UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

RESEARCH

CNS Effects of Aldosterone :

Critical Roles in salt-sensitive hypertension and CHF.

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Renin–Angiotensin – Aldosterone System

- Circulatory RAAS
- Tissue RAAS: - arteries, heart
  - kidneys
  - brain

Aldosterone, Ang II and the CNS

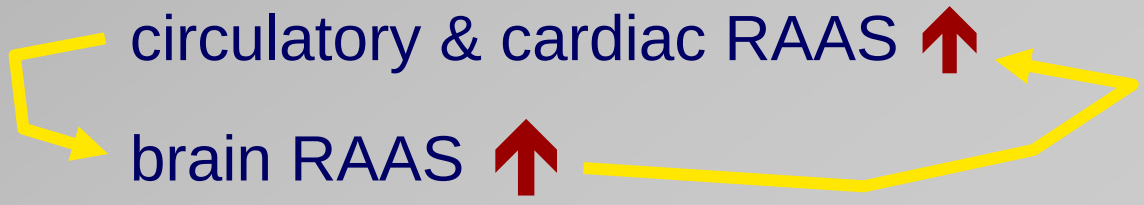
- **Source:** circulation or locally produced?
- **Function:** irrespective of source

Salt – Sensitive hypertension : circulatory RAAS ↓

brain RAAS ↑

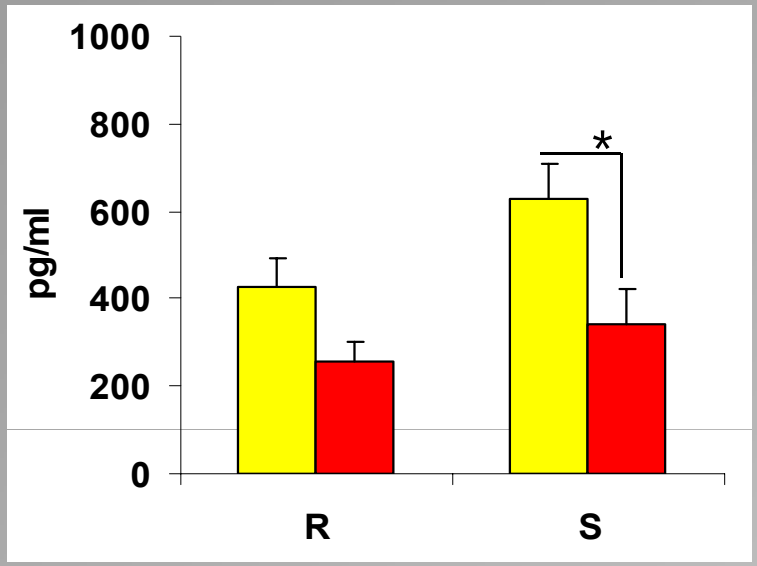
CHF post MI : circulatory & cardiac RAAS ↑

brain RAAS ↑

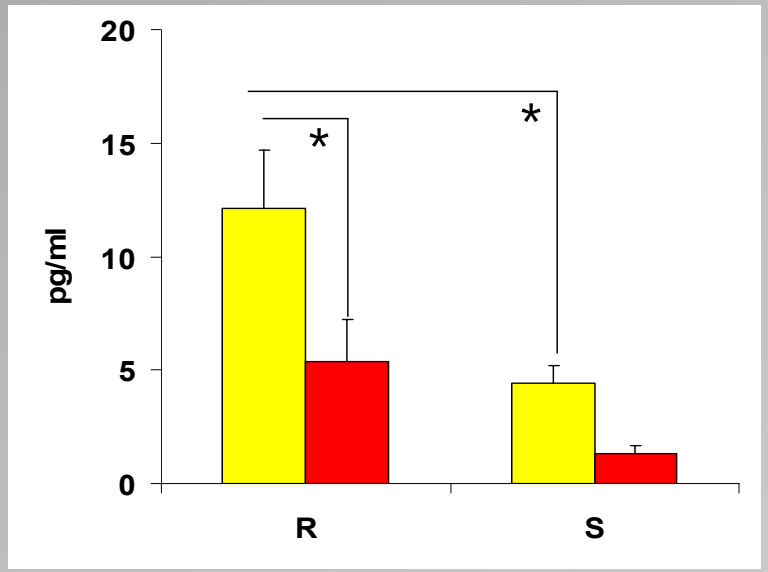


Salt and Circulatory RAAS in Dahl R and S rats.

Plasma Aldosterone



Plasma Ang II

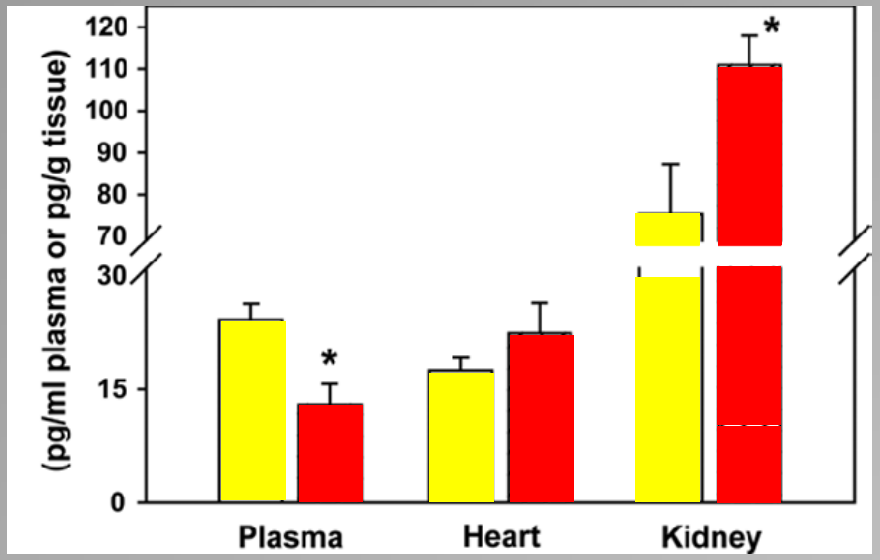


Reg Salt

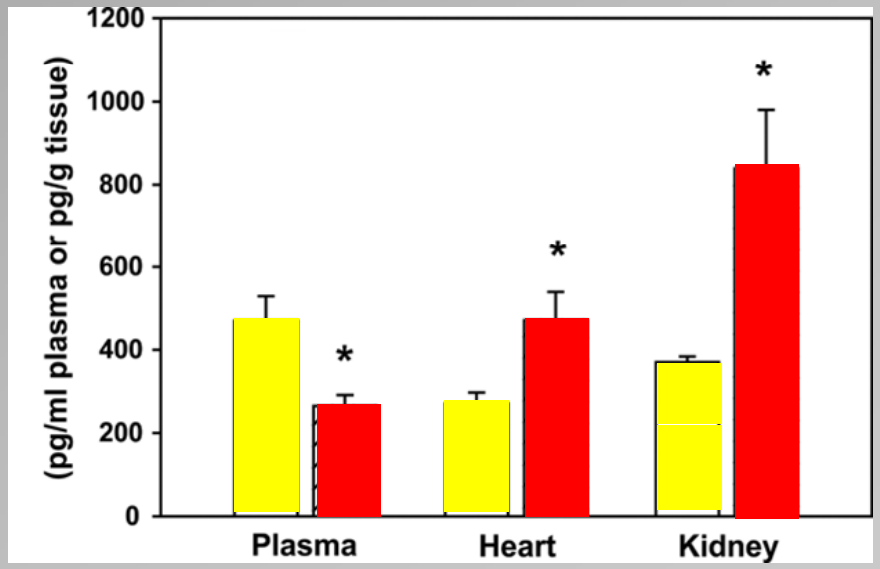
High Salt for 4 weeks

Salt and tissue RAAS in Dahl S

Angiotensin II



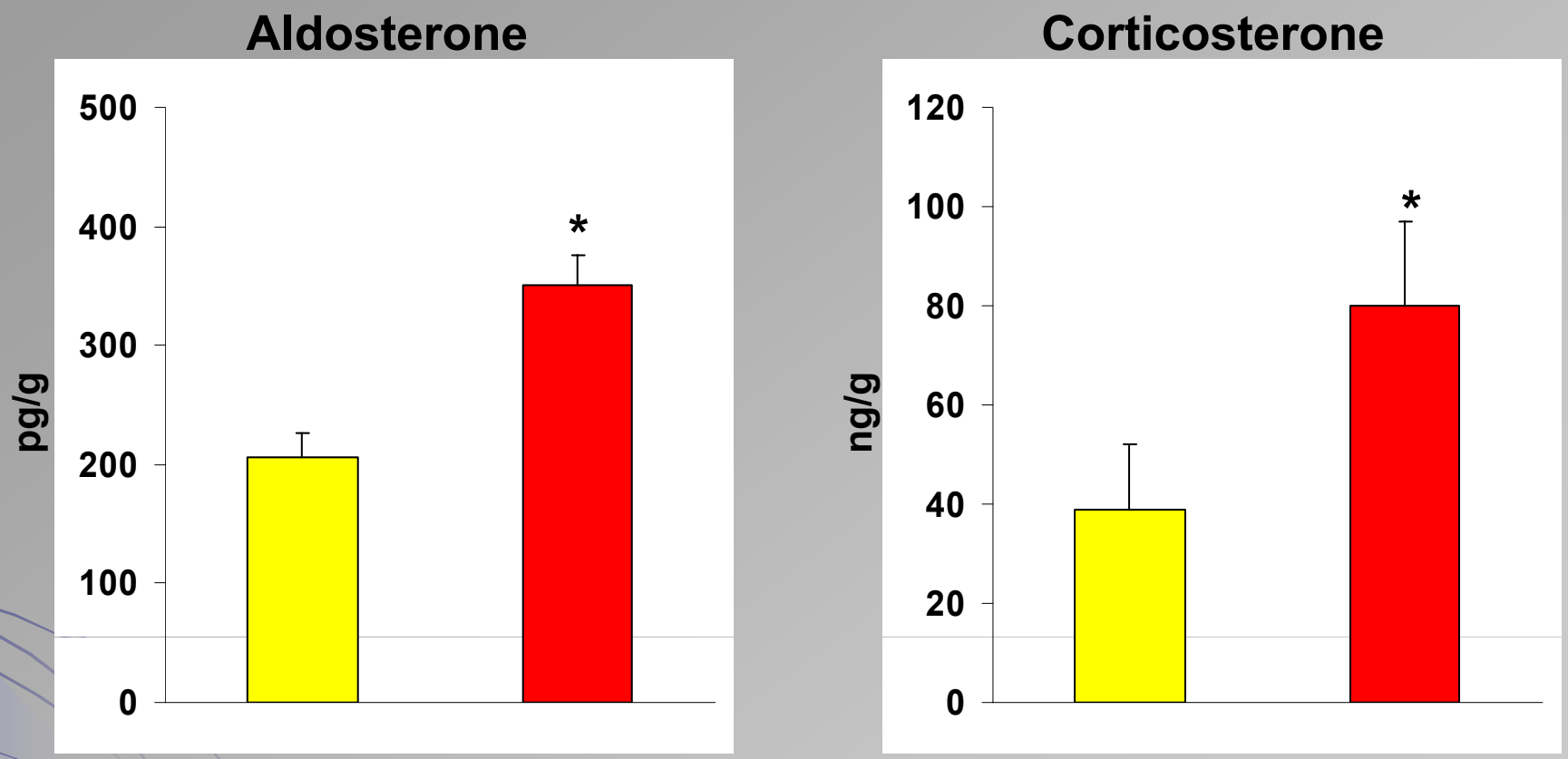
Aldosterone



Control
8% for 3 wks

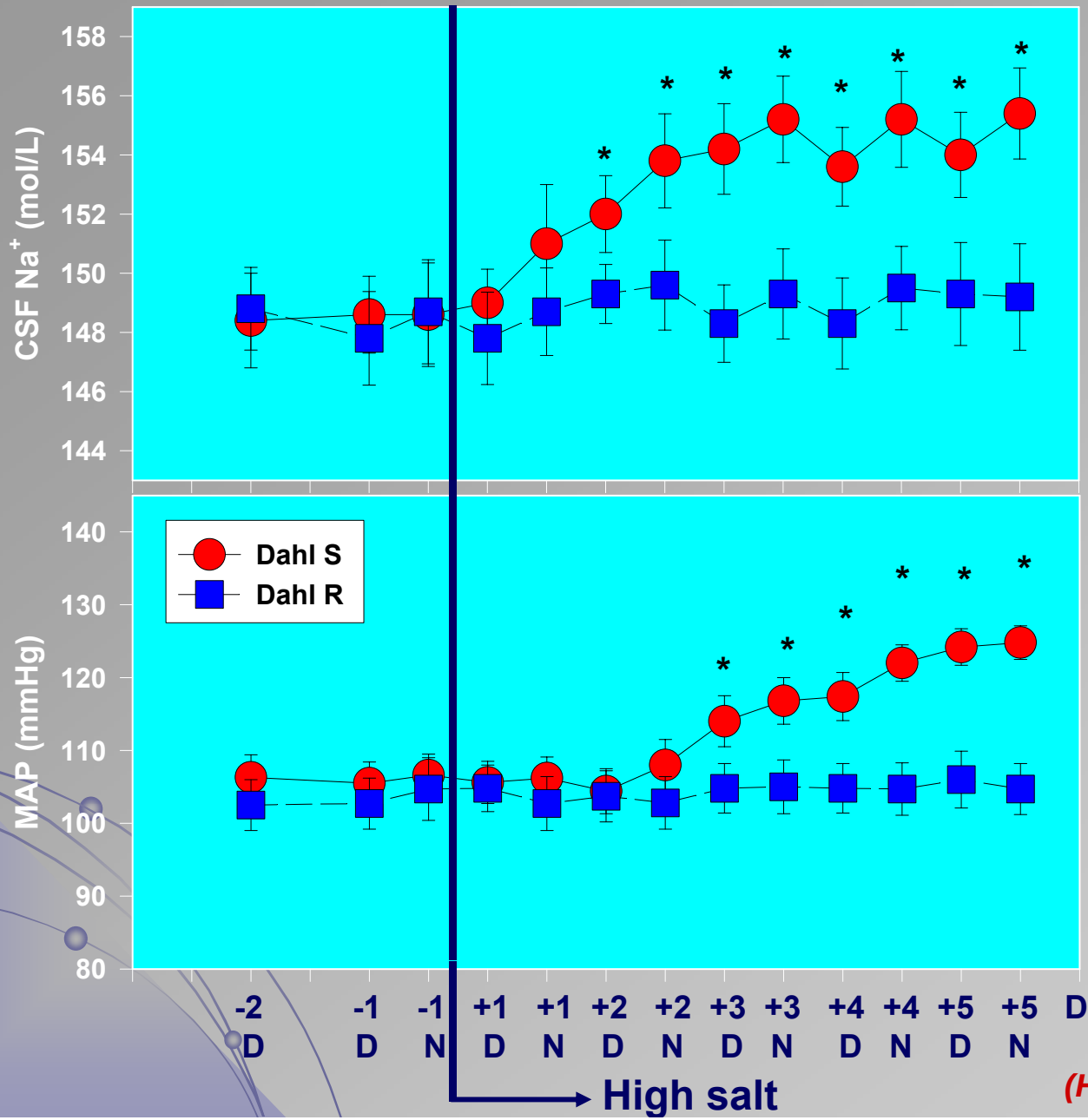
(Bayorh et al. Clin Exper Hypertens 2005)

