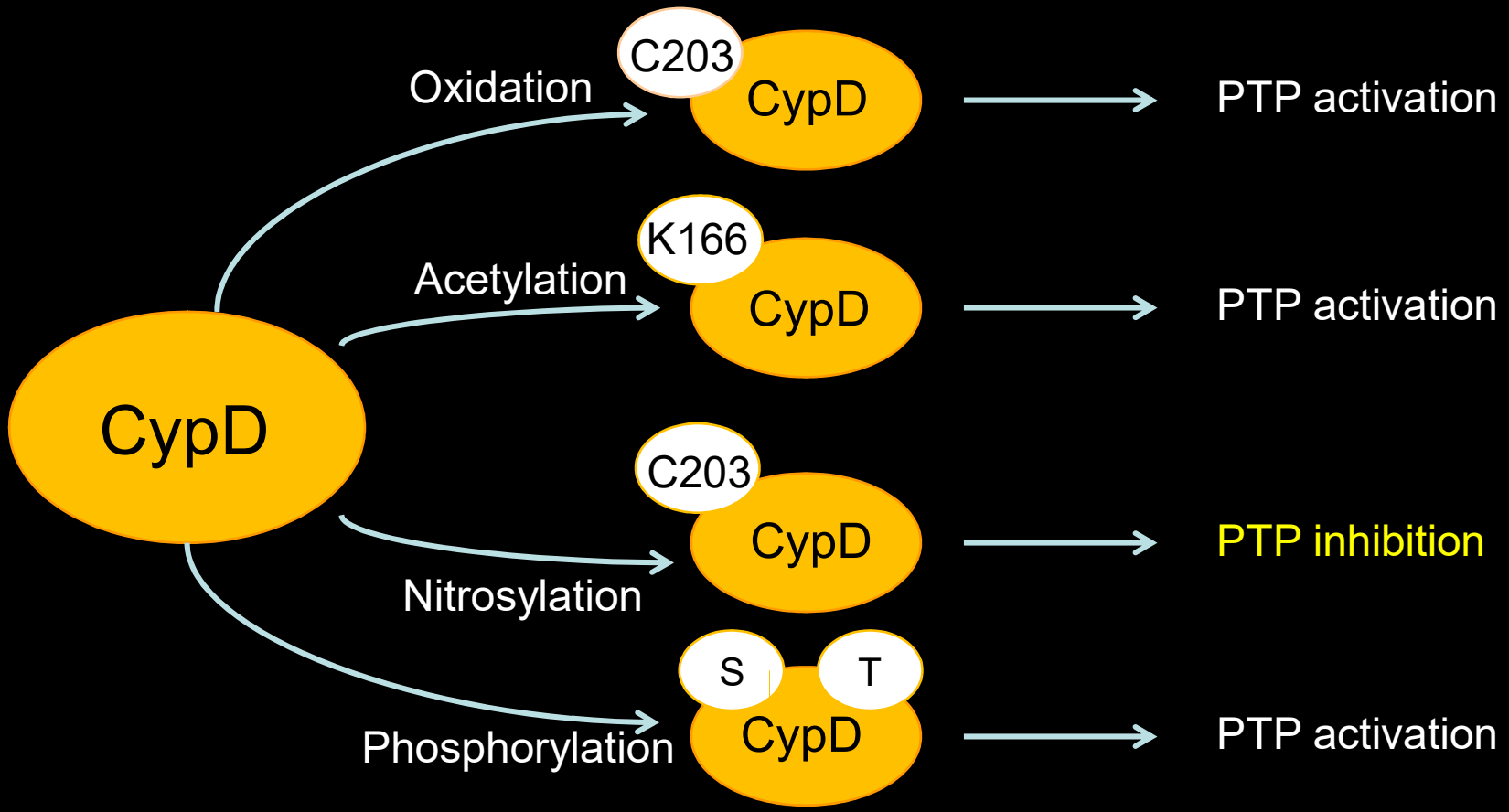
Ventura-Clapier et al., 2017

ANDROGENY

- ↑ riziko ICHS
- ↑ hypertense
- ↑ homocystein
- ↑ synteza katecholaminů
- ↑ endothelin – 1
- srdeční hypertrofie

