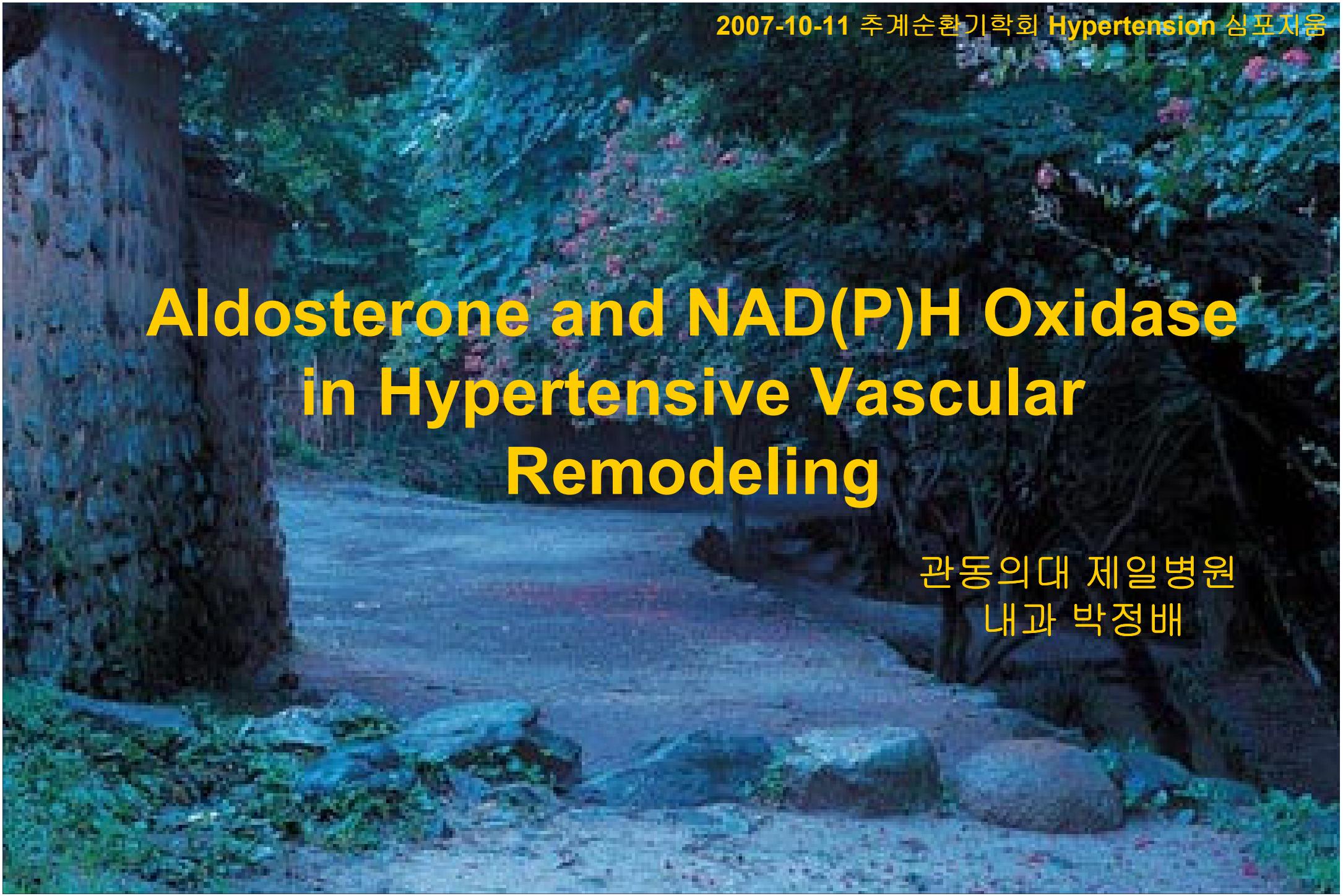


Aldosterone and NAD(P)H Oxidase in Hypertensive Vascular Remodeling

관동의대 제일병원
내과 박정배

Contents:

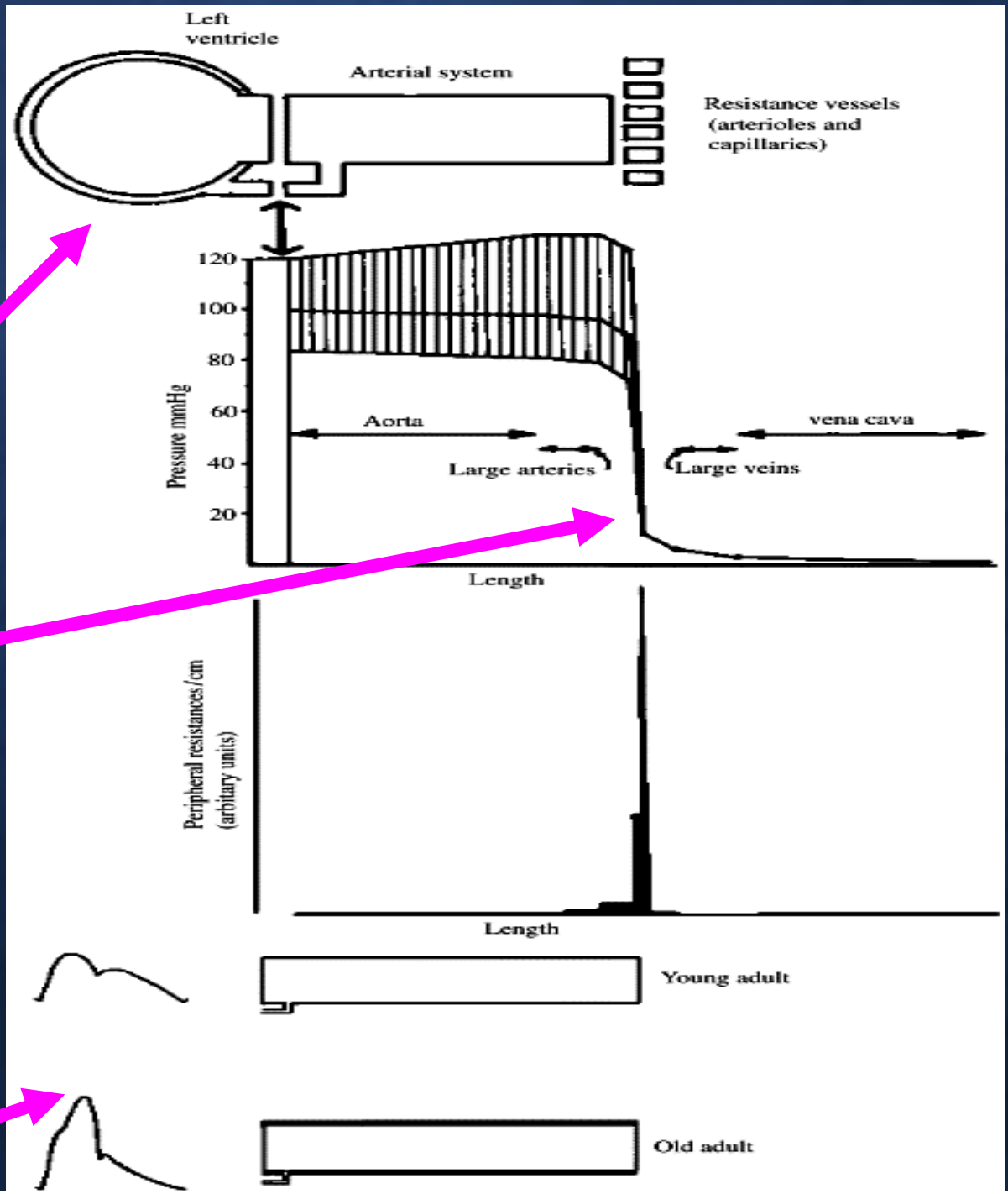
- Hypertensive Vascular Remodeling?
- Aldosterone on Vascular Remodeling.
- Aldosterone and NAD(P)H Oxidase: a link?

A Model of the Systematic Circulation.