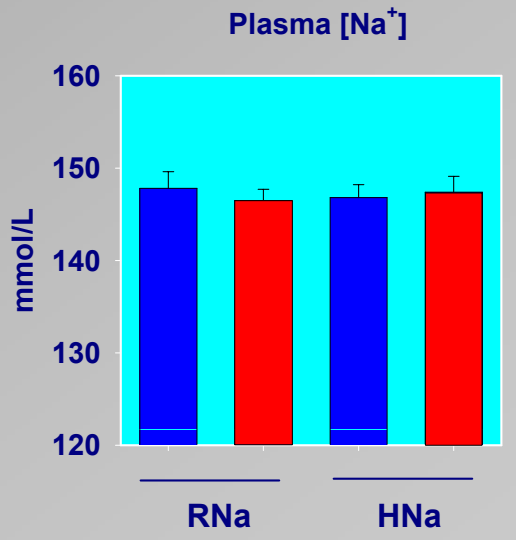
Salt and hypothalamic aldosterone and corticosterone in Dahl S



* p<0.05 vs RNa

CSF [Na^+] & MAP on high salt in Dahl S versus R

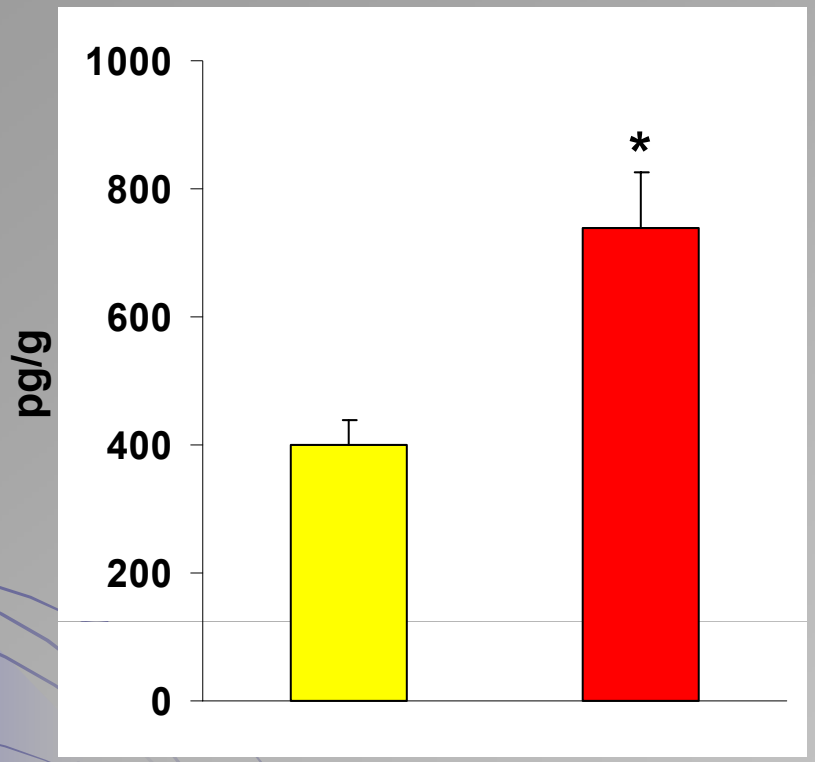


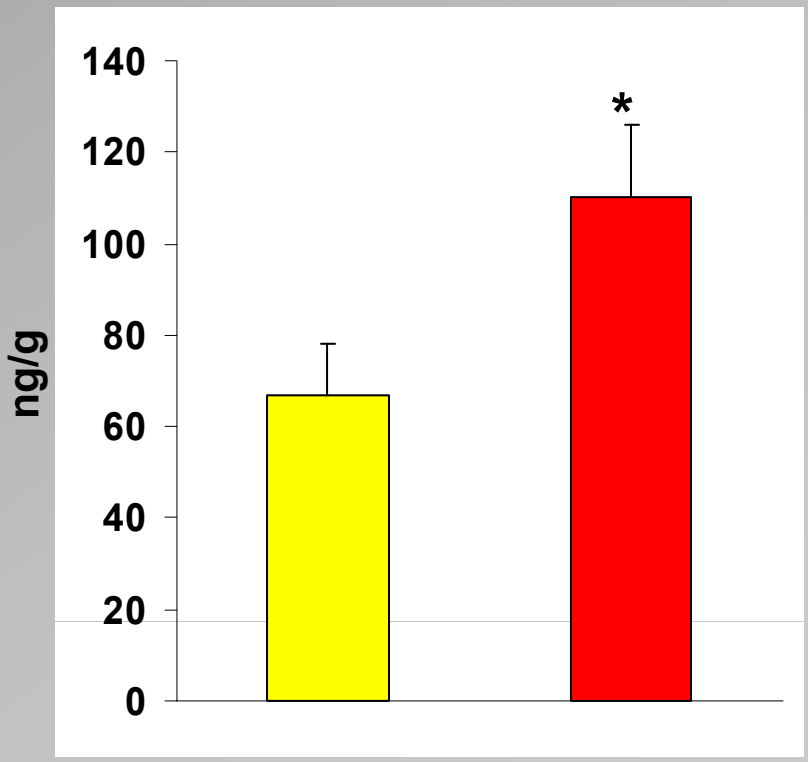


* $p<0.05$ vs RNa

(Huang et al. Am J Physiol 2004)

CSF [Na^+] ↑ and hypothalamic aldosterone and corticosterone



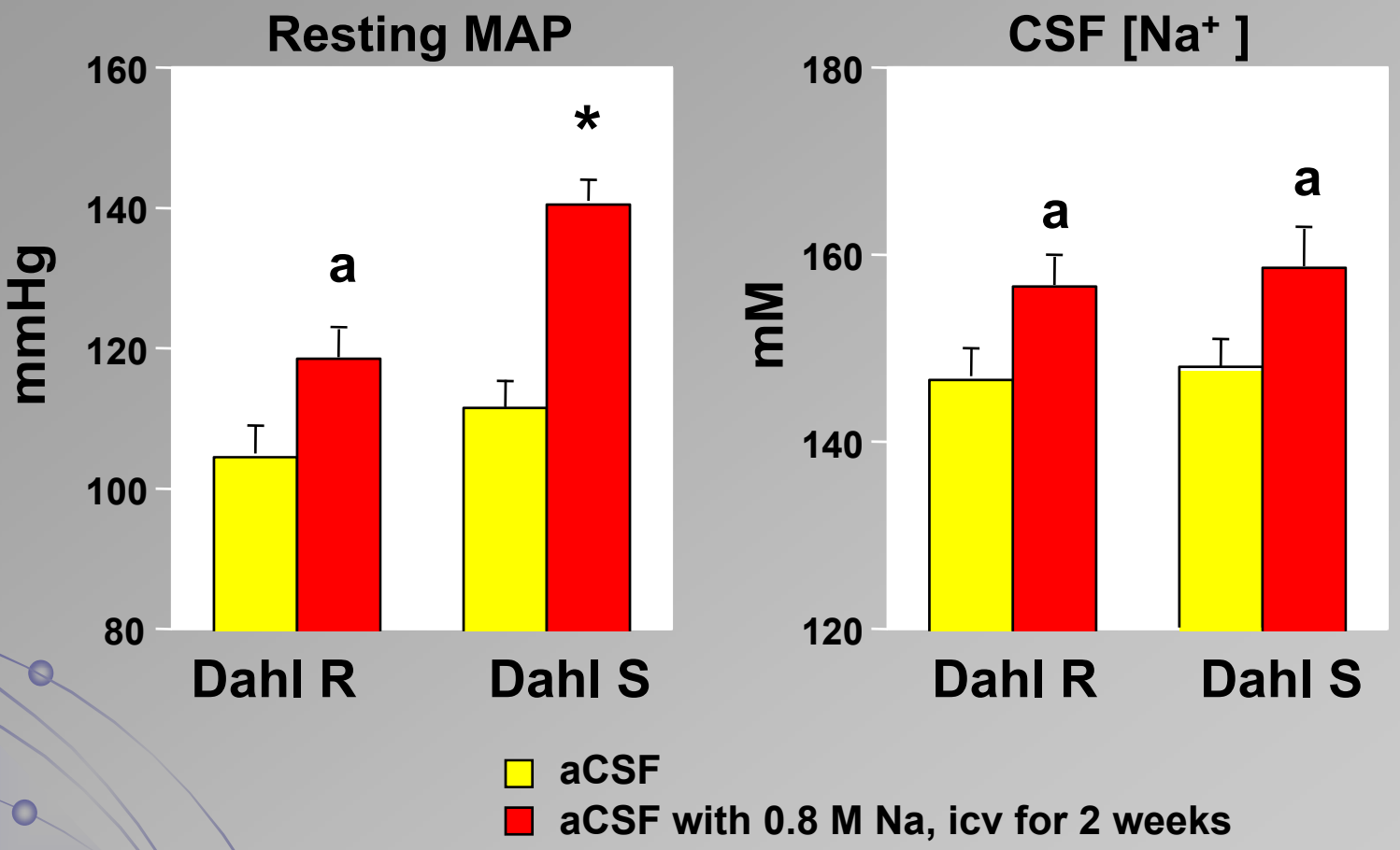


Icv aCSF

Icv Na^+ rich aCSF for 2 weeks

* p<0.05 vs others

Enhanced BP ↑ to CSF [Na^+] in Dahl S vs R



* p< 0.05 vs other a: p< 0.05 vs aCSF

(Huang et al. Am J Physiol 2001)

Activation of neural mechanisms by high salt in Dahl S

- **Genetic dysregulation of CNS Na^+-homeostasis :**

Enhanced Na^+ - transport from blood into CSF

↓

CNS aldosterone ↑

↓

Neuronal activation ↑

↓

Sympathetic activity ↑

↓

Hypertension

Functional role of aldosterone in the CNS

- **Central MR Blockade**

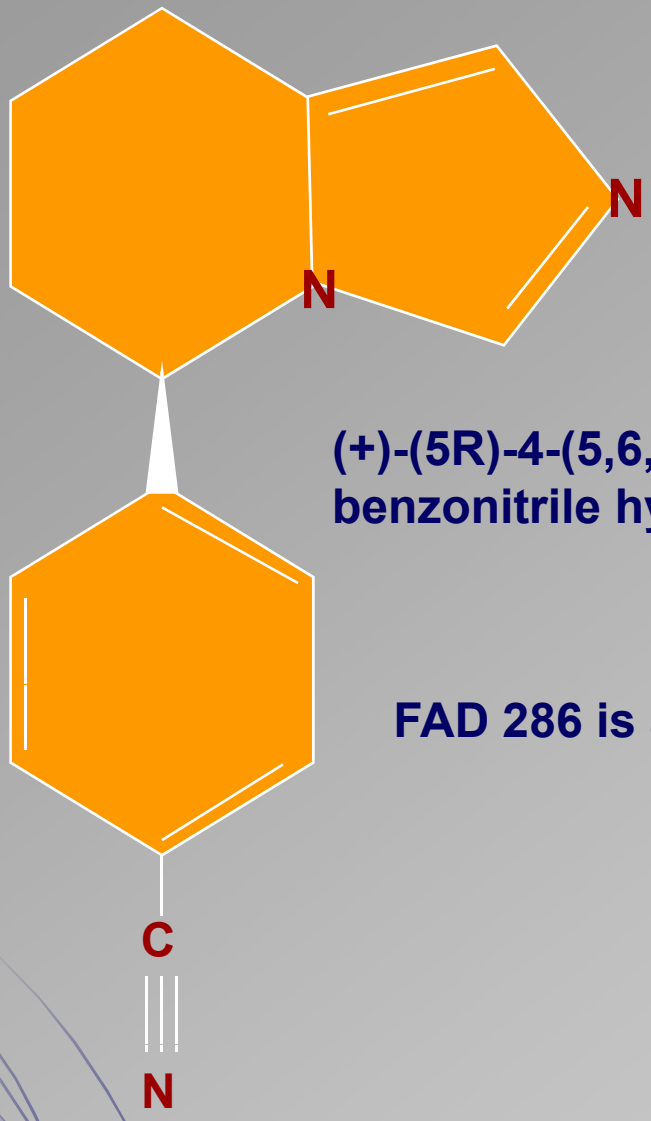
  Limitations: not specific for aldosterone

  not specific for locally produced steroid

- **Aldosterone synthase inhibition**

- **1 vs 2 → MR activation due to locally produced aldosterone.**

Aldosterone synthase inhibitor



(+)-(5R)-4-(5,6,7,8-terahydroimidazo[1,5-a]pyridin-5-yl) benzonitrile hydrochloride

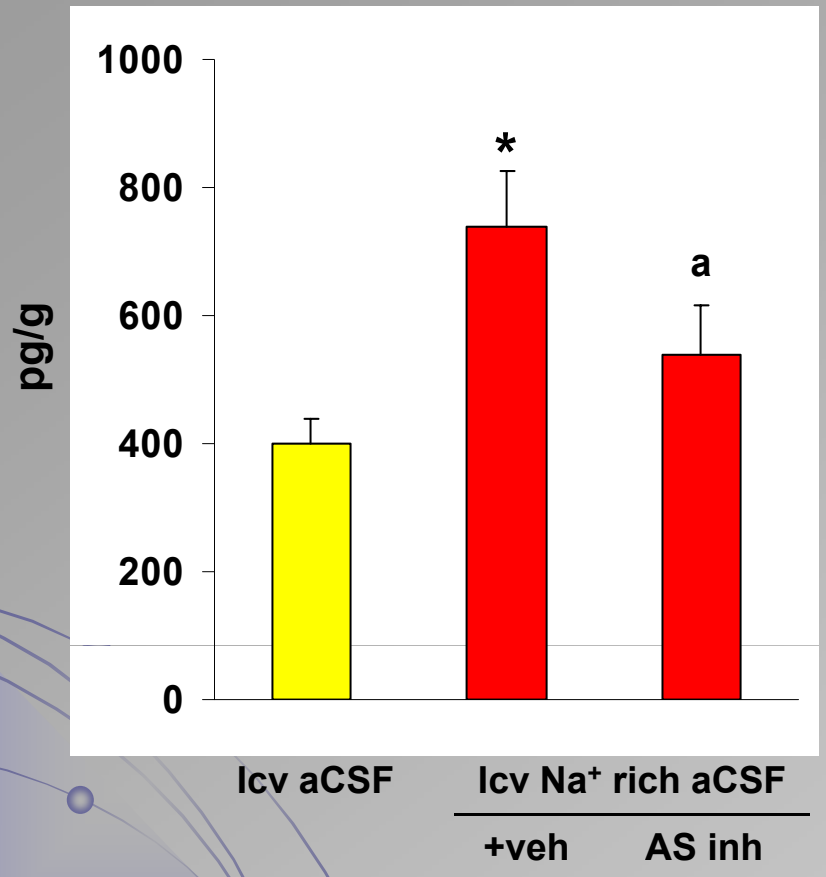
FAD 286 is a single (+) -enantiomer

(Fiebeler et al. Circulation 2005)