Dubey et al., 2002

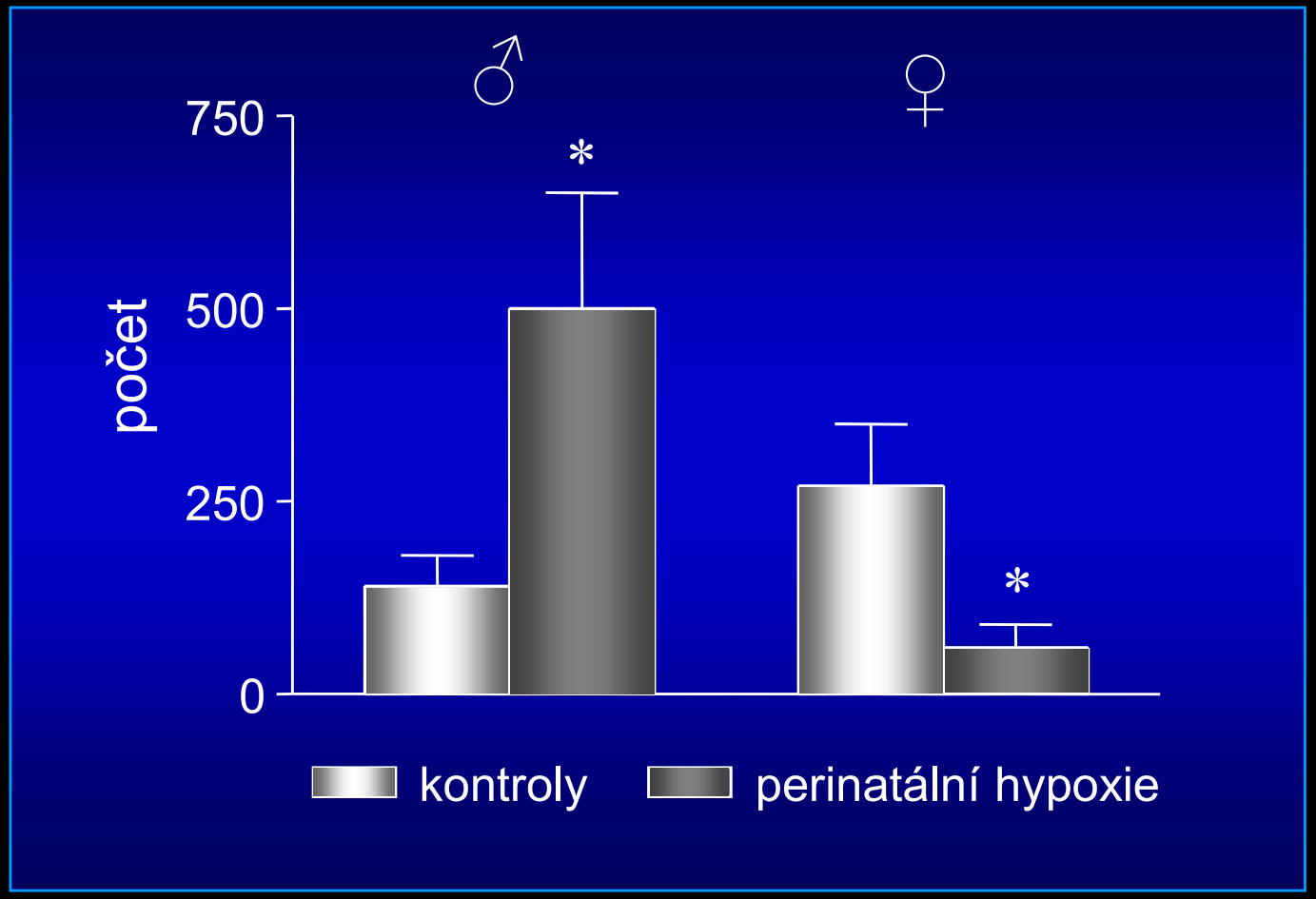
MAIN POST-TRANSLATIONAL MODIFICATIONS OF CYCLOPHILIN D



Javadov et al., 2017

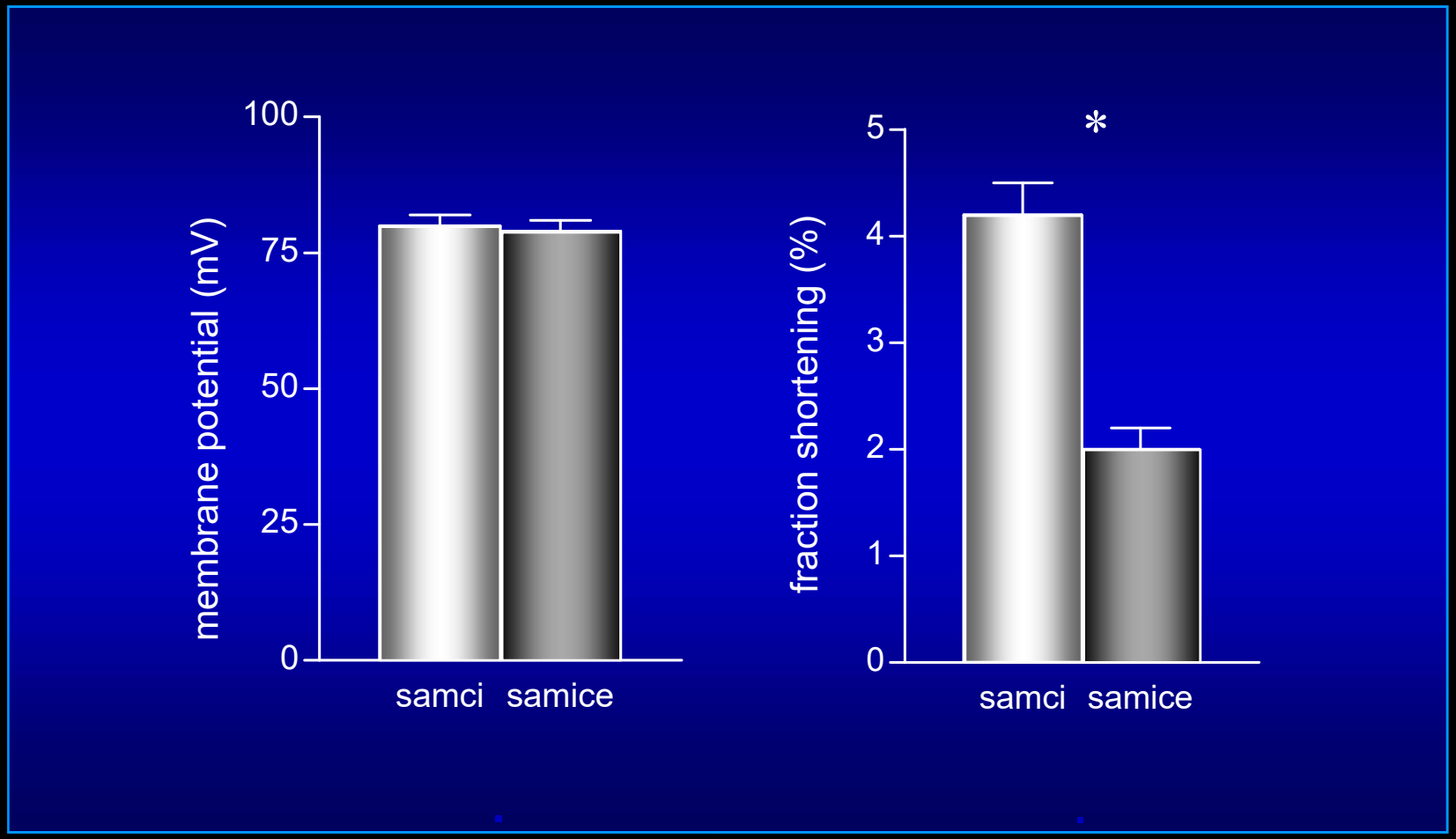
POZDNÍ DŮSLEDKY ČASNÉ HYPOXIE - ODOLNOST SRDCE K ISCHEMII

ischemické arytmie



Netuka a spol. 2006

SEX DIFFERENCES
contractile parameters - isolated myocytes



Farrell a spol. 2010

ČESKÁ KARDIOLOGICKÁ SPOLEČNOST

WWW.KARDIO-CZ.CZ

Deklarace konfliktu zájmů

	Nemám konflikt zájmů	Mám konflikt zájmů	Specifikace konfliktu (vyjmenujte subjekty, firmy či instituce, se kterými Vaše spolupráce může vést ke konfliktu zájmů)
Zaměstnanecký poměr	✔		
Vlastník / akcionář	✔		
Konzultant	✔		
Přednášková činnost	✔		
Člen poradních sborů (advisory boards)	✔		
Podpora výzkumu / granty	✔		
Jiné honoráře (např. za klinické studie či registry)	✔		