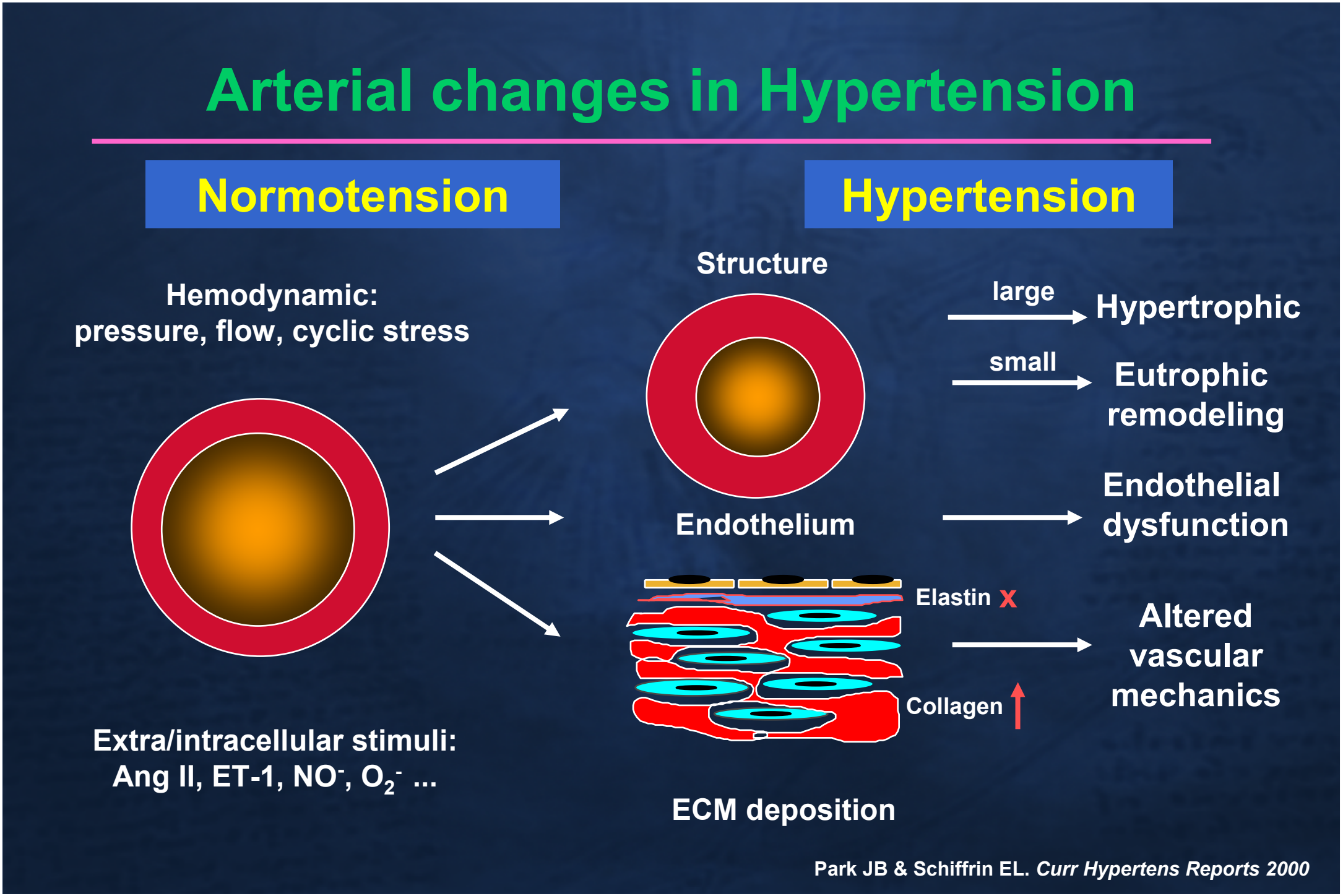
Mean BP = CO x TPR

Diastolic

Systolic BP = CO x stiffness

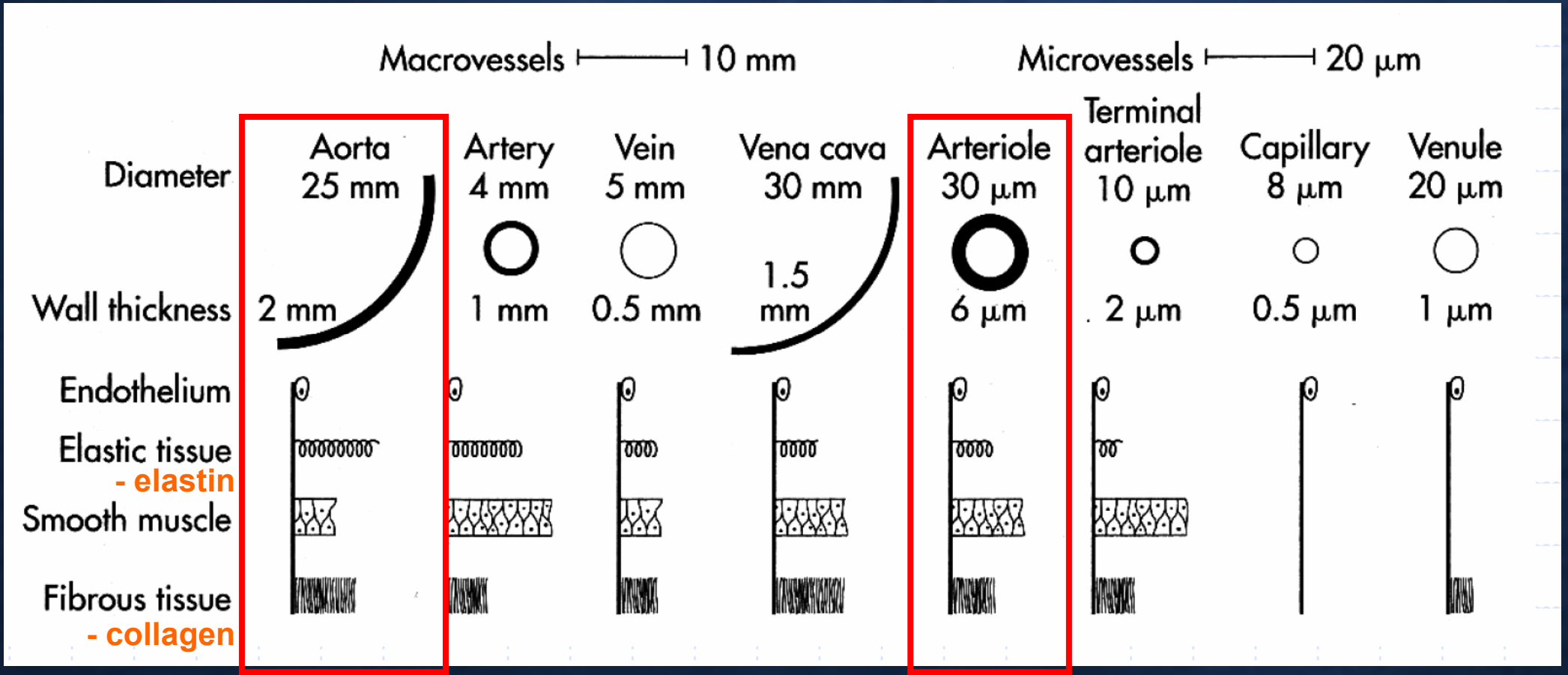


Arterial changes in Hypertension



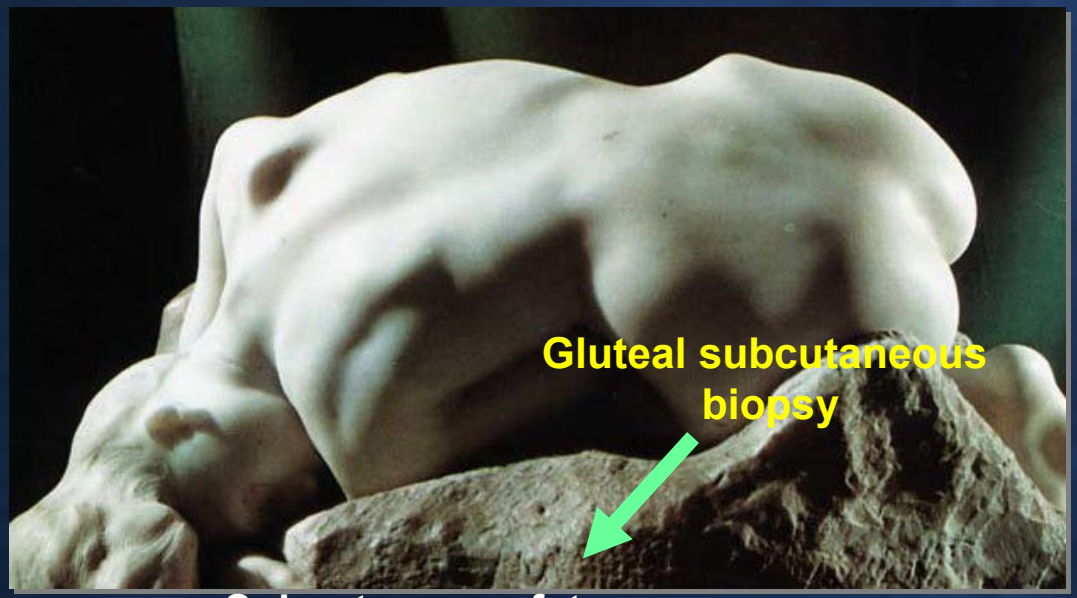
Park JB & Schiffrin EL. *Curr Hypertens Reports 2000*

Large and small artery

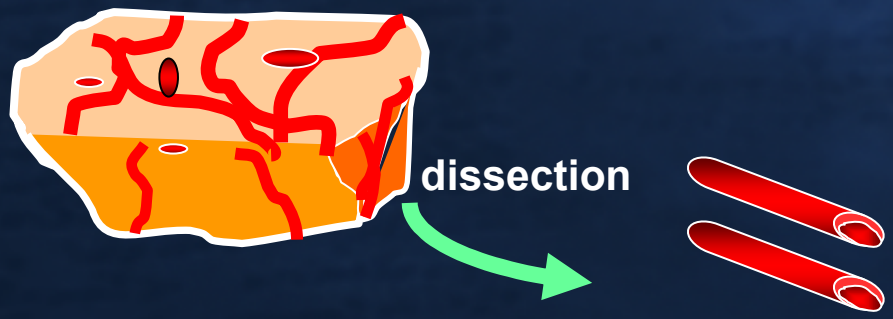


Peak Eeff (effective Young's modulus)
: collagen; ~10^8, elastin; 3x10^5, smooth muscle; ~ 10^5-10^6 ? N/m^2

Resistance Artery Study in Human

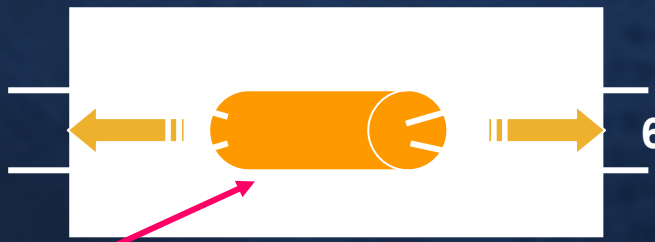


Subcutaneous fat



Park JB. 2000

Small artery studies (isobaric)



Structure; media to lumen ratio

Function; ach and nitroprusside

Mechanics

-intraluminal pressure = 3 - 140 mmHg

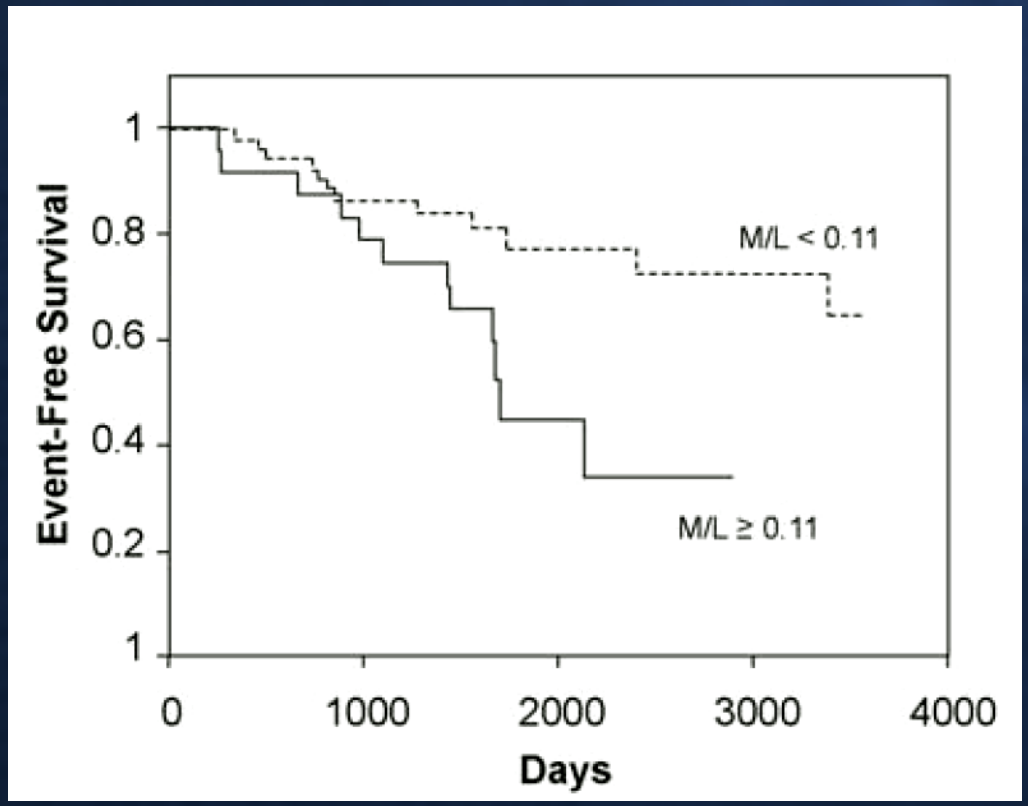
-lumen and media measurements

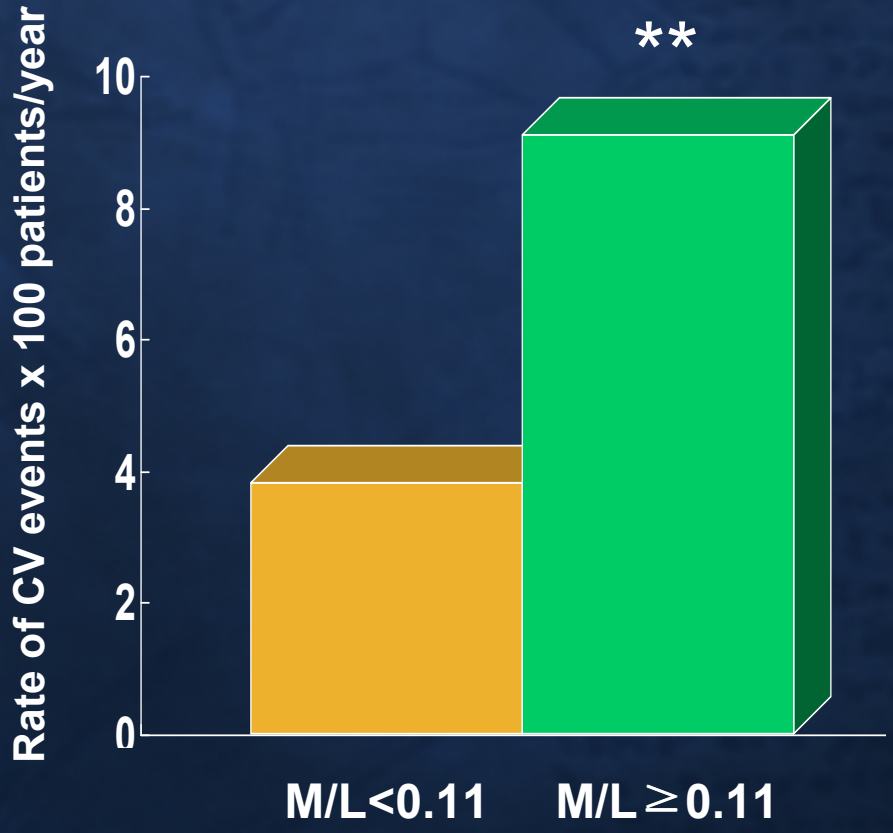
Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension.