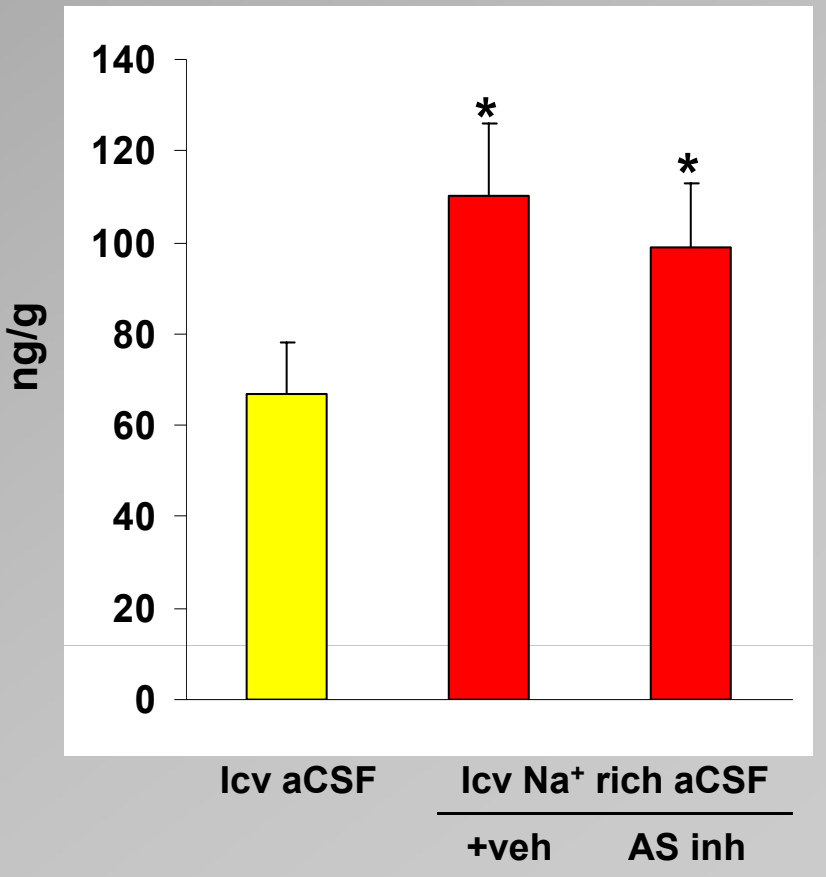
CSF [Na^+] ↑ and hypothalamic aldosterone and corticosterone

Central aldosterone synthase inhibition

Aldosterone



Corticosterone



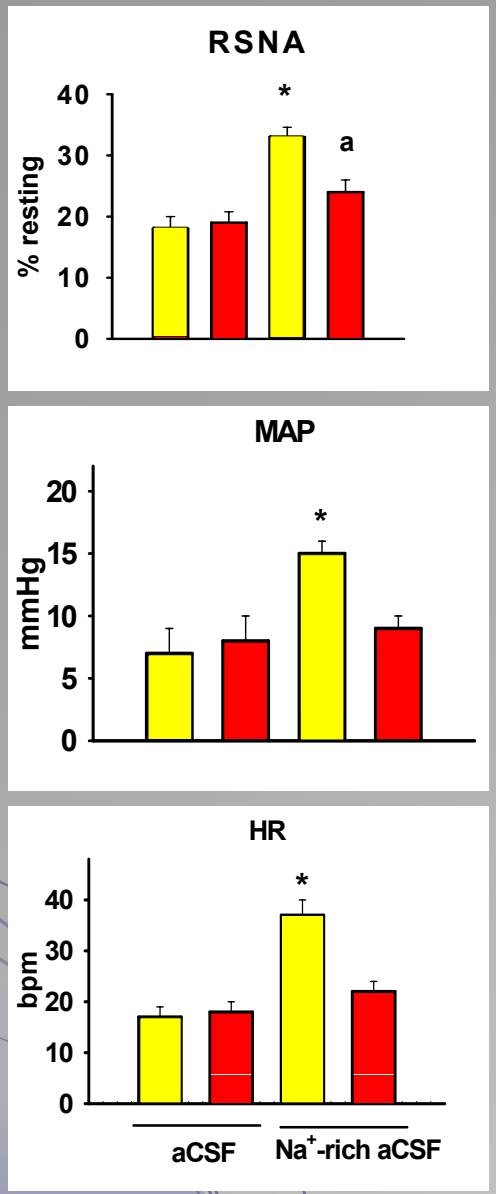
* p<0.05 vs others

100 µg/kg/day

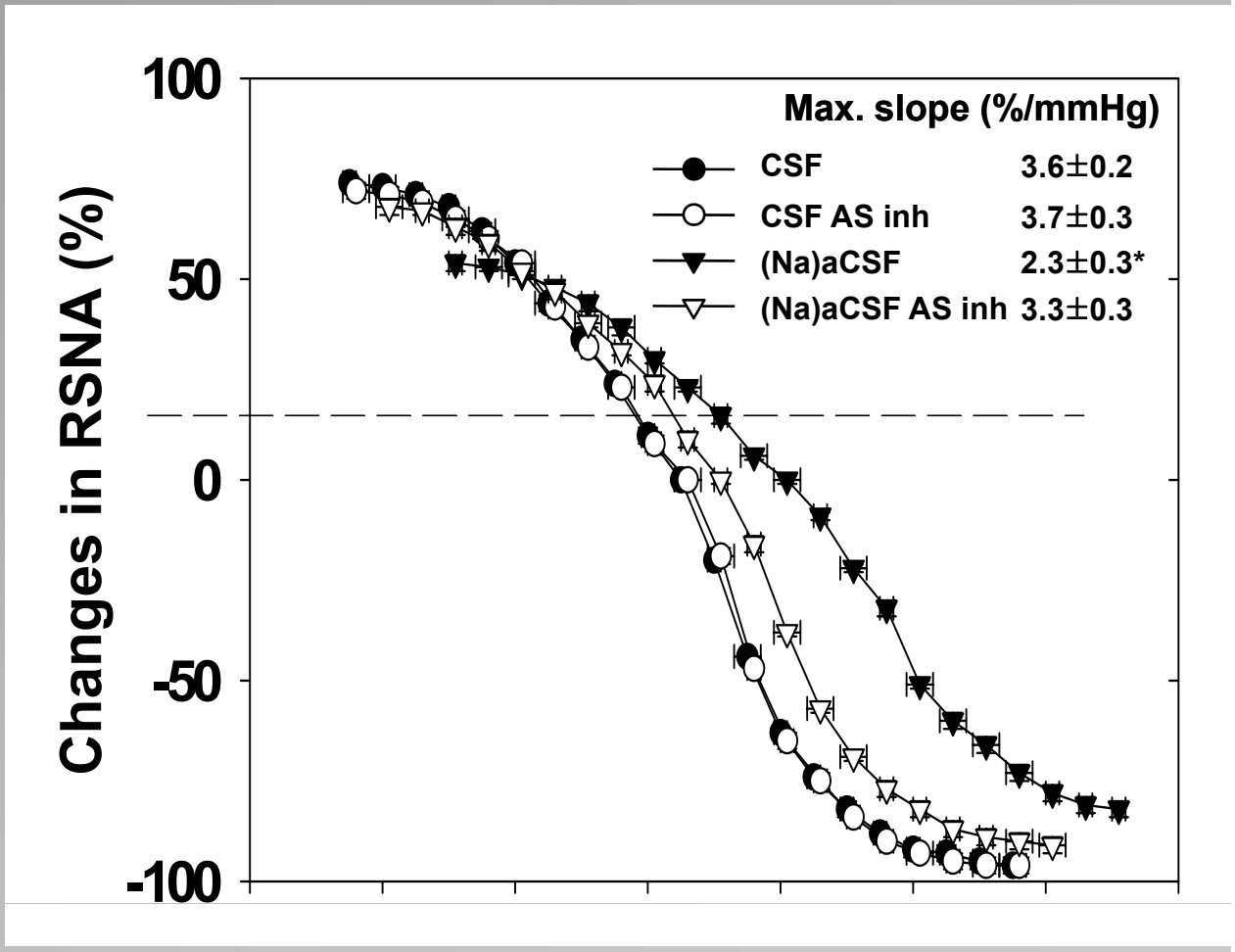
CSF [Na+] and sympathetic activity

Central aldosterone synthase inhibition

Air Stress



Baroreflex control of RSNA

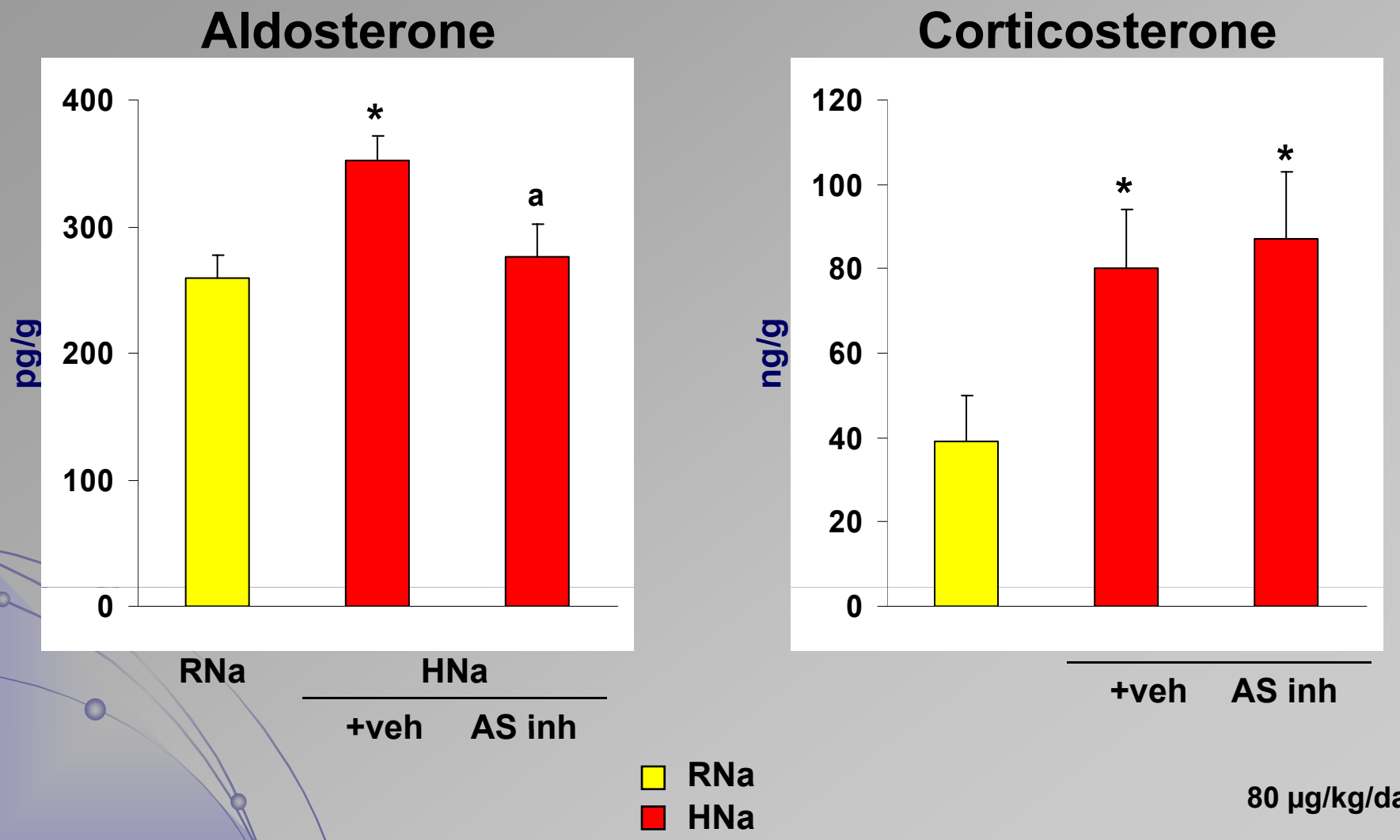


* p<0.05, vs aCSF with/without AS inh; a: p<0.05, vs Na+ -rich aCSF+veh

* p<0.05, vs others

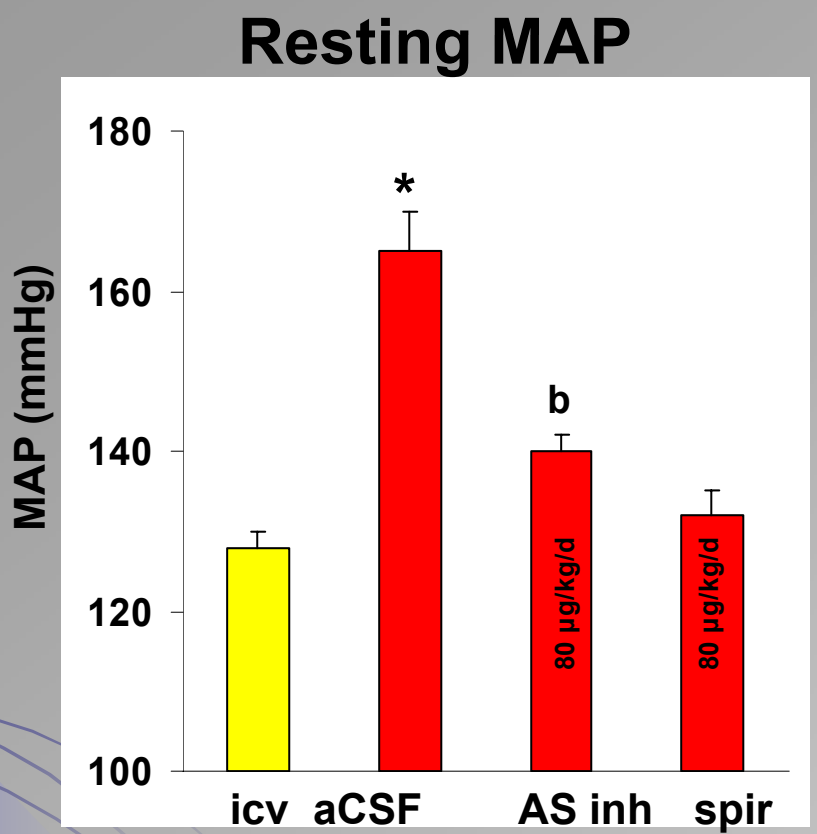
Dahl S on HNa for 4 weeks

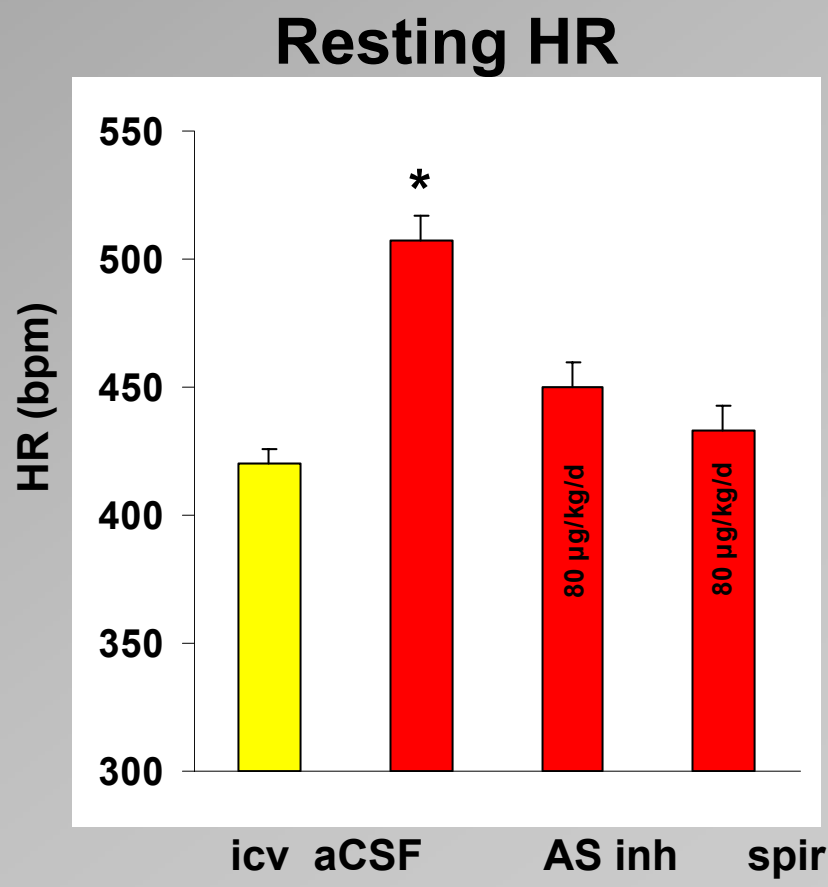
Central aldosterone synthase inhibition



BP and HR in Dahl S on high salt

Central aldosterone synthase inhibitor vs MR blocker





*p<0.05 vs others
b: vs RNa+aCSF

CONCLUSION

- **Central blockade of aldosterone synthesis or MR prevents to a large extent the salt-induced hypertension in Dahl S.**