	Hypertension	Prevalence (%)
Resistance Artery Vascular Remodeling - Media/Lumen ratio	↑	63 - 97
Endothelial Function - Ach response	↓	34 - 58
Vascular Stiffness - E_{inc} vs stress	↔	No change
LV Mass ECG/ECHO	↑	26 - 34

Park JB, Schiffrin EL. *J Hypertens* 2001;19:921

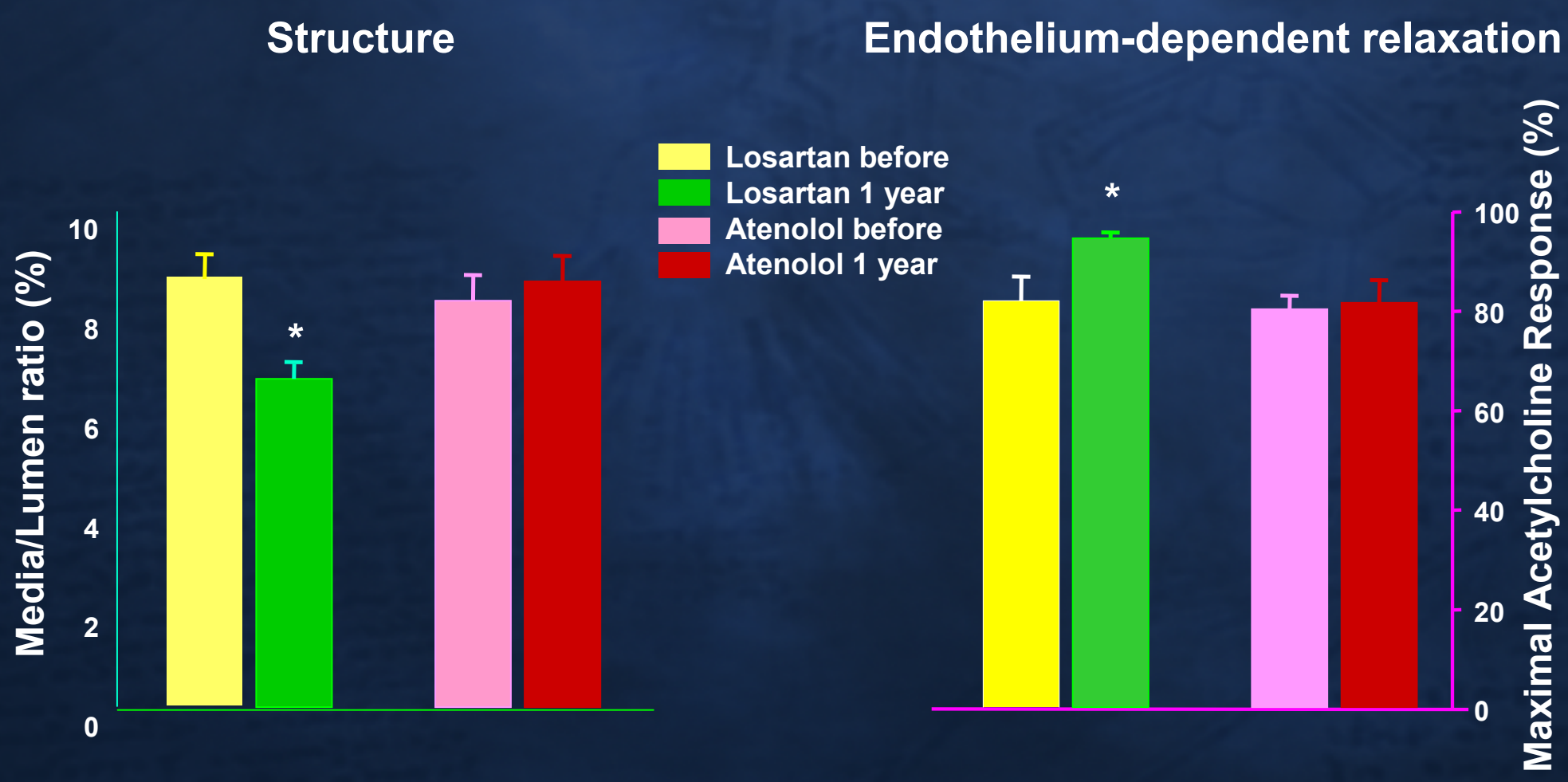
Event-free survival in a group of patients with essential hypertension or diabetes mellitus and with a media–lumen (M/L) ratio of subcutaneous small arteries and Incidence of cardiovascular events





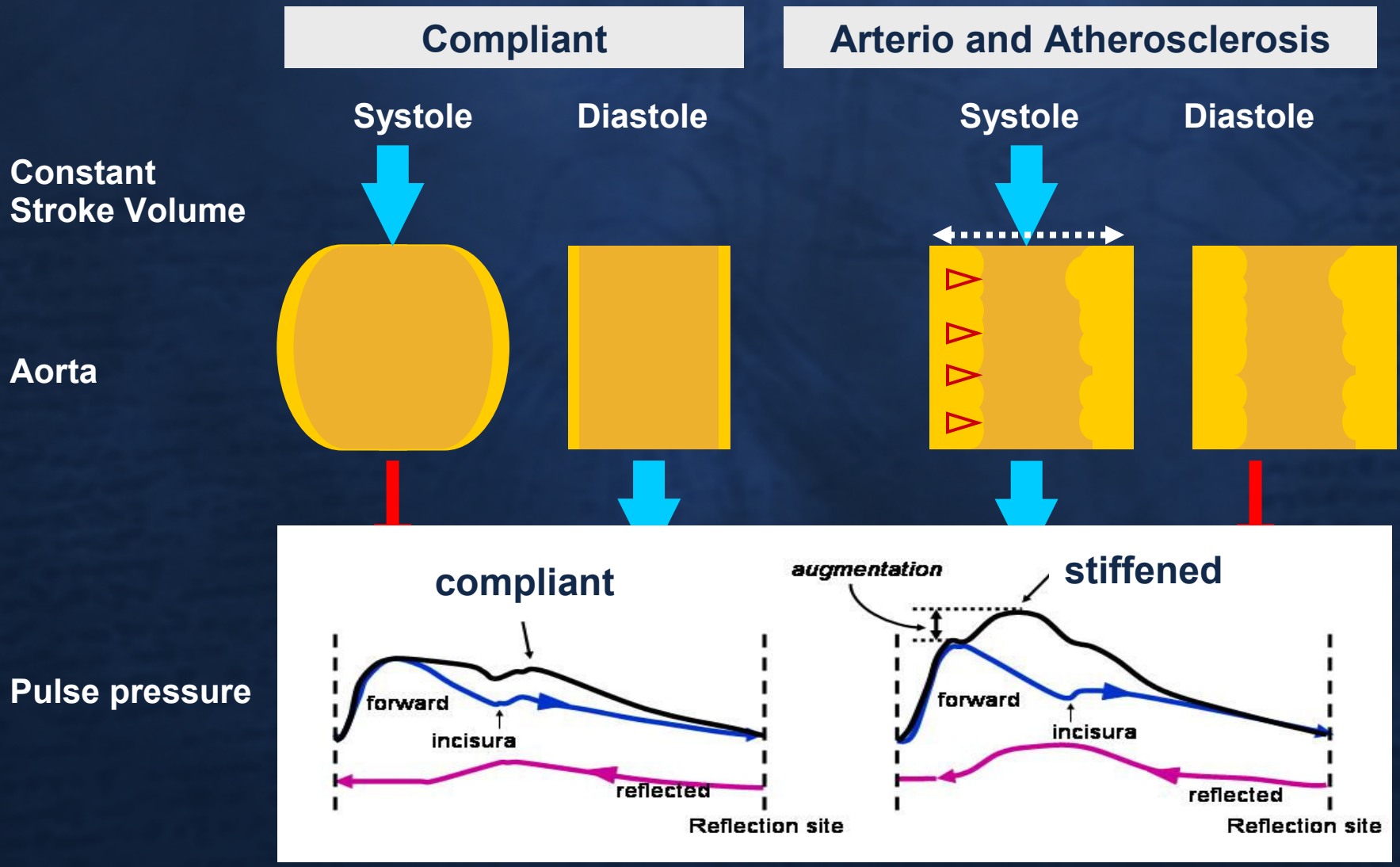
Rizzoni et al. Circulation 2003;108:2230

1-Year Treatment Effects of Losartan and Atenolol on Small Artery Structure and Function in Hypertension



Schiffrin and Park..Circulation 2000

Arteriosclerosis & atherosclerosis of large artery



Summary of Large and Small Artery Alterations in Hypertension

Large Artery Remodeling

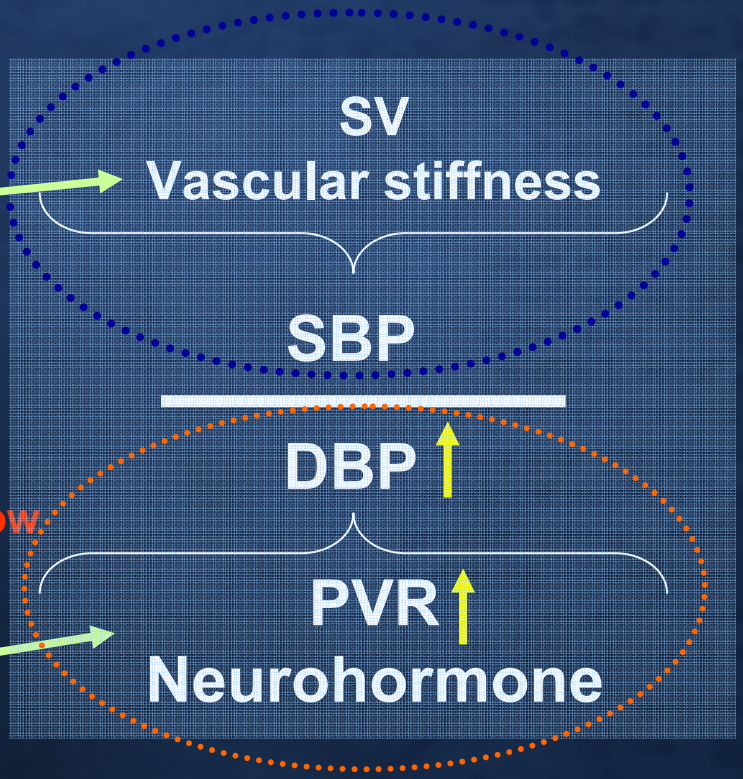
- Pulse wave velocity ↑
- Arterial augmentation ↑
- Characteristics impedance ↑

Small Artery Remodeling

- Eutrophic remodeling
- Endothelial dysfunction

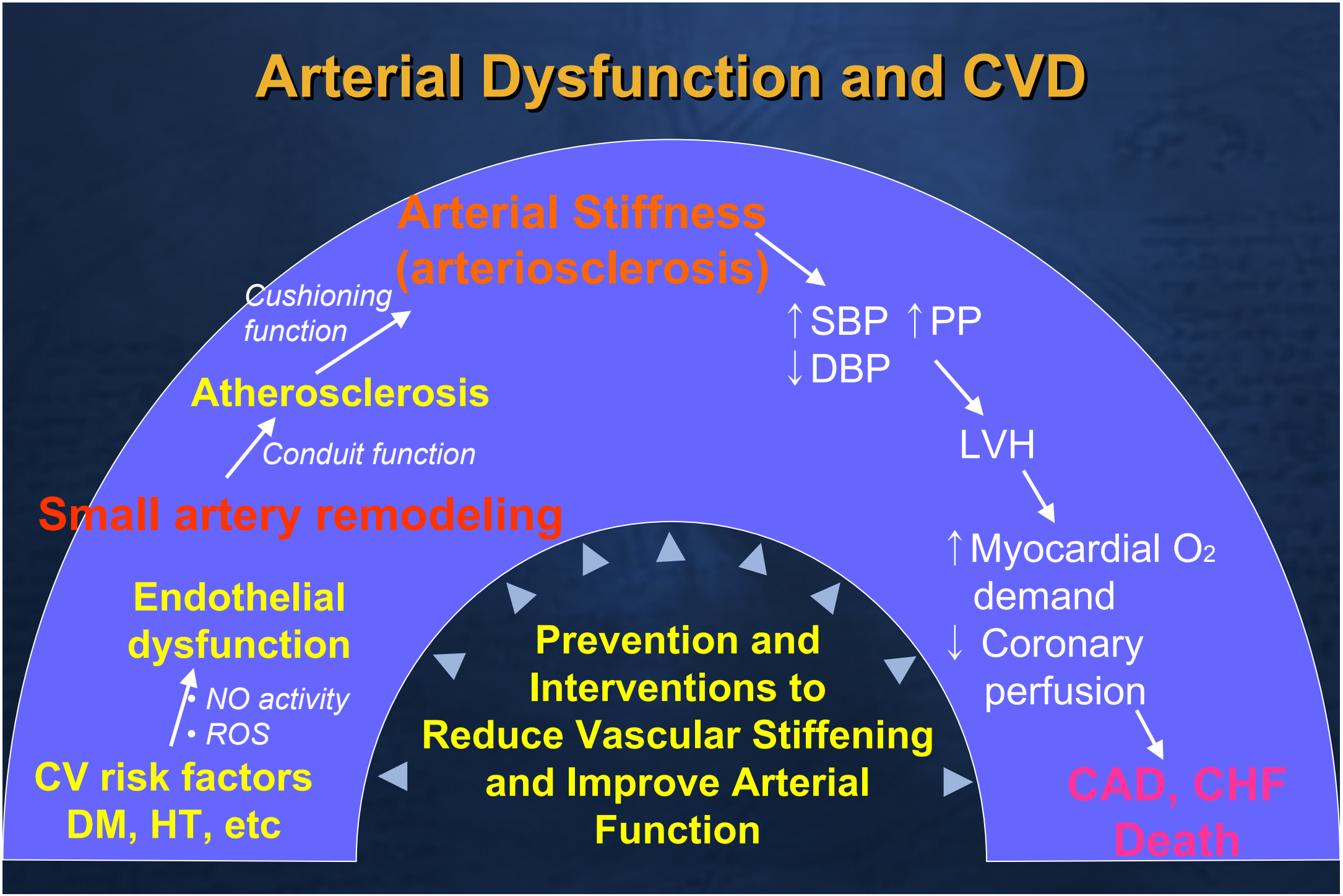
- Unaltered stiffness, initially
  ⇒ stiffened, later

Resistance to flow
$= \frac{8 \eta L}{\pi r^4}$ ↓

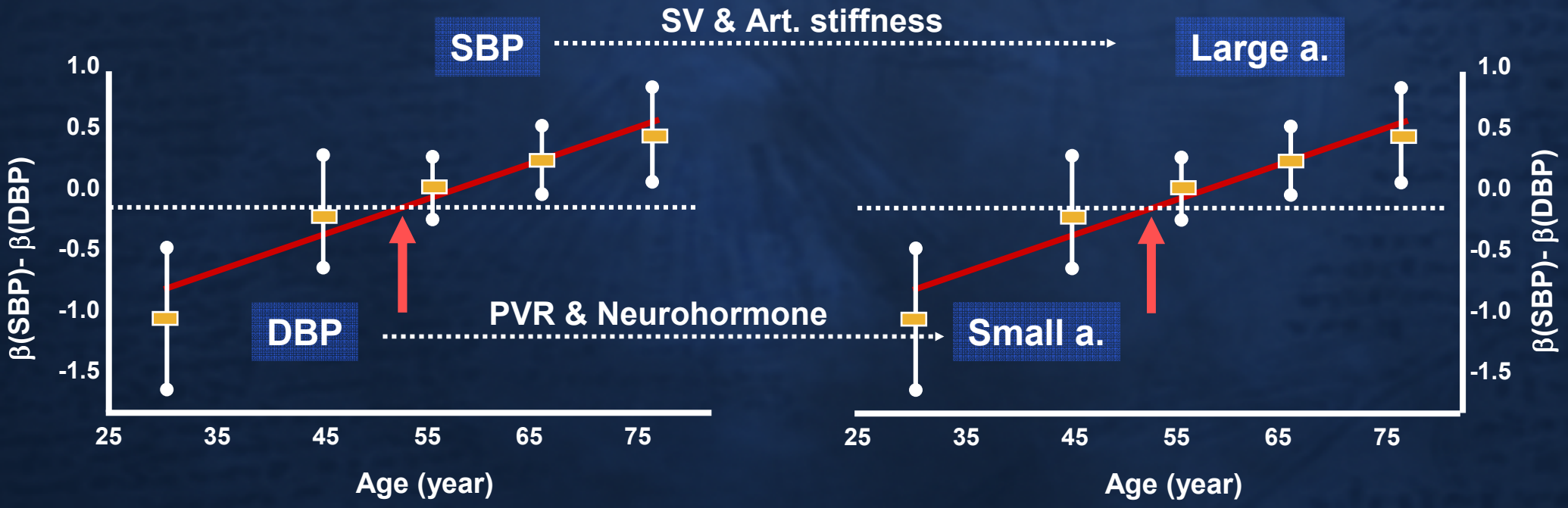


Park JB. 2007

Arterial Dysfunction and CVD



Difference of CVD prediction between systolic and diastolic BP as a function of age



2003 JNC VII

Park JB 2006

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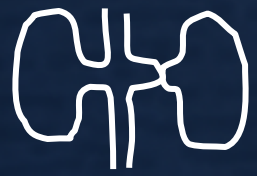
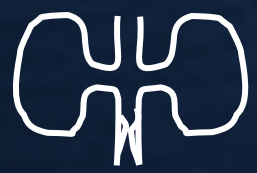
Myocardial fibrosis experimental model (Aldosterone-salt Hypertension)



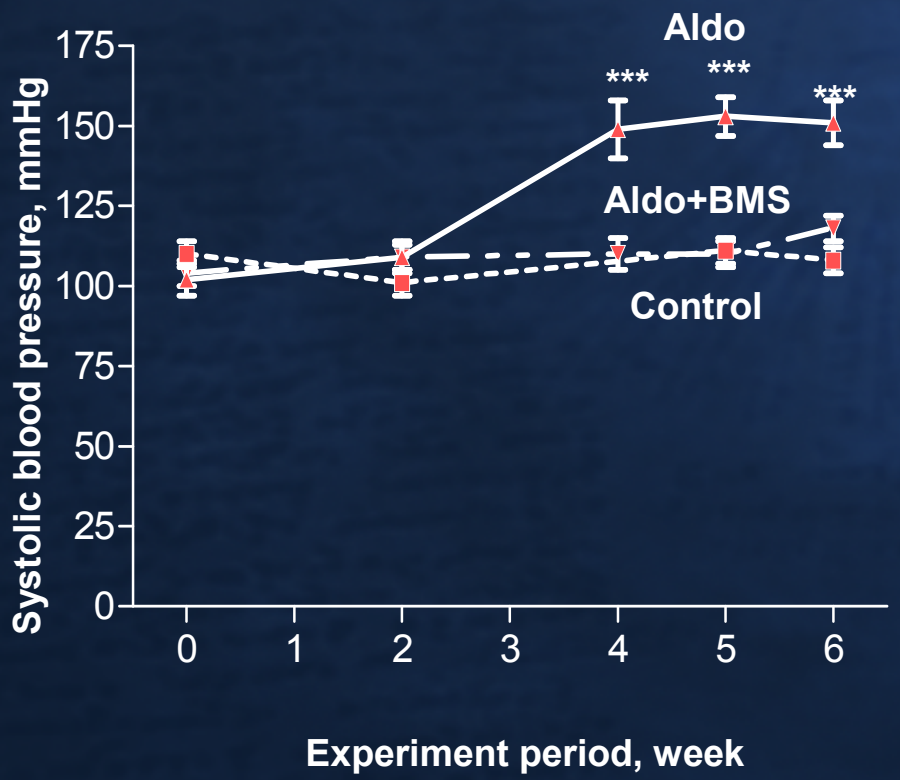


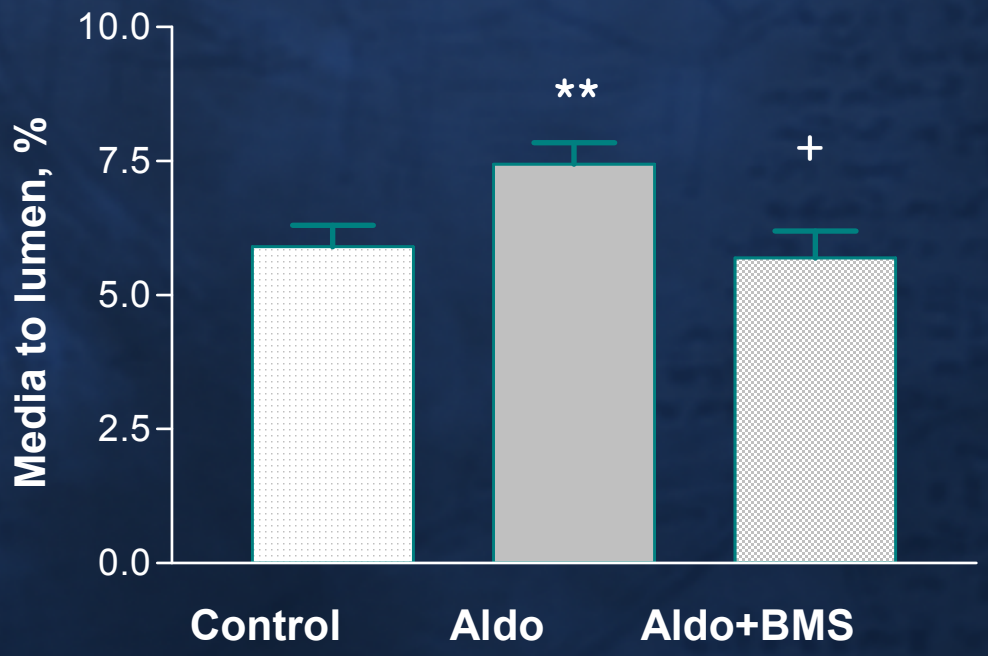
	HBP	LVH	Fibrosis	Artery
Ang II ↑ Aldo ↑	+	+	+	hypertrophic
Ang II → Aldo ↑	+	+	+	hypertrophic
Ang II → Aldo →	+	+	-	eutrophic

Modified from Weber K group.