  → ***locally in the CNS produced aldosterone via MR plays a major role***

New Paradigm:

- **High salt diet via CSF [Na^+] ↑ <u>activates</u> aldosterone – MR and sodium transport in the CNS.**

Shift in Paradigm from Kidney to CNS

Old Paradigm:

- **Intrinsic changes in renal function lead to a defect in the kidneys' ability to excrete salt and to an increase in BP until sodium balance is restored.**

"the Guyton Dogma"

New Paradigm:

- **Kidneys of genetic models of salt – induced hypertension do not require hypertension, and the animals live happy *(happier ?)* without.**
- **Kidneys are a "sensor and /or effector" organ like the arteries and the heart, and in general the CNS determines the set – point of BP.**

Changing Face of CHF

Past and Present

Hypertension → LVH → LV dysfunction → CHF

Present and Future

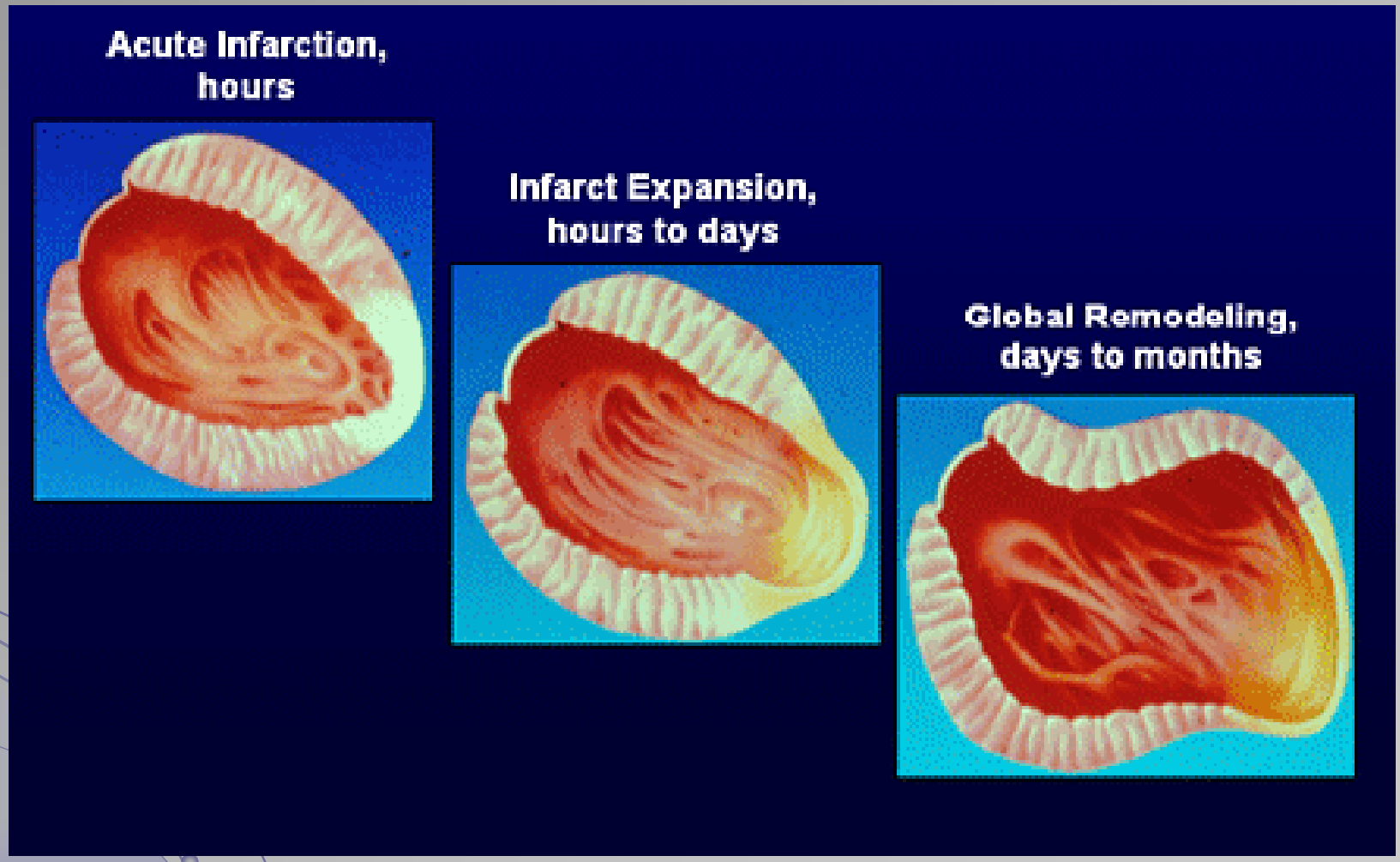
Hypertension
Dyslipidemia → Atherosclerosis → MI → LV remodeling/dysfunction
Diabetes ↓
Smoking **CHF**

ALLHAT

CHF mortality still very high

(Davis et al. Circulation, 2006)

LV remodeling following MI



Stimuli for cardiac remodeling post MI

Cardio-centric view: diastolic wall stress ↑

systolic wall stress ↑

→ progressive LV dilation and hypertrophy

Cardio-renal view: reduced cardiac output and renal perfusion

→ activation of circulatory RAAS

salt and water retention

Neuro-hormonal view: sympathetic hyperactivity

circulatory, cardiac, renal RAAS ↑

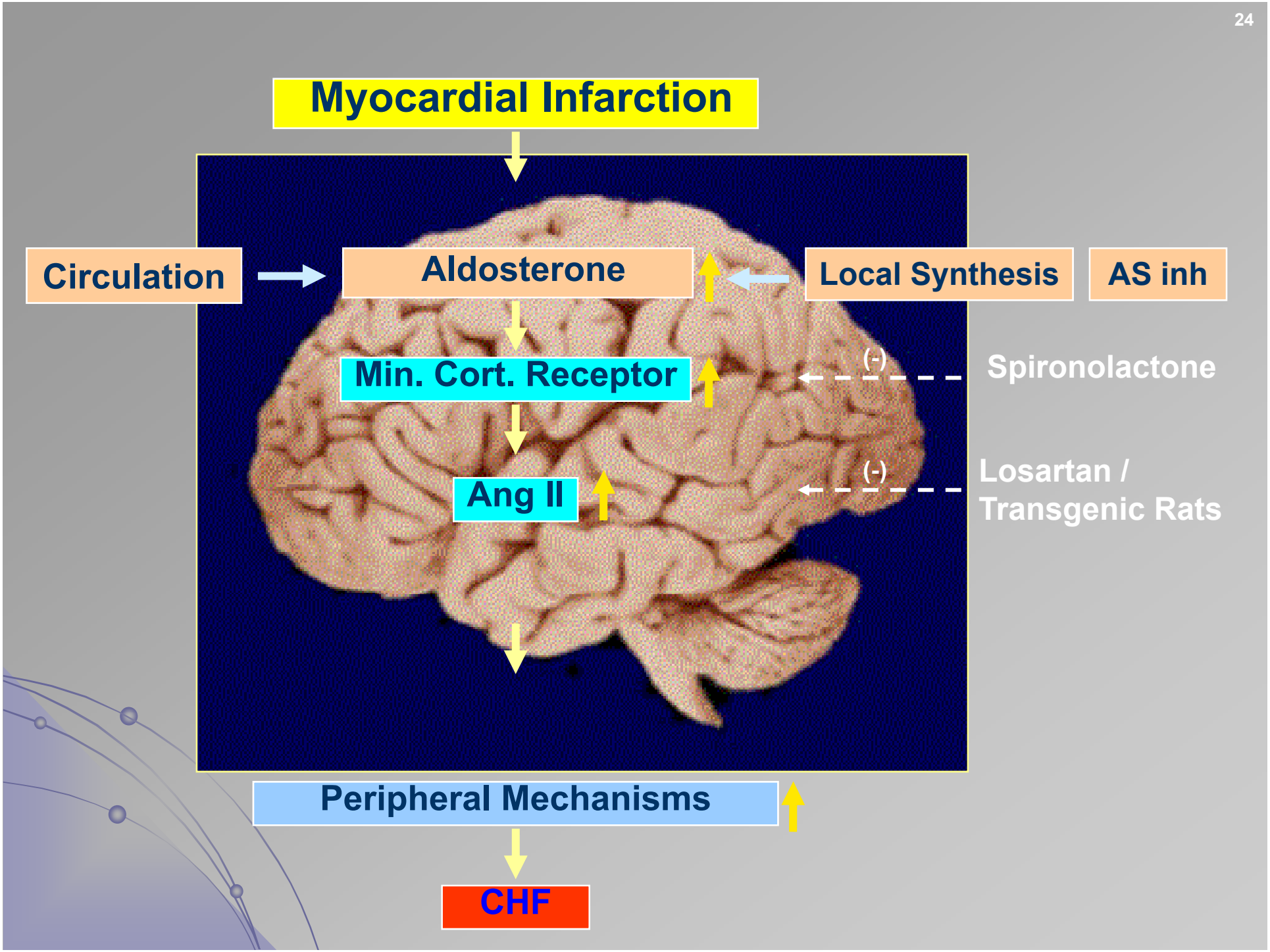
vasopressin ↑

pro-inflammatory cytokines ↑

CNS and CHF Post MI

Brain RAAS: locally produced aldosterone
➔ MR & AT_1–rec stimulation

- **sympathetic activity**
  & other peripheral mechanisms ↑
- **cardiac remodeling / dysfunction post MI**


Myocardial Infarction
Circulation
Aldosterone
Local Synthesis
AS inh
Min. Cort. Receptor
(-)
Spironolactone
Ang II
(-)
Losartan /
Transgenic Rats
Peripheral Mechanisms
CHF

Transgenic Rats

To assess the role of Angiotensins locally produced in the brain

Glial fibrillary acidic protein promoter + **Angiotensinogen Antisense DNA**

↓

Angiotensinogen antisense RNA (glia only)

↓

Angiotensinogen mRNA ⊗ **Angiotensinogen**

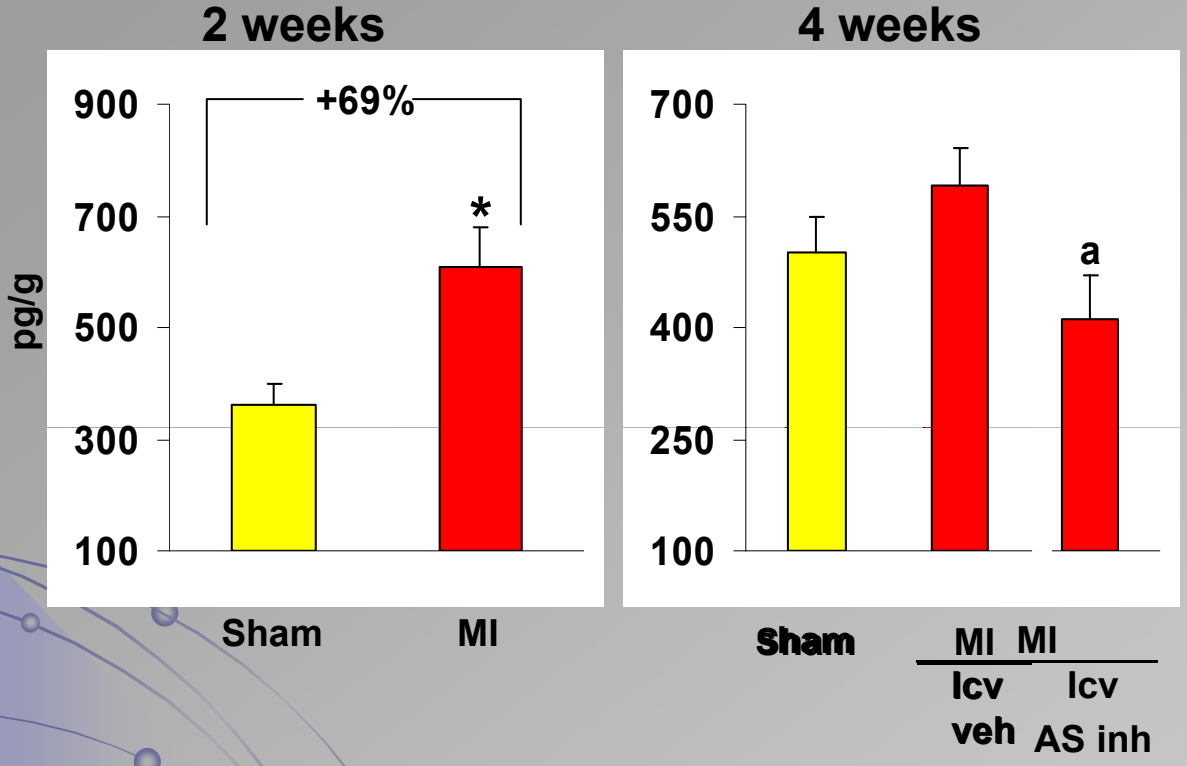
	SD	TG Rats
Hypothalamic Angiotensinogen, pmol/mg protein	1.5	0.1
Plasma Angiotensinogen, nmol/ml	1.4	1.4

(Schinke et al. PNAS, 1999)