ET_A Receptor Antagonist Prevents Blood Pressure Elevation and Vascular Remodeling in Aldosterone-Infused Rats

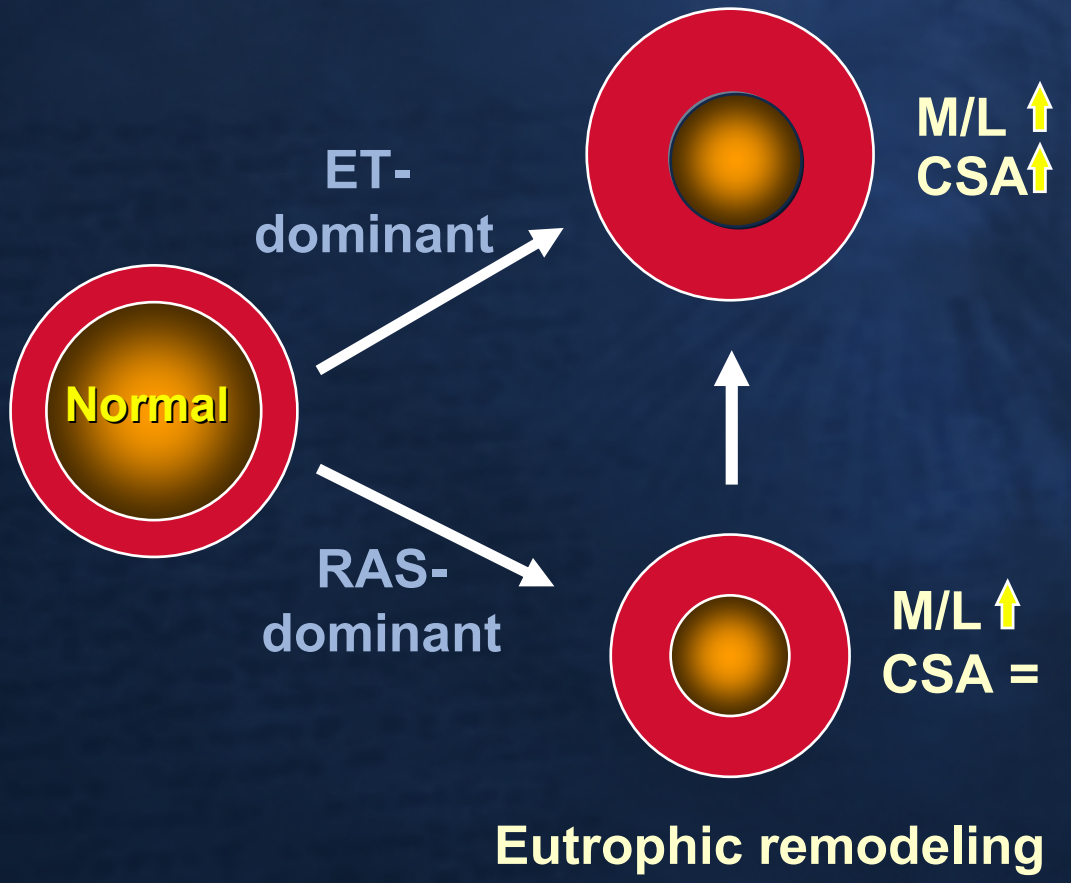
Jeong Bae Park, Ernesto L. Schiffrin





Hypertension 2001

Arterial Remodeling of Resistance Arteries in Hypertension



Experimental Hypertension	Human Hypertension
DOCA salt 1-k 1c Dahl SS	Renovascular HT Pheochromocytoma
Aldosterone	
SHR 2-k 1c	Mild ~ moderate HT

Intengan H and Schiffrin EL.
2000 Hypertension (Modified)

Cardiac and Vascular Fibrosis and Hypertrophy in Aldosterone-Infused Rats: Role of Endothelin-1