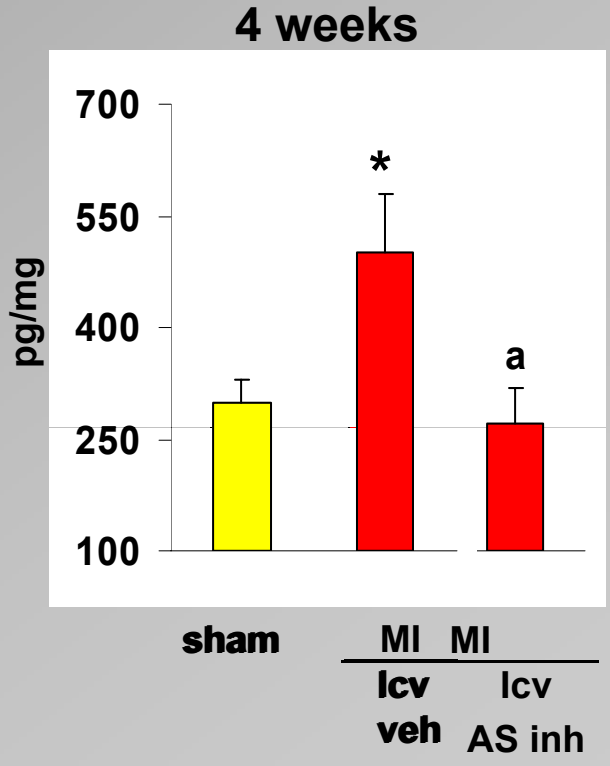
CNS aldosterone post MI

Central aldosterone synthase inhibitor

Hypothalamus



Hippocampus

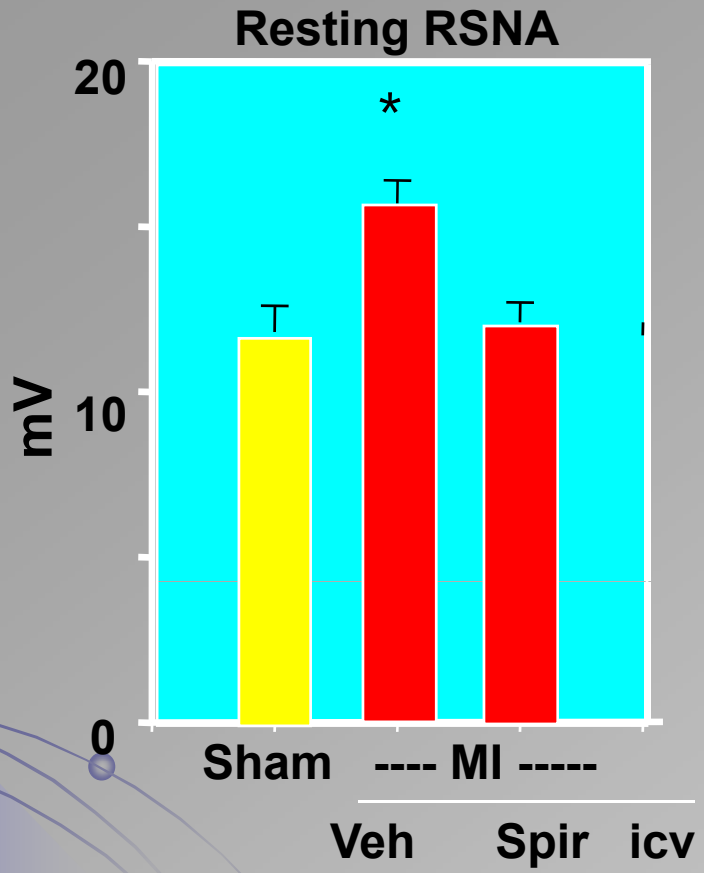


* p ≤ 0.05

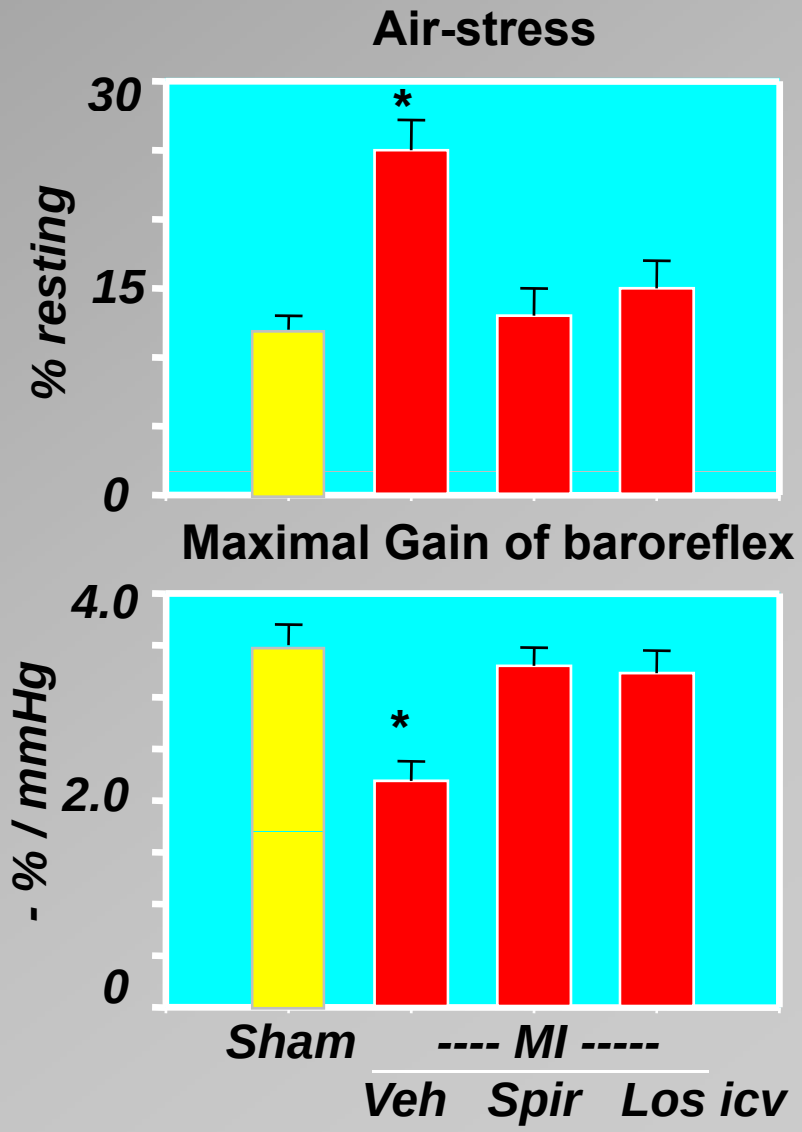
Sympathetic Hyperactivity in CHF post MI

- set point ↑
- reactivity ↑
- baroreflex-control ↓

Blockade of Brain MR–AT_1-rec prevents sympathetic hyperactivity post MI

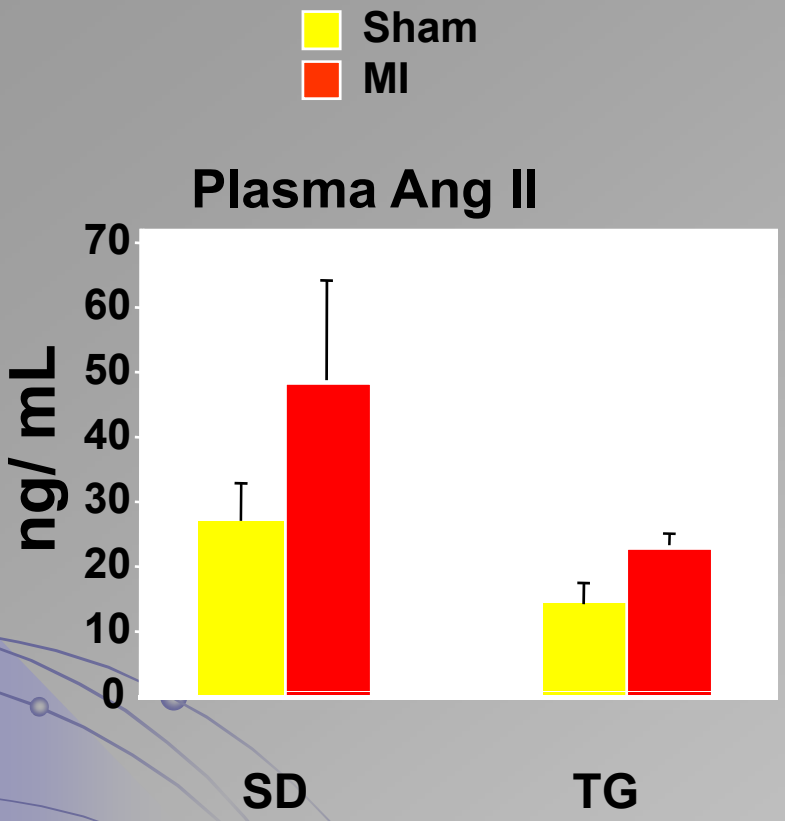


(Francis et al. AJP, 2003)

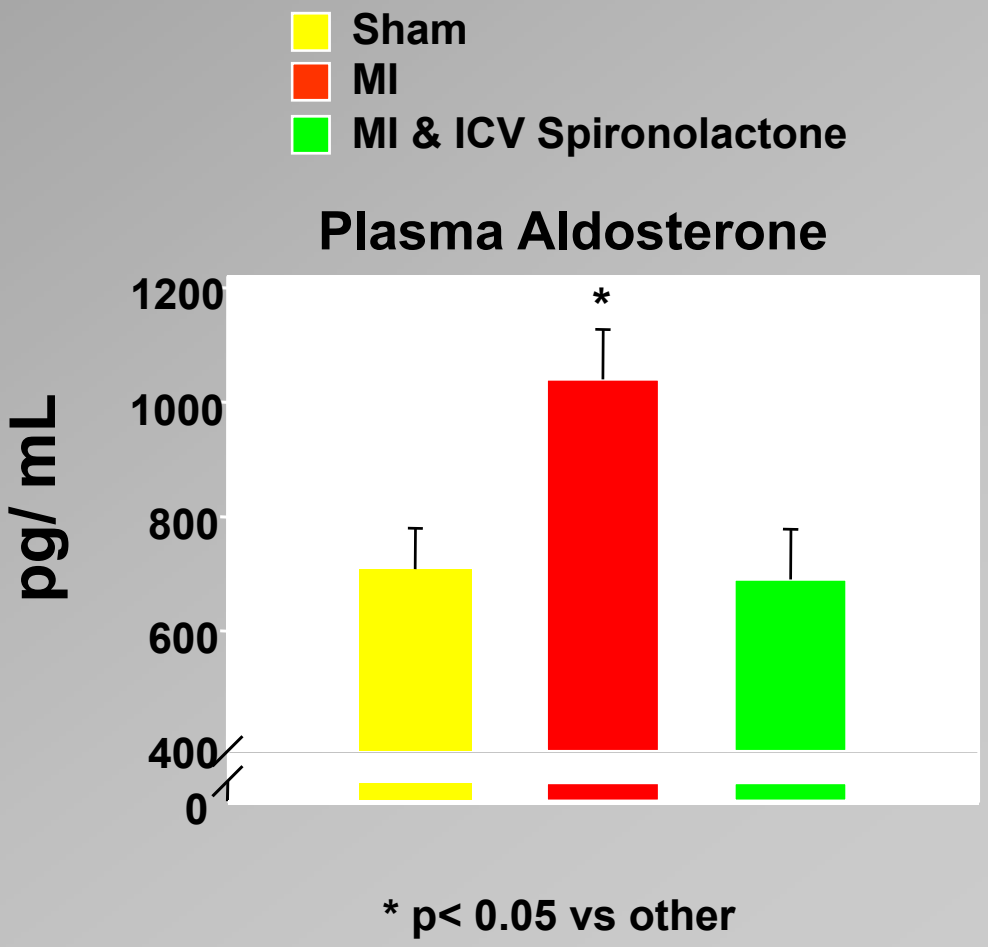


(Huang et al. AJP, 2005)

Blockade of brain RAAS prevents plasma Ang II and aldosterone ↑ post MI



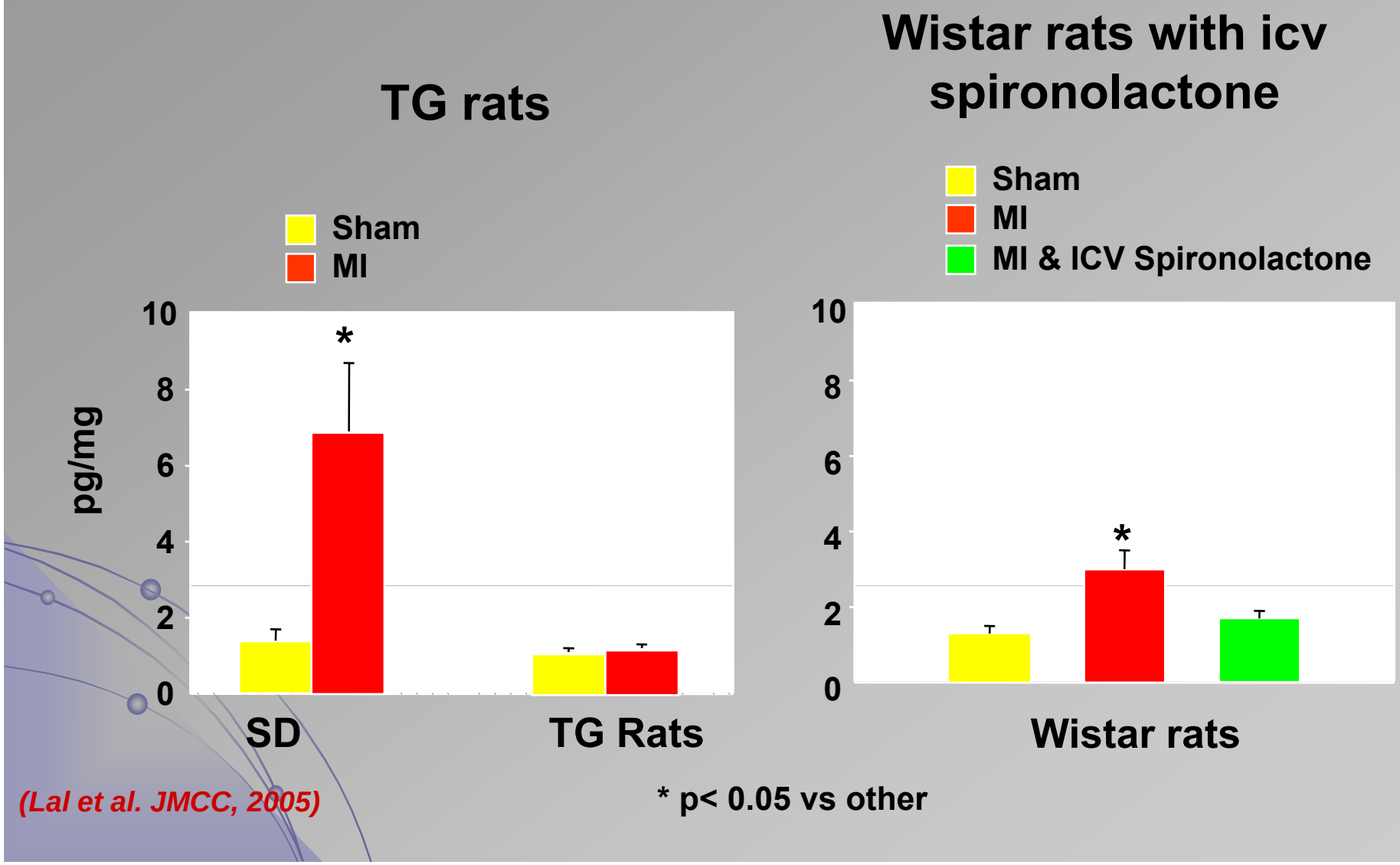
(Wang et al. Circ Res, 2004)



* p< 0.05 vs other

(Lal et al. Card vasc Res, 2004)

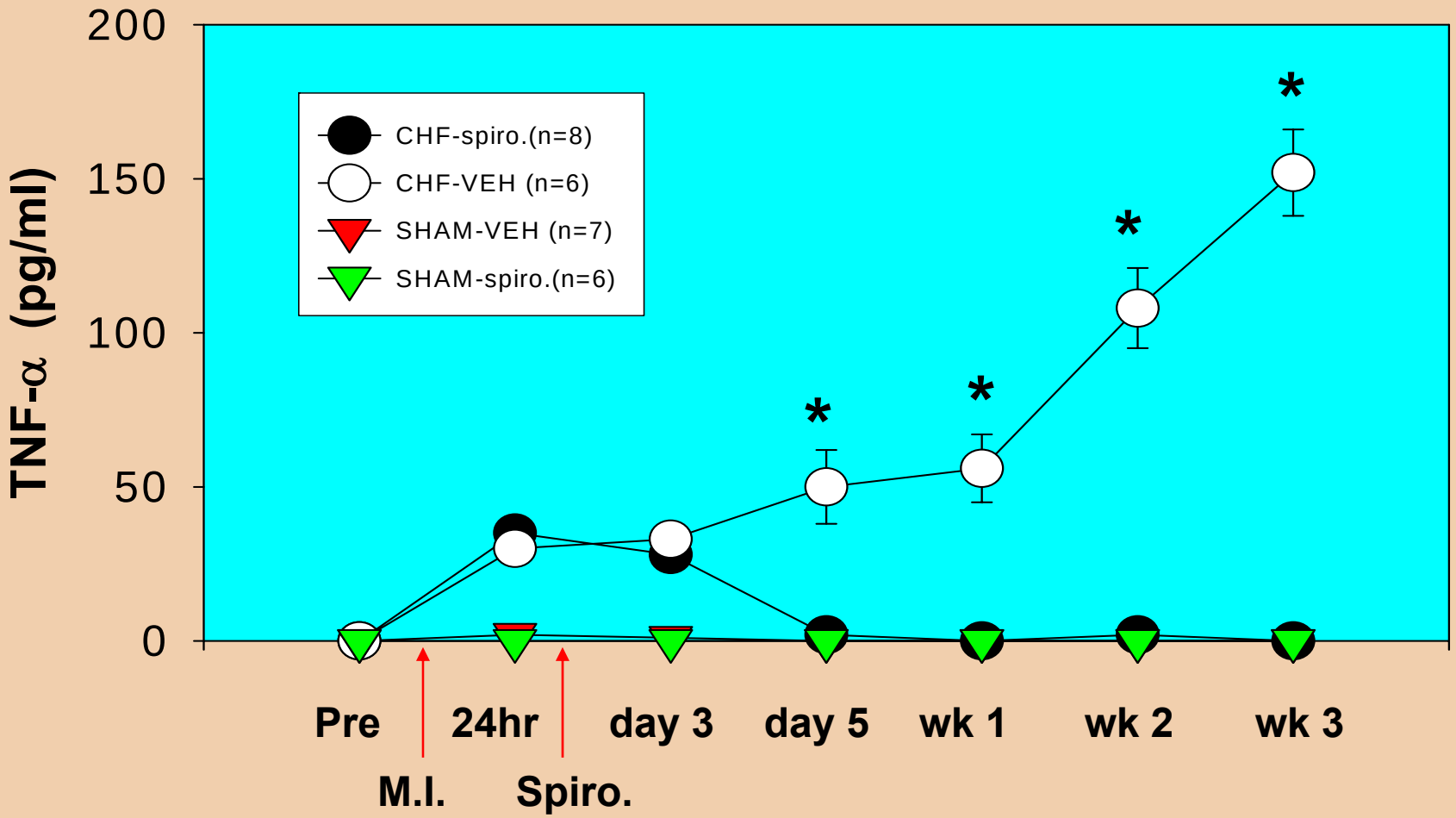
Blockade of brain RAAS prevents LV aldosterone ↑ post MI



(Lal et al. JMCC, 2005)

* p< 0.05 vs other

Blockade of brain MR prevents plasma TNF–α ↑ post MI



* p<0.05, vs other

(Francis et al, AJP, 2004)

CNS and CHF Post MI

Brain RAAS: locally produced aldosterone
➔ MR & AT_1–rec stimulation

- **sympathetic activity**
  & other peripheral mechanisms ↑
- **cardiac remodeling / dysfunction post MI**

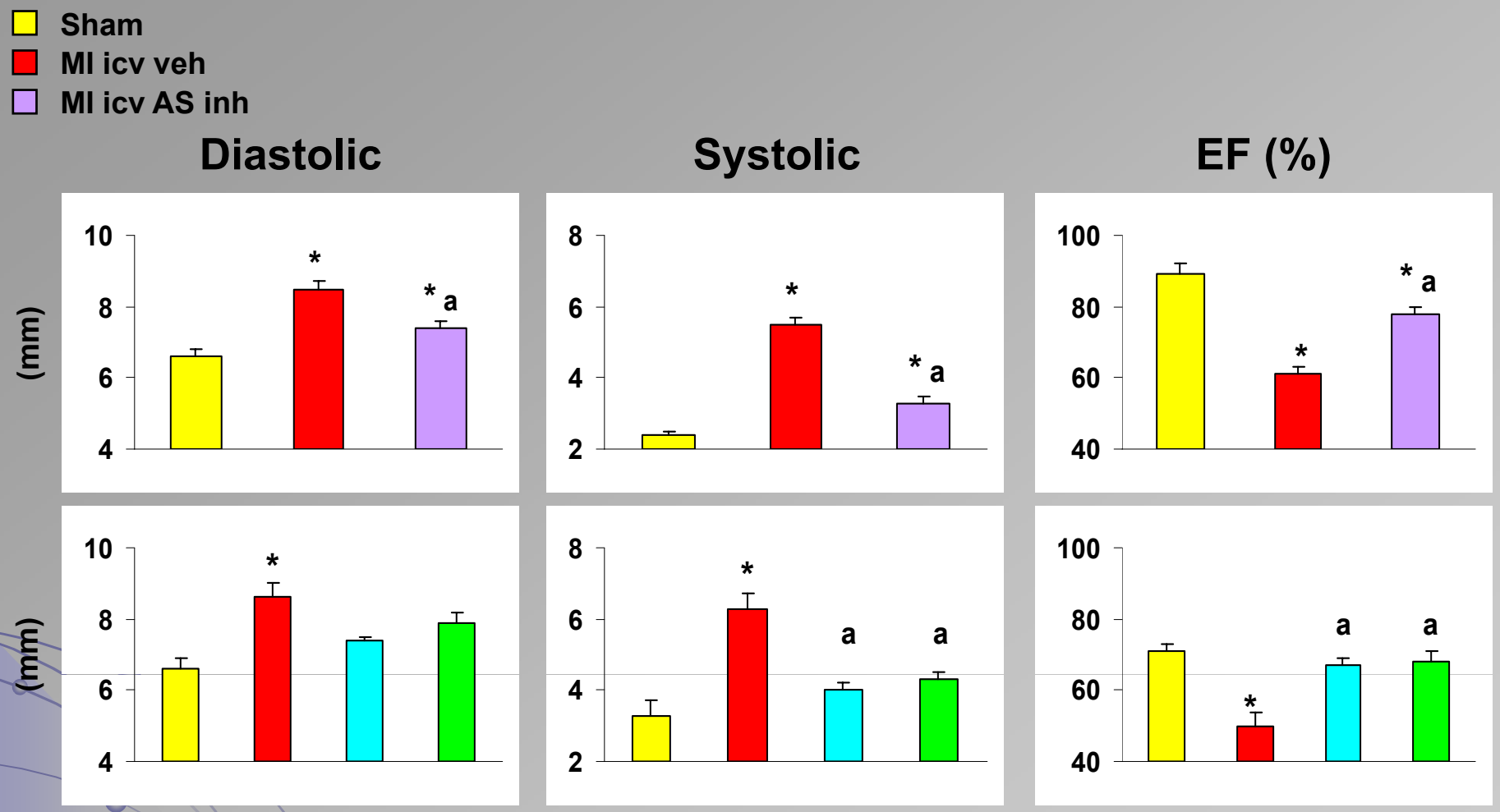
Parameters of LV remodeling

- LV diameter
- cardiomyocyte numbers and size
- extracellular matrix - collagen

Parameters of LV dysfunction and CHF

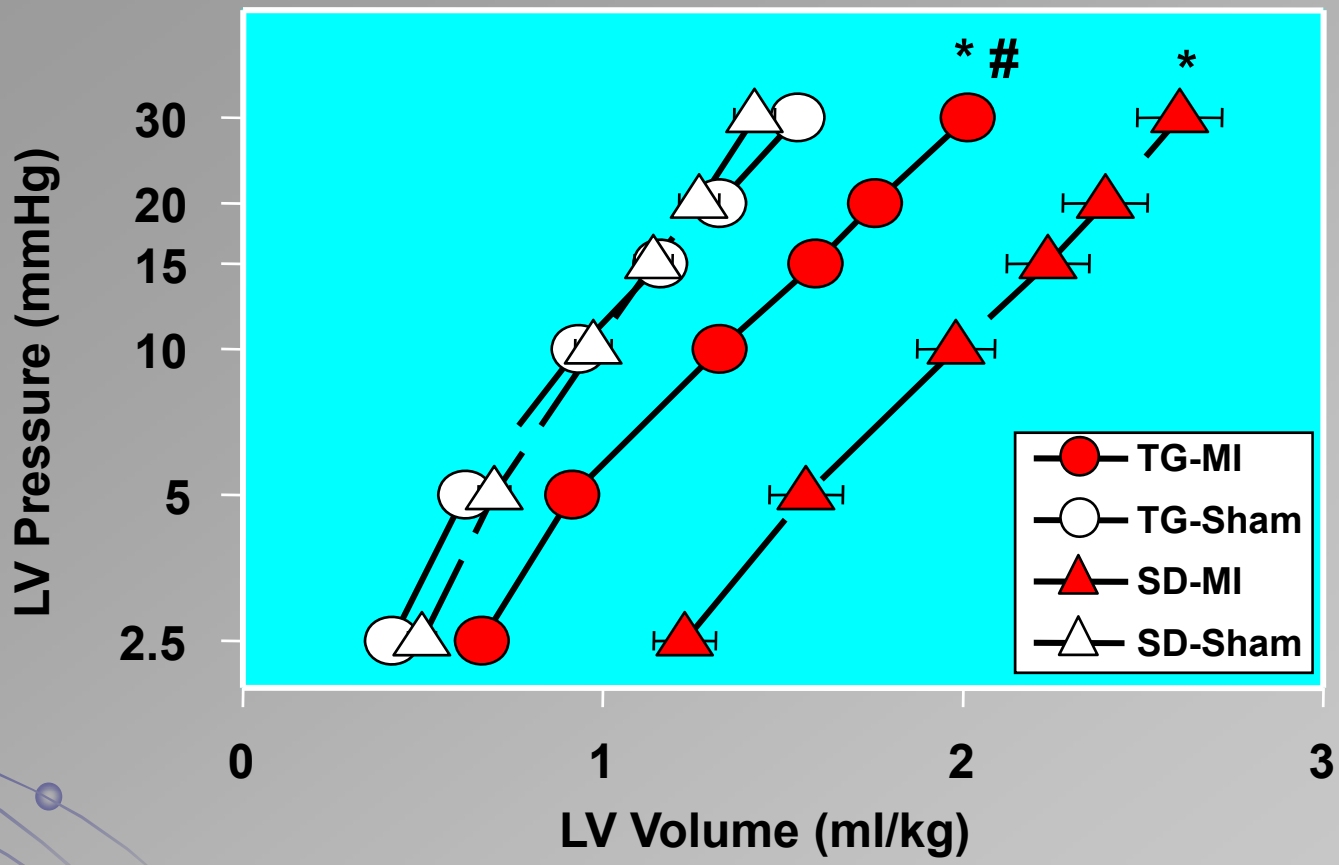
- LVEDP, LVPSP, LV dP/dt max
- lung weight
- RV weight and diameter

LV dimensions at 4 weeks post MI
Central Blockades



* p<0.05 vs sham; [a]p<0.05 vs MI +veh

LV pressure-volume curves in transgenic vs. SD rats at 8 wks post MI



* P<0.05 vs sham; # P<0.05 vs SD MI

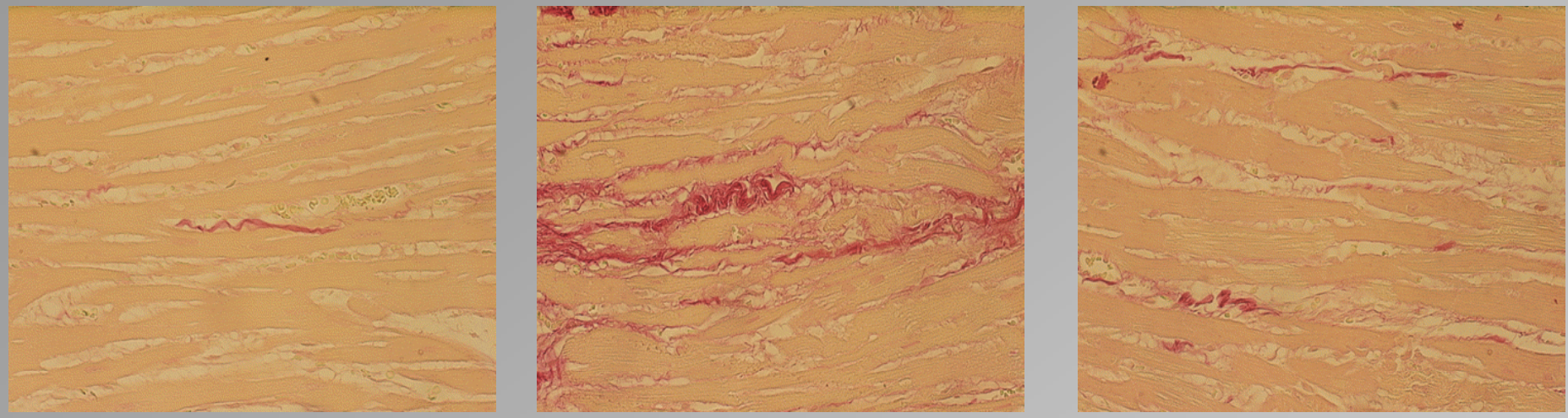
M I size : 40 ± 3 for TG and 40 ± 4 for SD

(Wang et al. Circ Res, 2004)