Jeong Bae Park and Ernesto L. Schiffrin

Control
Aldo
Aldo+BMS

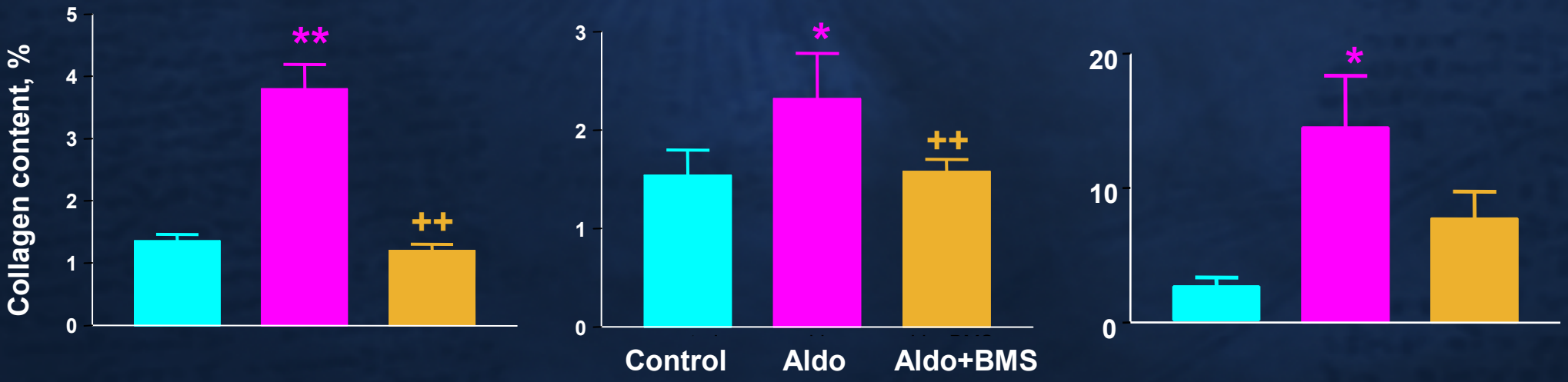
Heart

Aorta

LV perivascular collagen

RV perivascular collagen

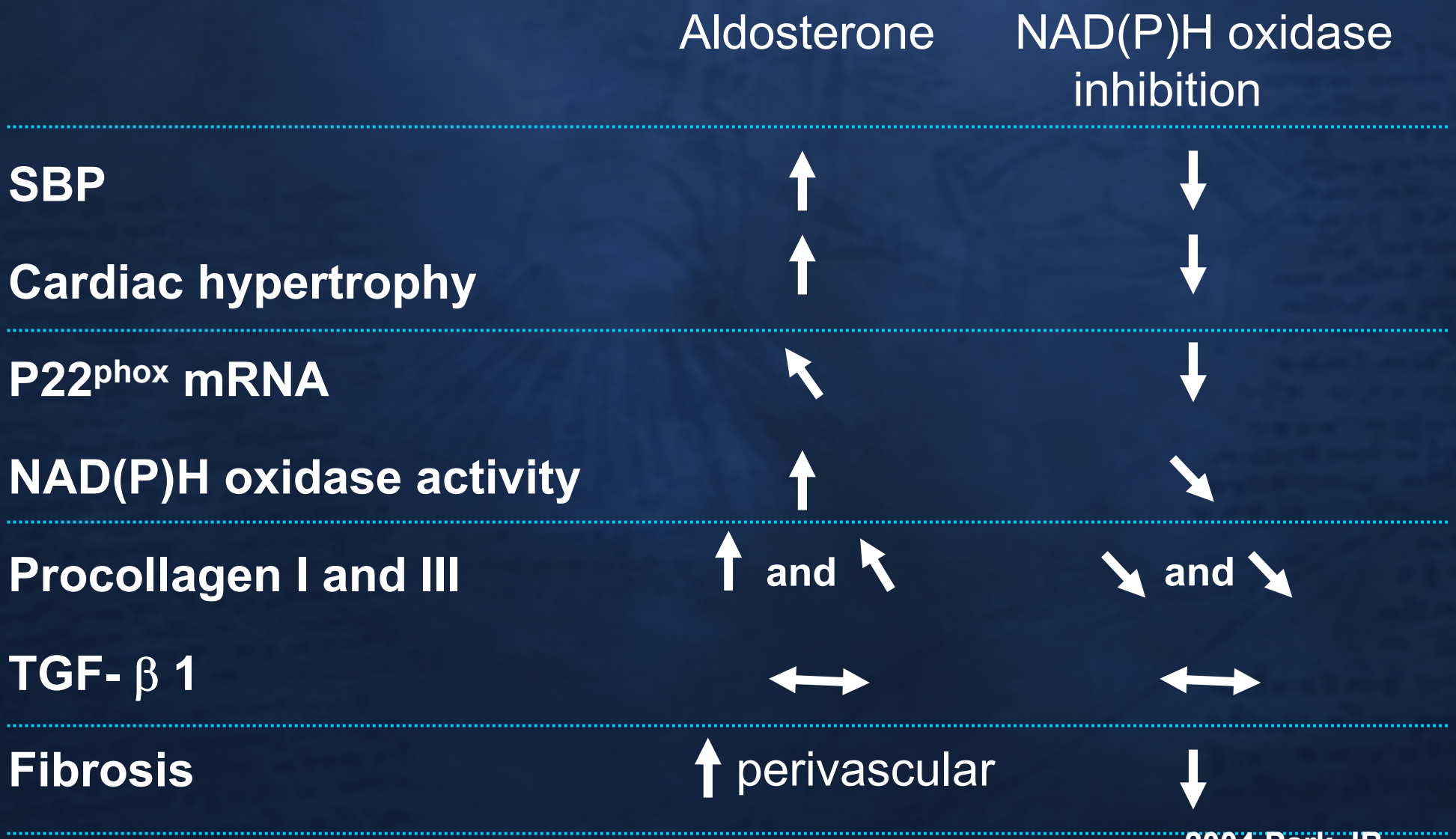
intima-media collagen



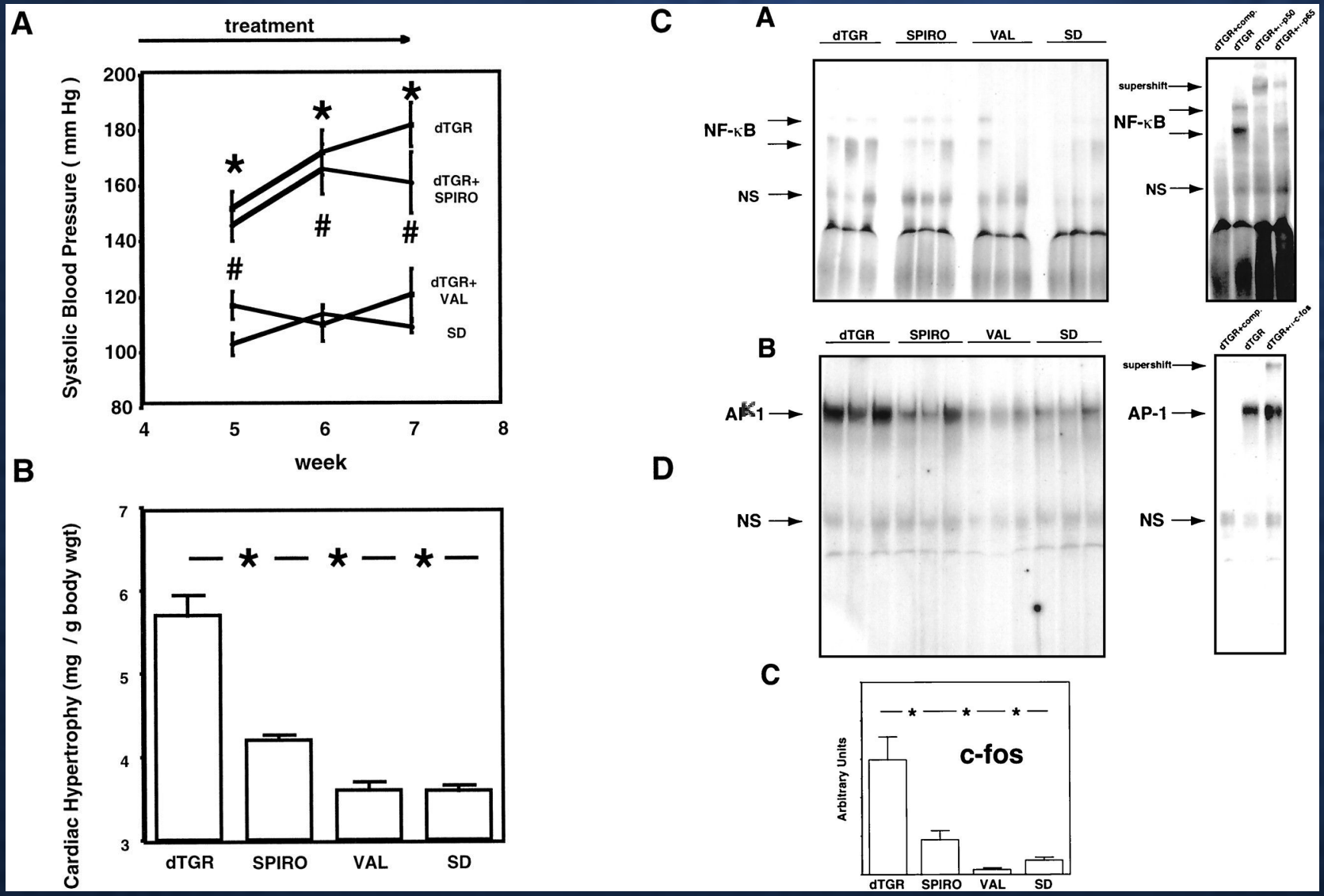
BMS (BMS 182874) ETA-selective endothelin antagonist

Am J Hypertens 2002

SUMMRY: NAD(P)H oxidase and cardiac fibrosis in aldosterone-salt rats



Mineralocorticoid Receptor Affects AP-1 and Nuclear Factor-κB Activation in Ang II–Induced Cardiac Injury



Fiebeler A.. Müller DN. Park J-K et al. Hypertension2001;37:787

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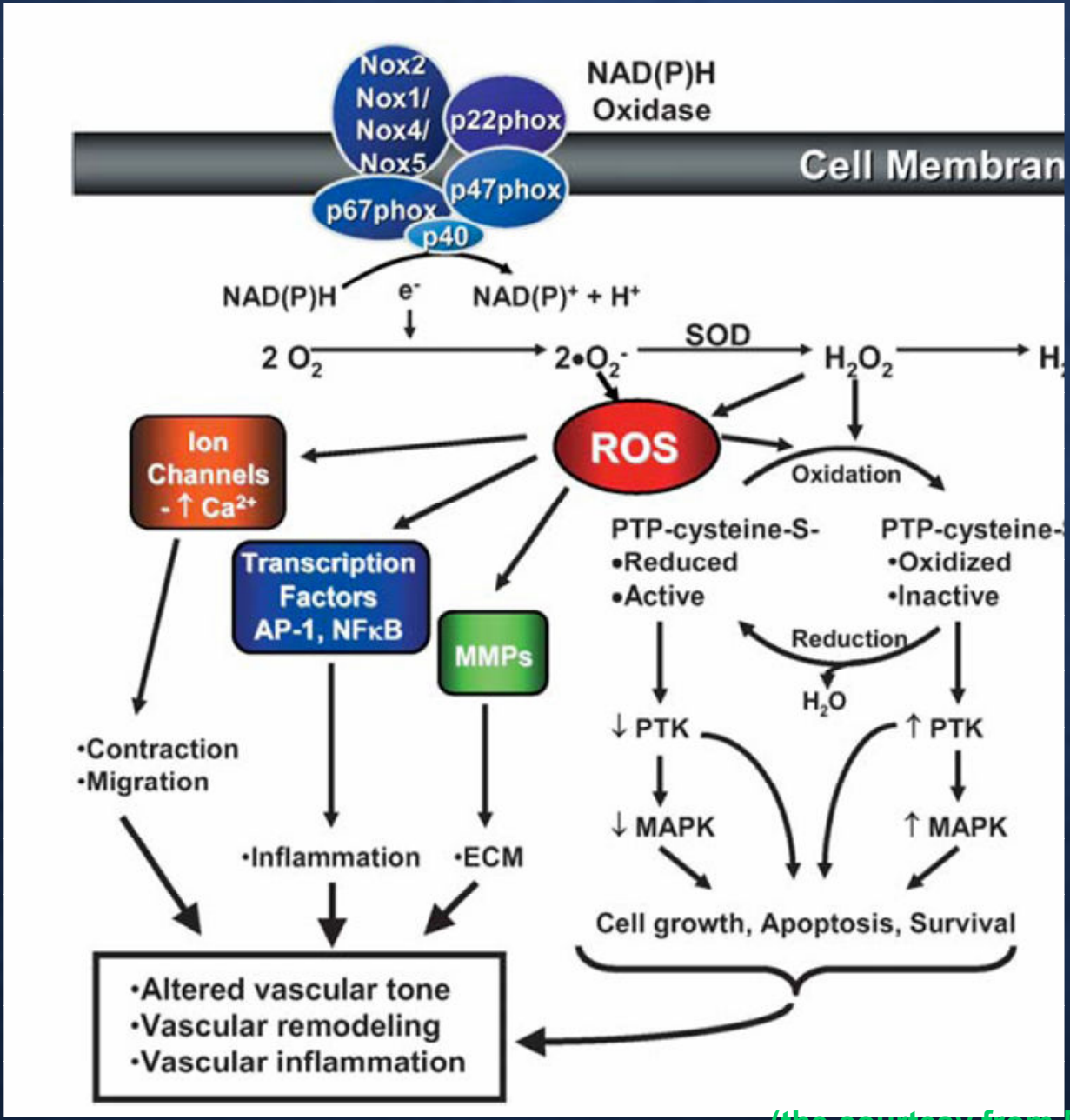
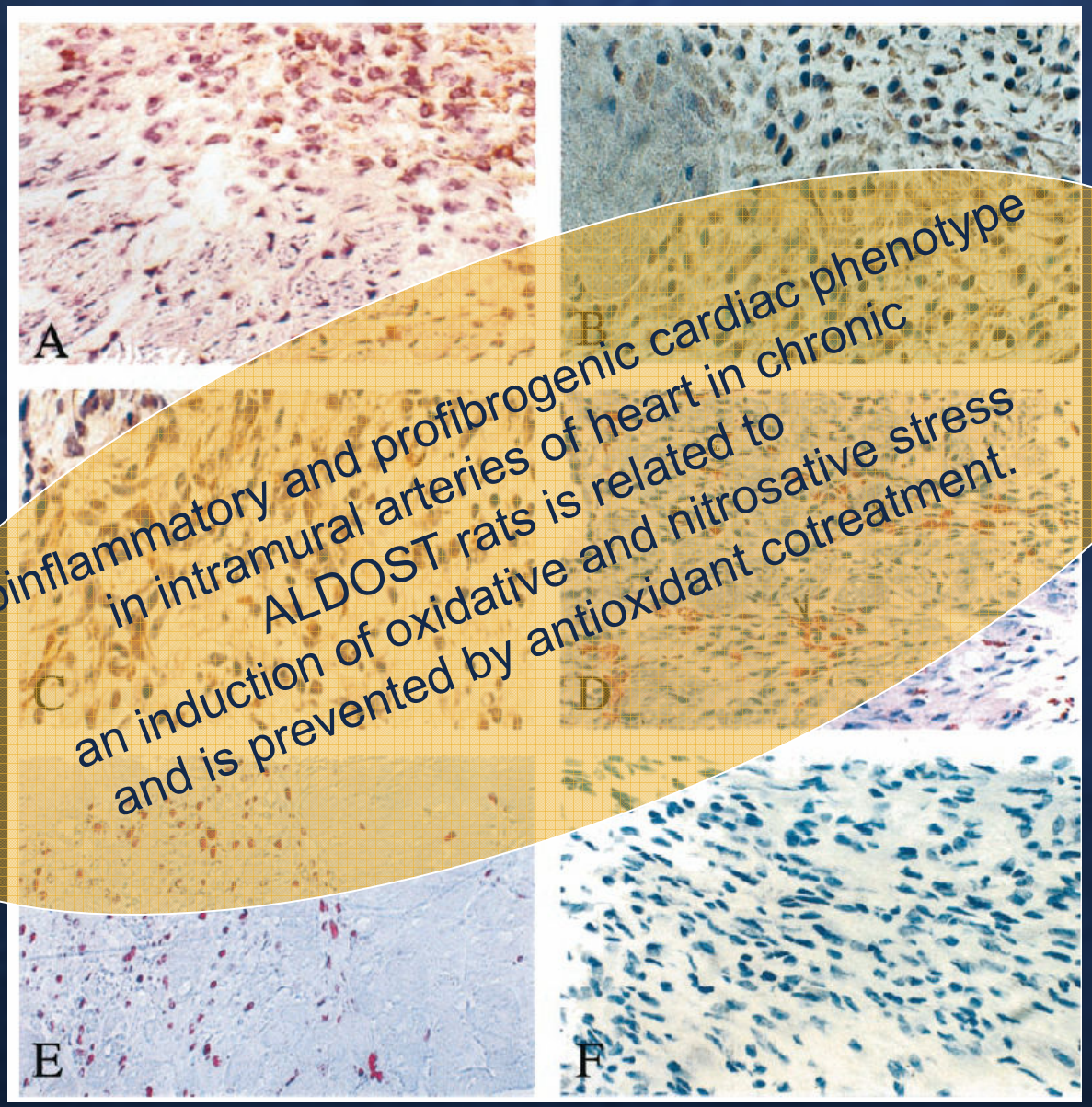
ROS and Vascular alterations



(the courtesy from Rhian M Touyz, 2004)

Aldosterone-Induced Inflammation in the Rat Heart
Role of Oxidative Stress



NADPH Oxidase Expression
gp91phox

3-Nitrotyrosine Staining

Activated NF-κB

ED-1-positive macrophages

BrdU-positive cells

Negative control

Proinflammatory and profibrogenic cardiac phenotype in intramural arteries of heart in chronic ALDOST rats is related to an induction of oxidative and nitrosative stress and is prevented by antioxidant cotreatment.