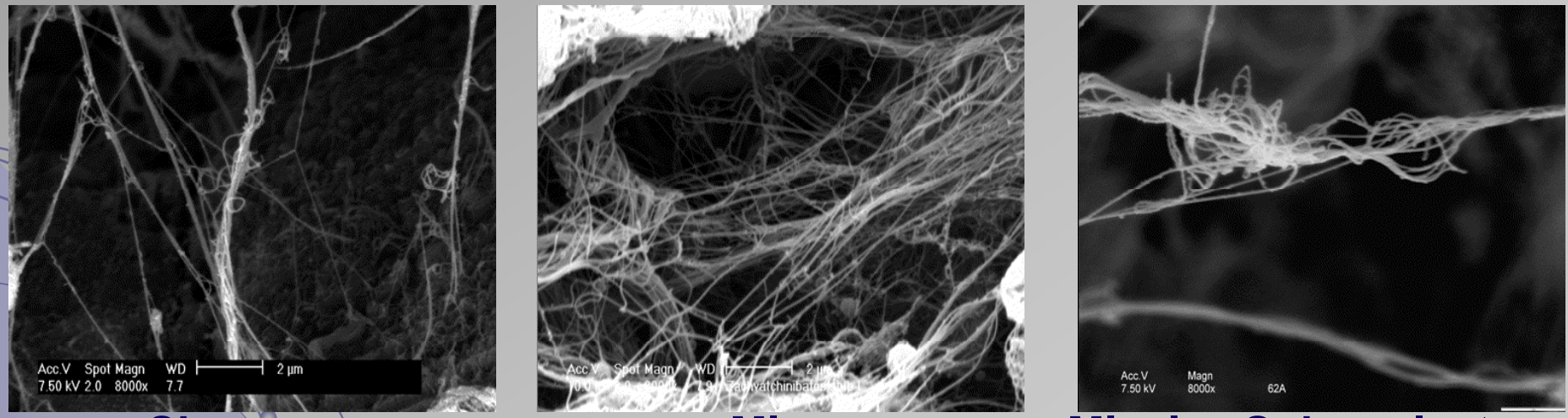
Interstitial Fibrosis in Peri-infarct Zone

Effect of central MR blocker

Interstitial fibrosis (magnification X400)



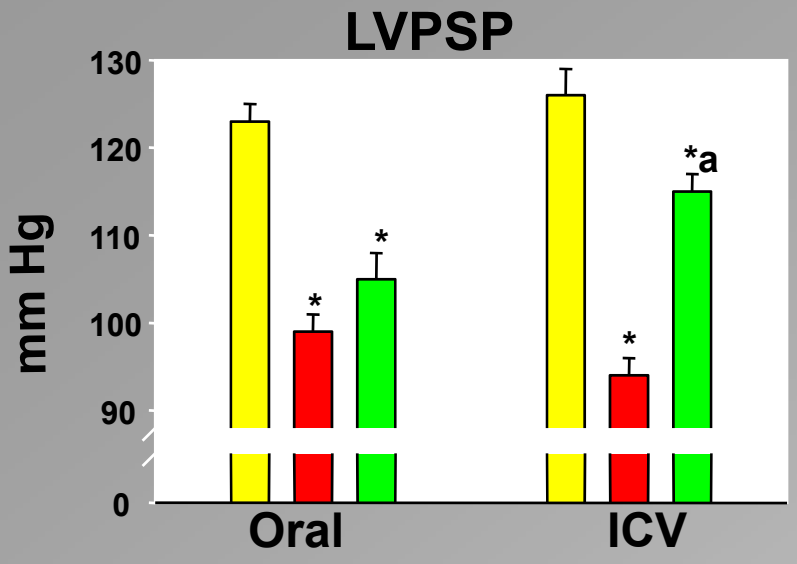
Fibrillar collagen by SEM (magnification X8000)

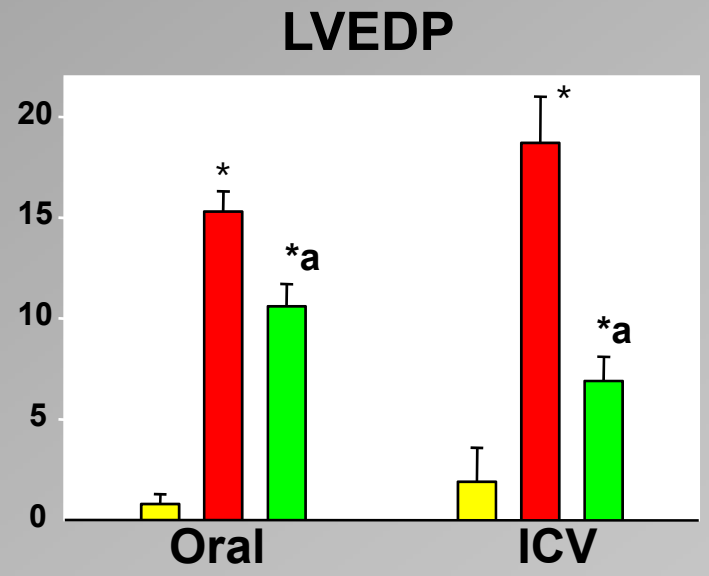


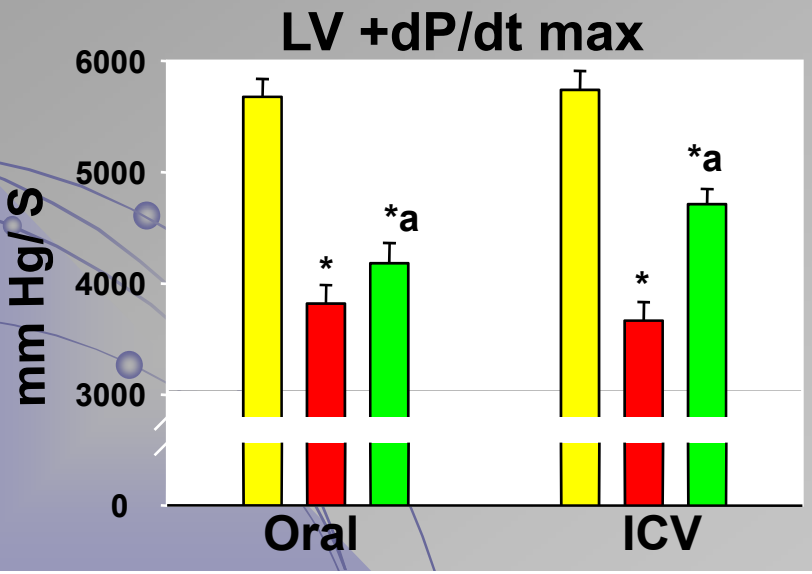
Sham **MI** **MI + Icv Spironolactone**

(Lal et al. Card vasc Res, 2004)

Oral vs icv spironolactone and MI-Induced changes in hemodynamics







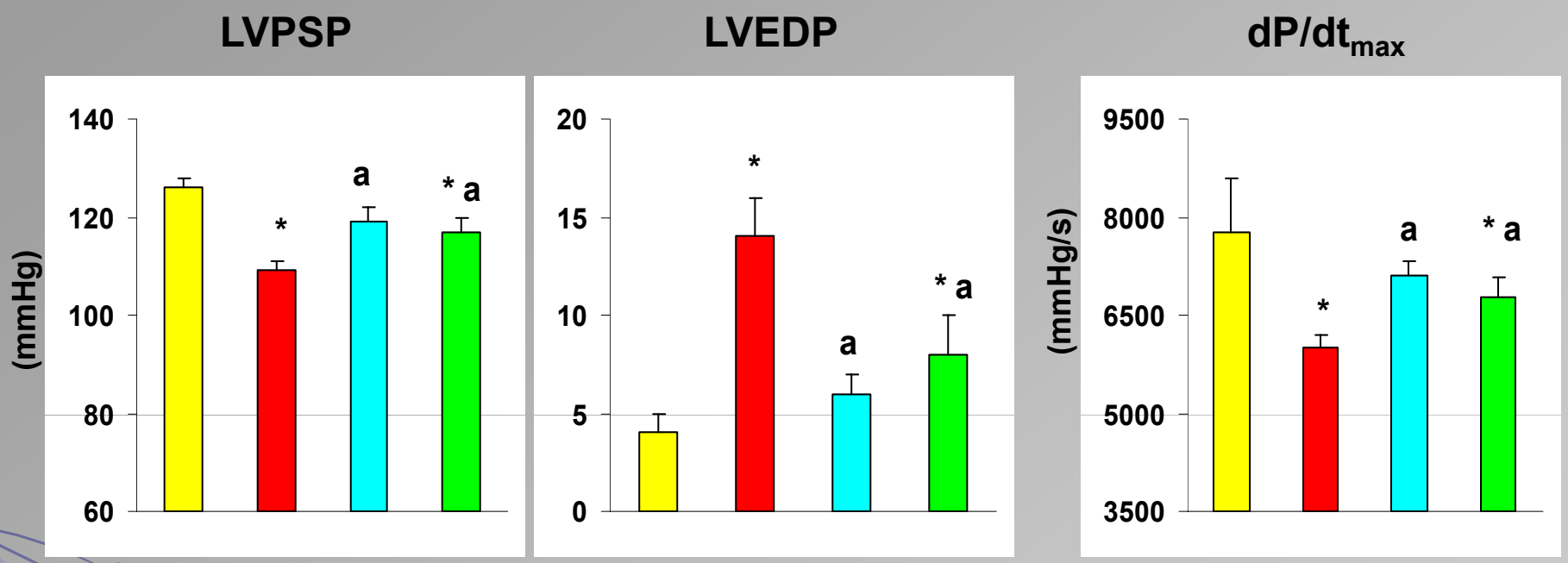
Sham
MI + Vehicle
MI + Spironolactone

* p< 0.05 vs sham; a p<0.05 vs MI+Vehicle

(Lal et al. Card vasc Res, 2004)

LV function at 4 weeks post MI

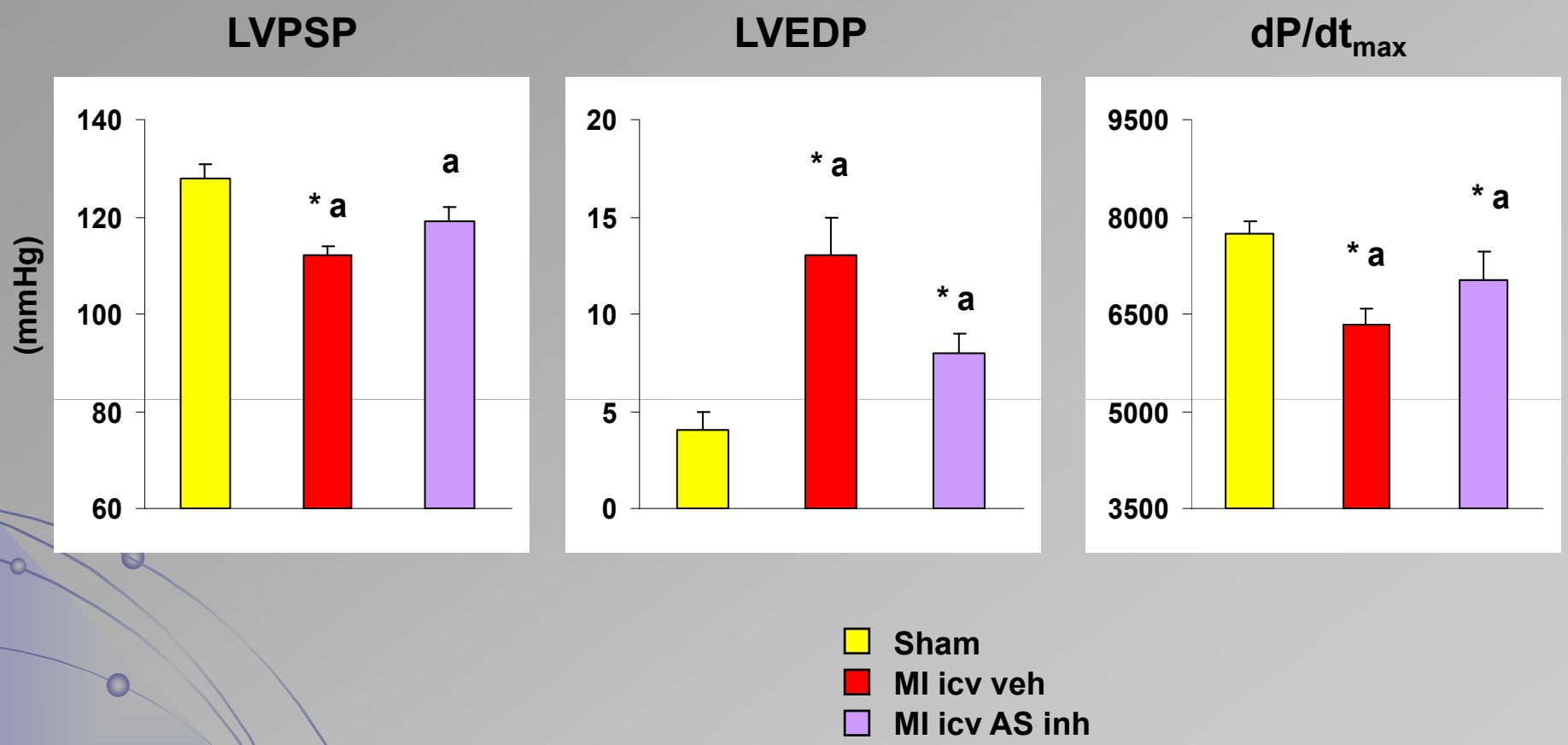
Icv losartan versus icv spironolactone



* p<0.05 vs sham; [a]p<0.05 vs MI +veh

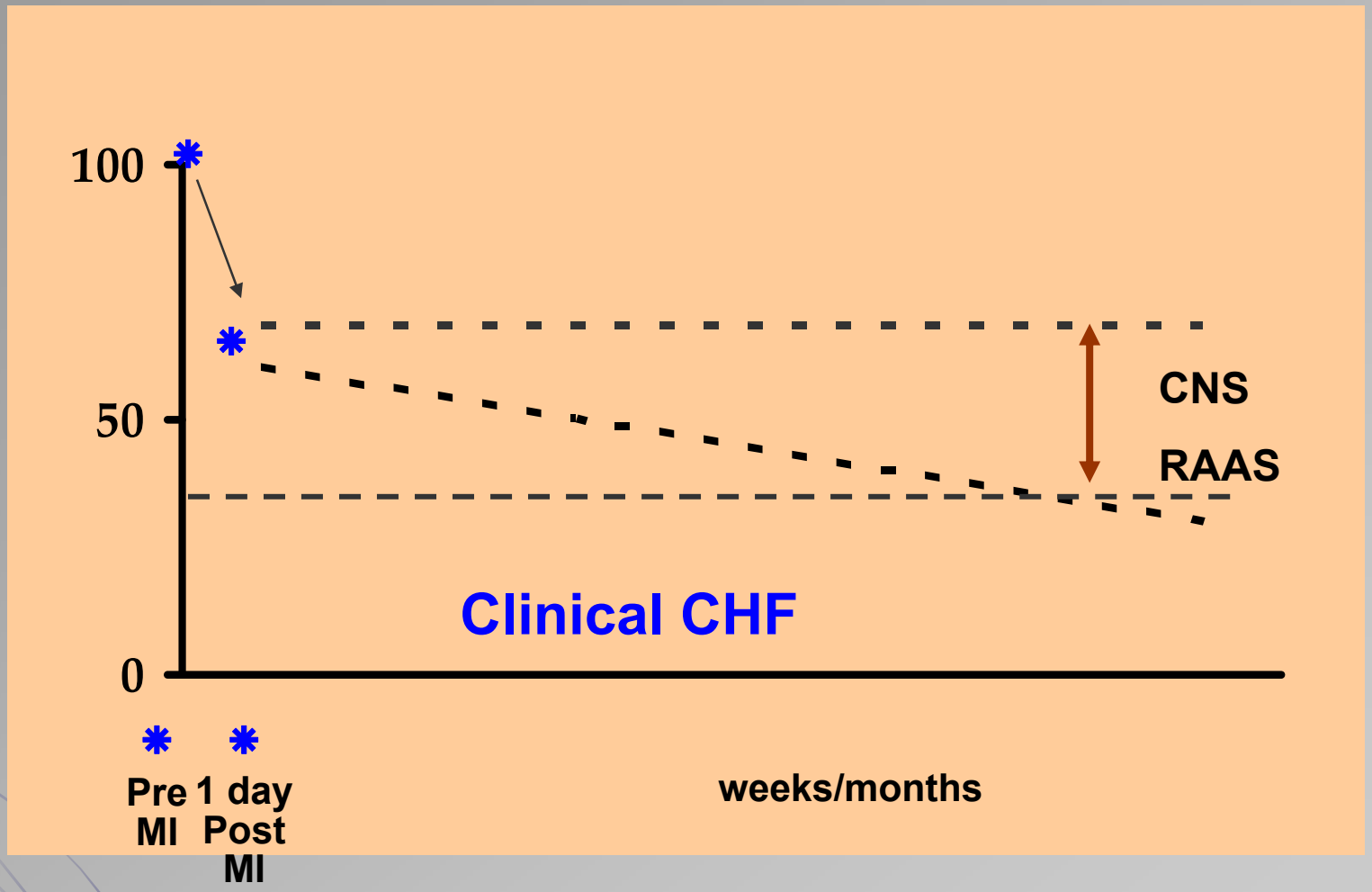
(Huang et al. JMCC 2007)