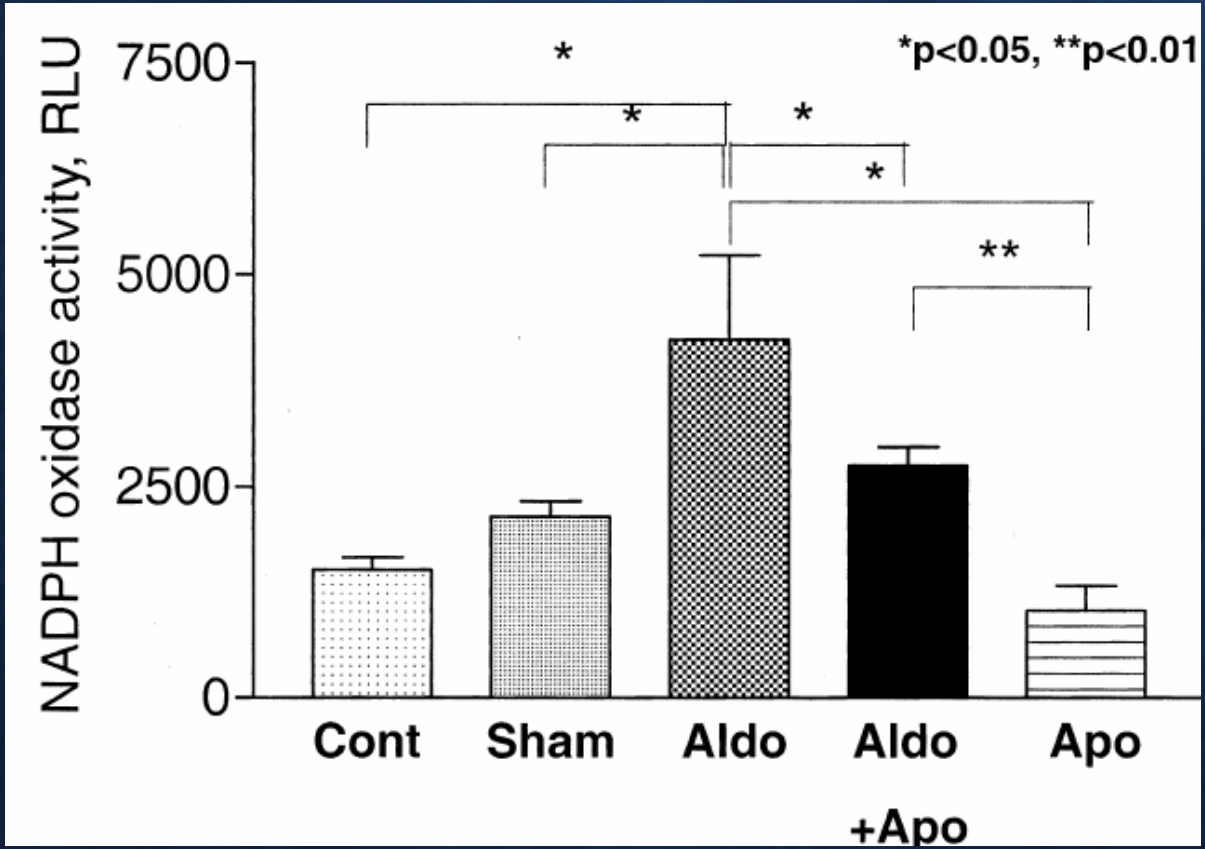
Sun Y et al.
Am J Pathol 2002

NAD(P)H oxidase inhibitor prevents blood pressure elevation and cardiovascular hypertrophy in aldosterone-infused rats☆

Young Mee Park,[a] Mi Young Park,[a] Yeon-Lim Suh,[b] and Jeong Bae Park[a,*]

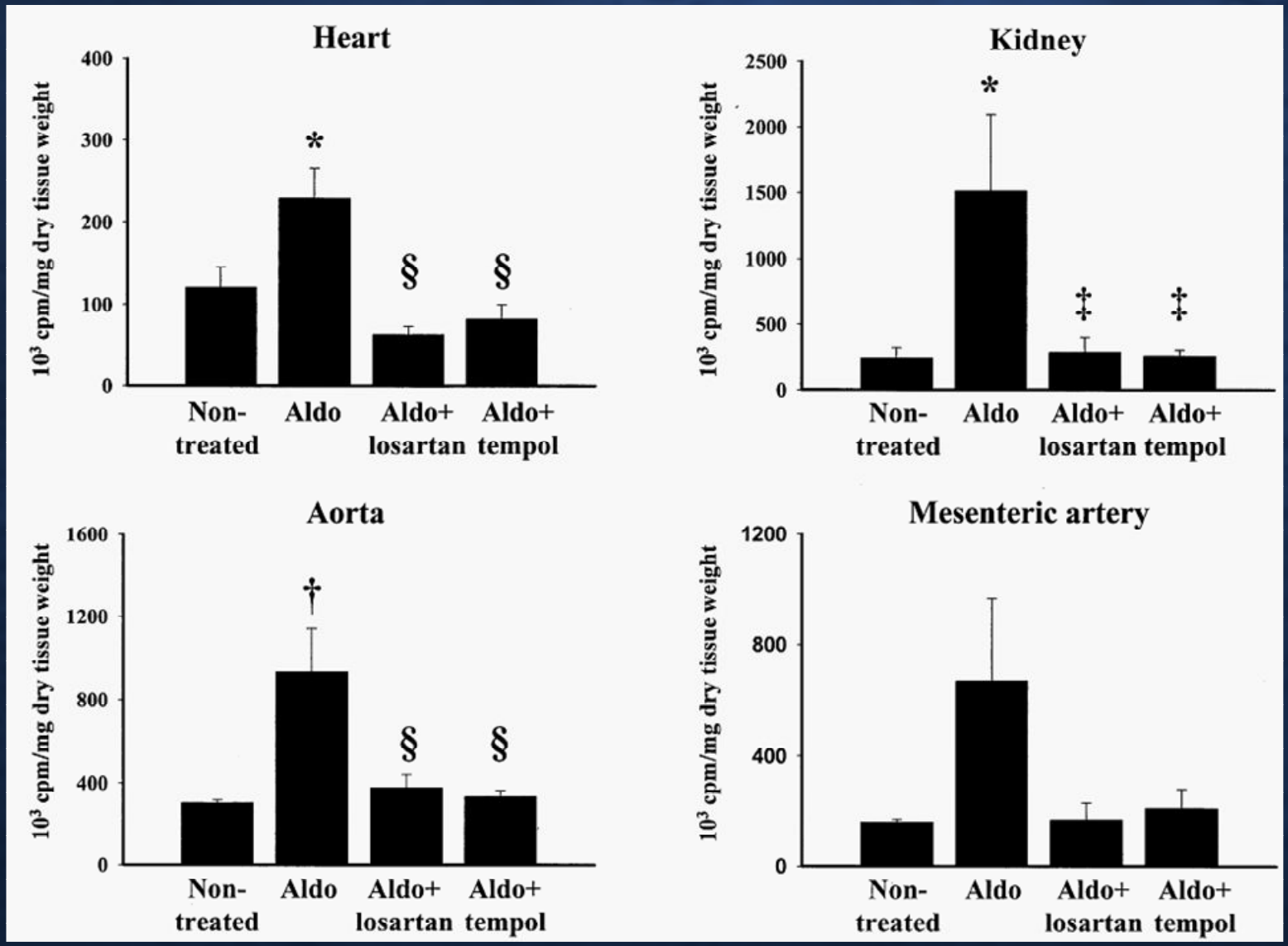
[a] *Department of Medicine/Cardiology, Samsung Cheil Hospital, Sungkyunkwan University School of Medicine and Samsung Biomedical Research Institute, Seoul, Republic of Korea*

[b] *Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*



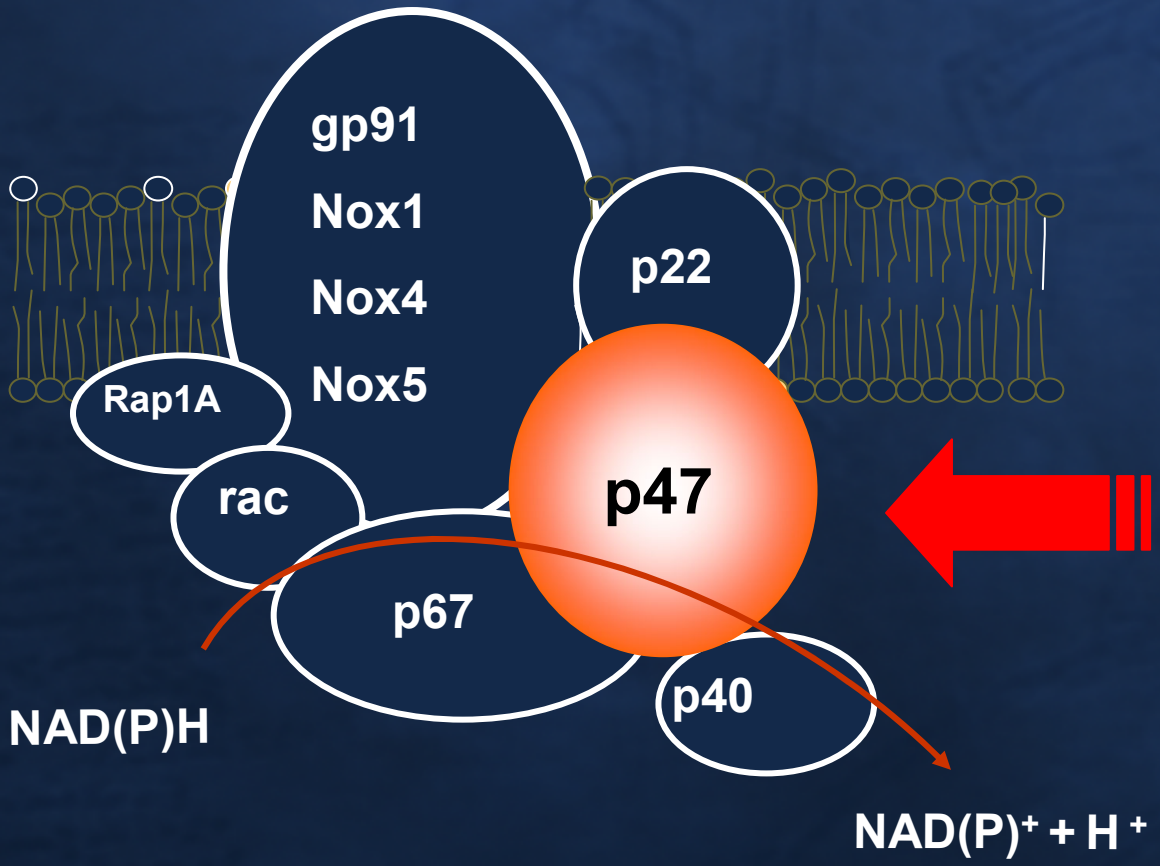
- BBRC 2004

Effect of aldosterone on NA(D)PH oxidase activity in aldosterone-induced fibrosis