LV function 4 weeks post MI
Central aldosterone synthase inh



* p<0.05 vs sham; [a]p<0.05 vs MI +veh

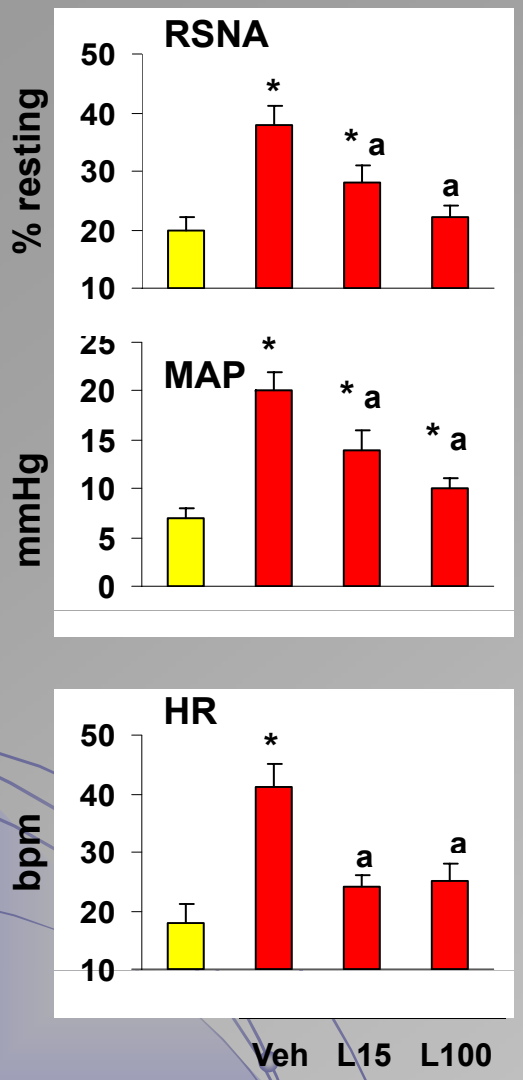
CNS and LV dysfunction post MI

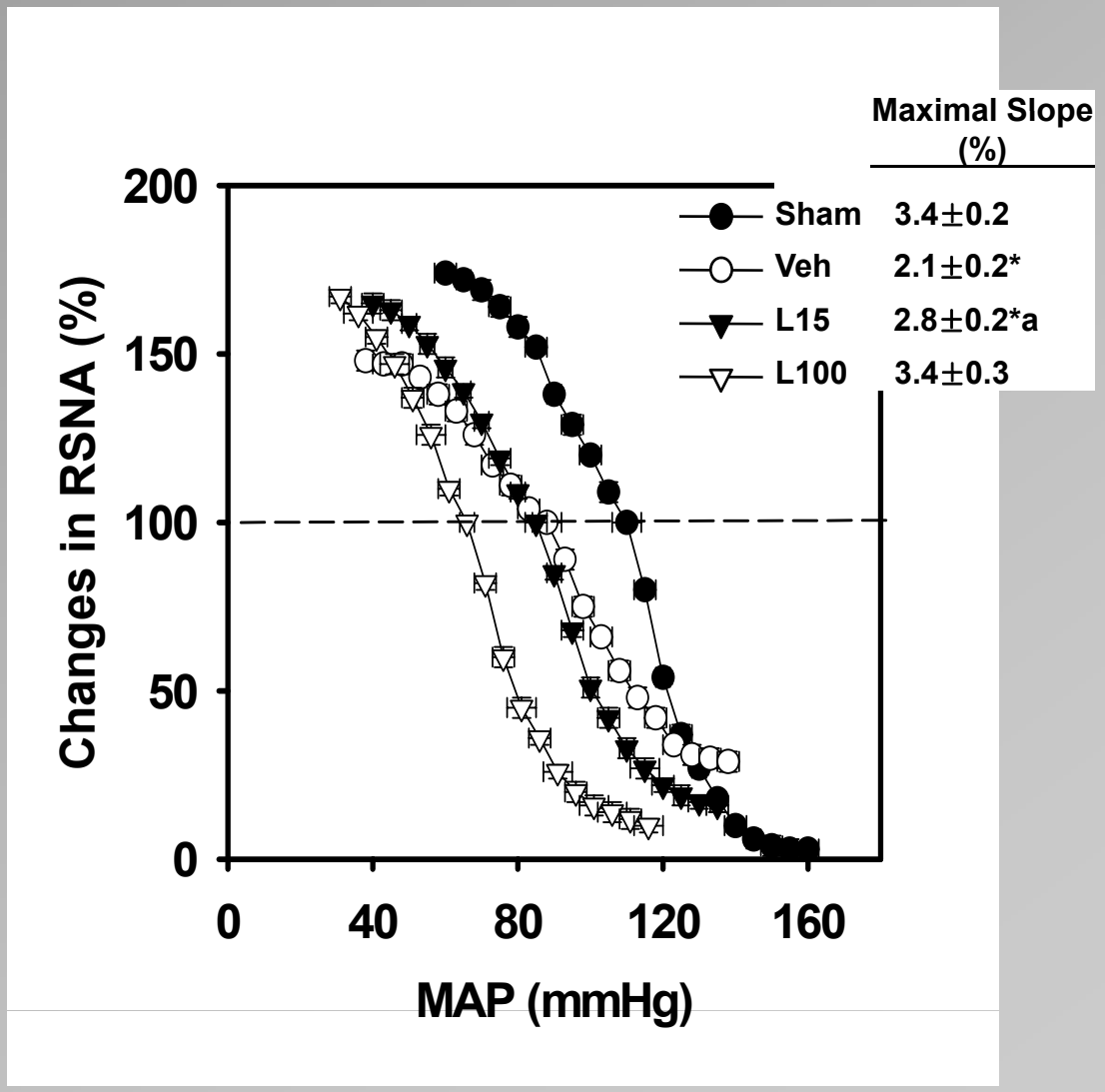


Sympathetic activity post MI

Effects of systemic losartan

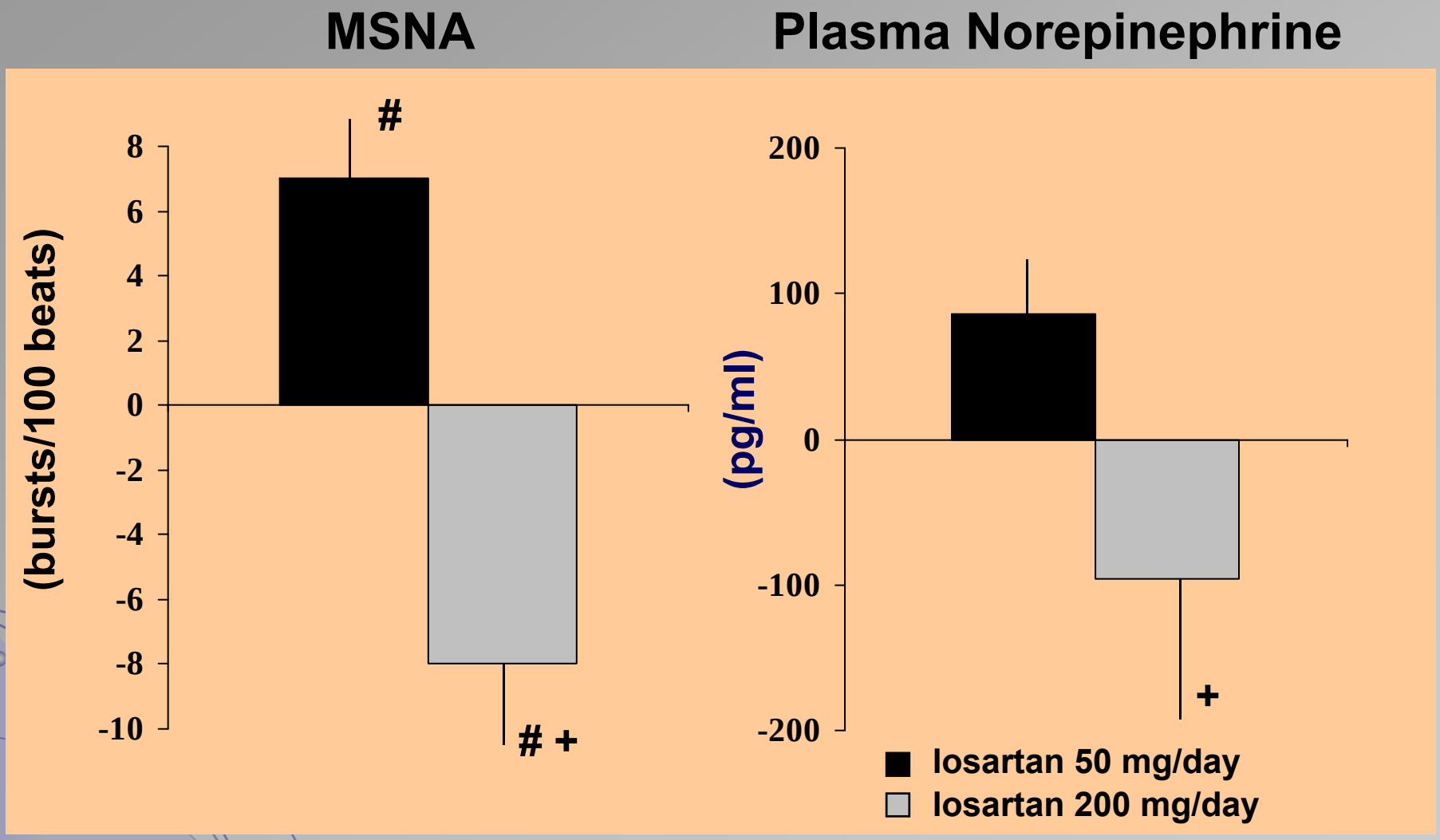
Air Stress





(Huang et al. JMCC, 2007)

Losartan and sympathetic activity in patients with CHF



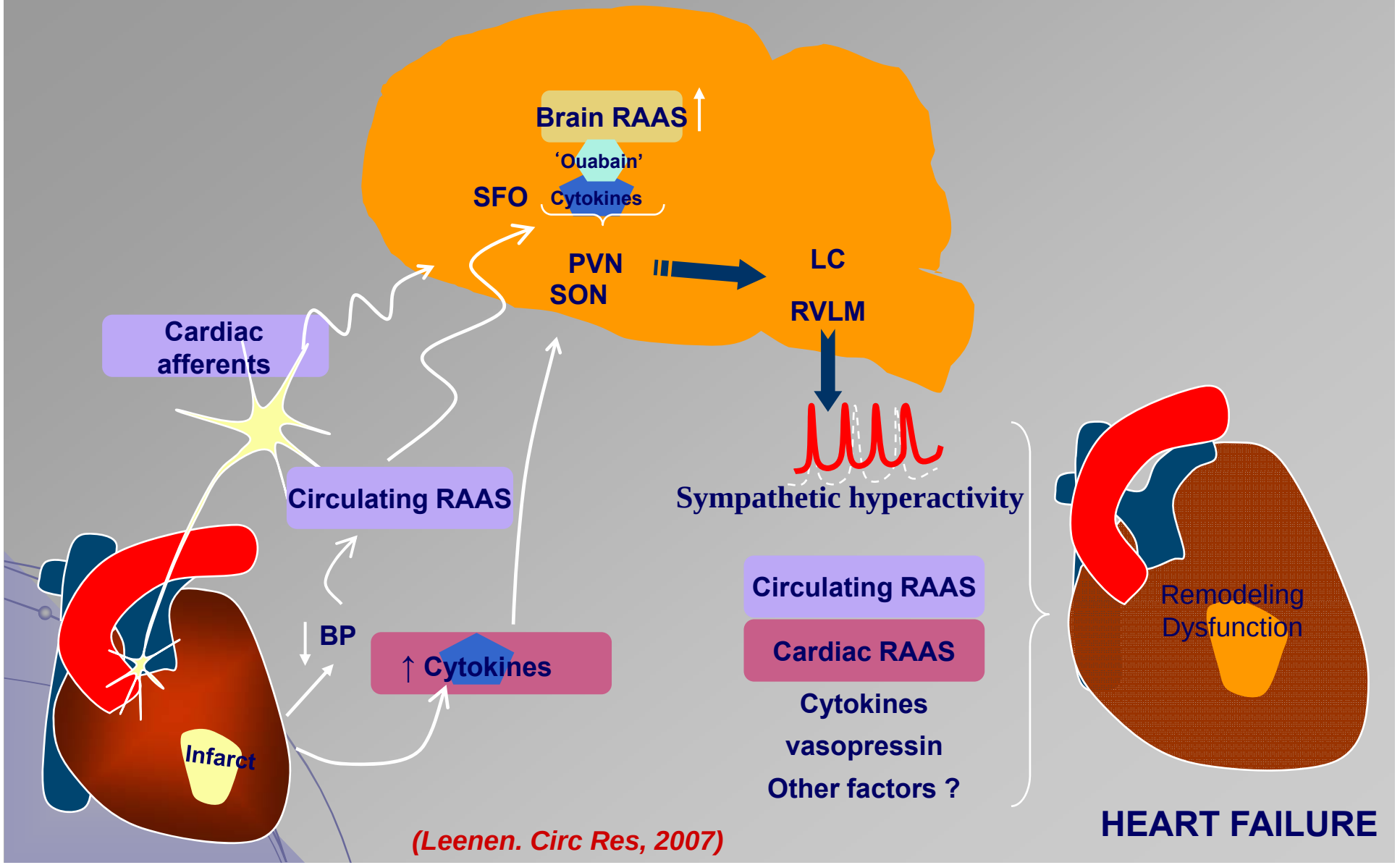
# p<0.05 vs baseline

+ p< 0.05 compared to losartan 50 mg/day

(Ruzicka et al. ESC, 2007)

The Brain:

The forgotten target in Heart Failure



(Leenen. Circ Res, 2007)