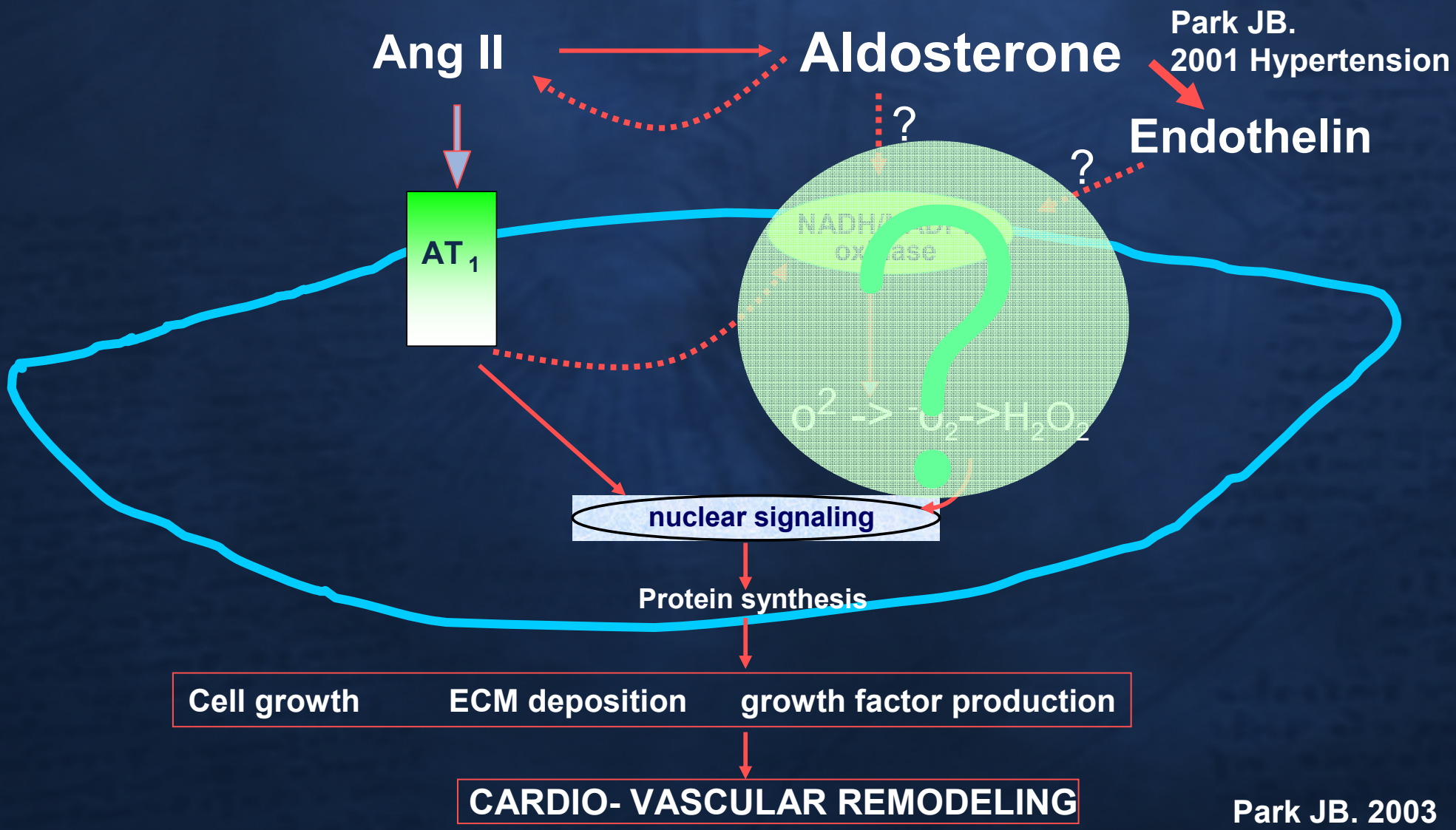


Iglarz M et al. 2004 AJH

Association of aldosterone with NAD(P)H oxidase subunits ($p47^{phox}$)?



Possible Pathway of Aldosterone on CV remodeling



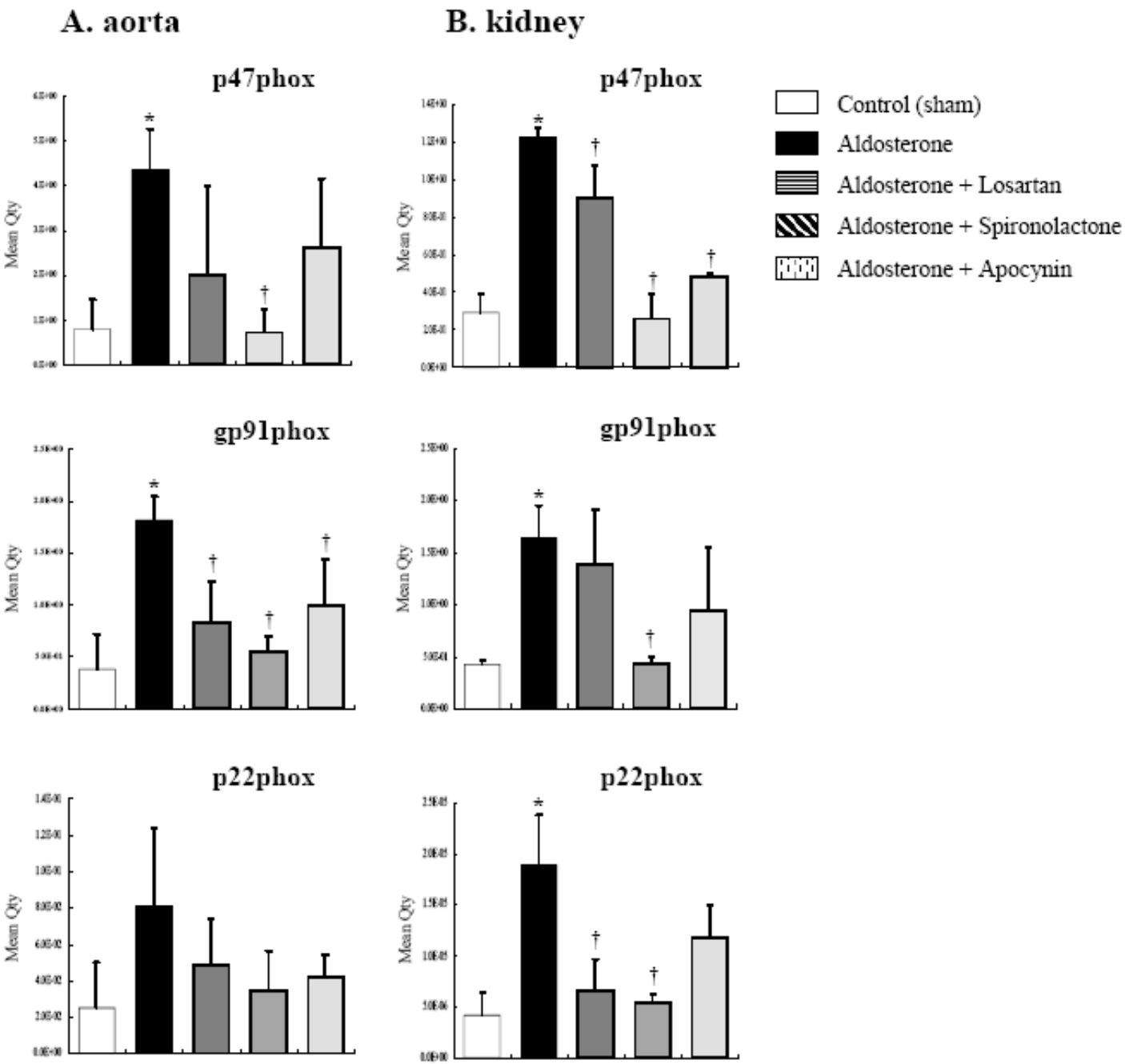
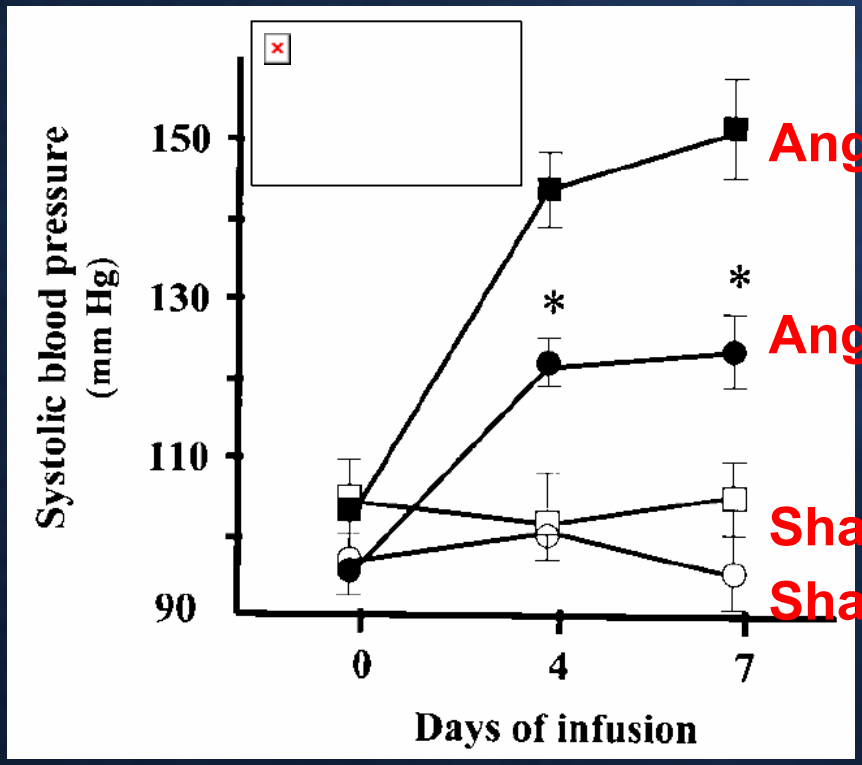
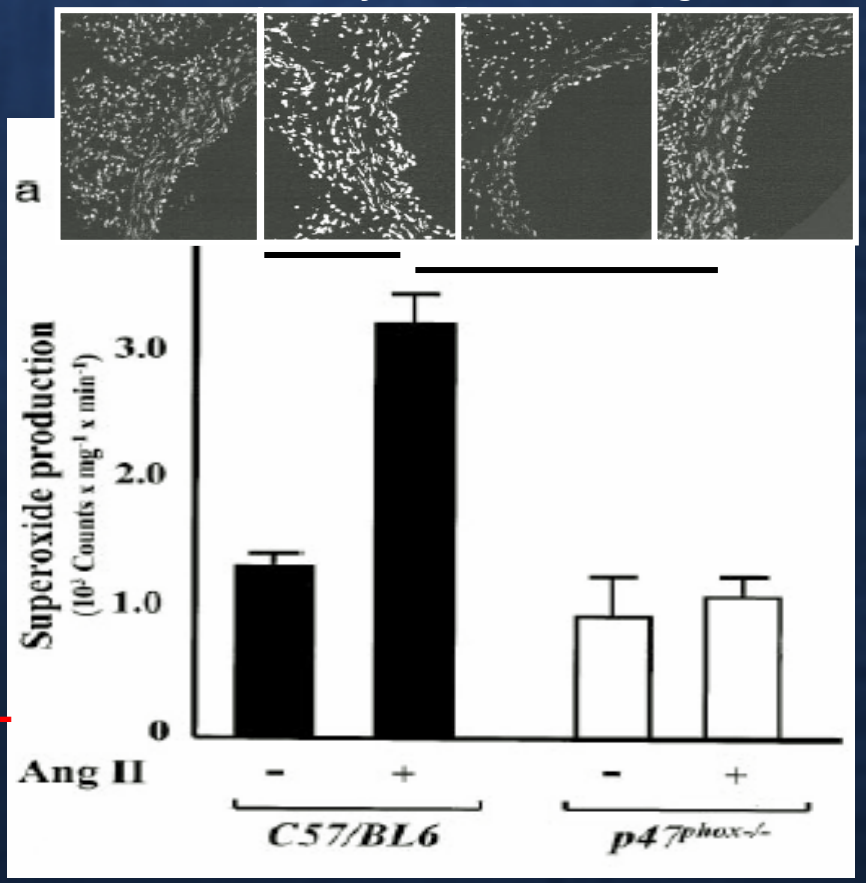


Figure 4. Treatment with spironolactone attenuated NAD(P)H oxidase mRNA expression in aorta(A) and kidney(B) of aldosterone-infused rats. The mRNA expression of the NAD(P)H oxidase subunits p47phox, gp91phox and p22phox was markedly increased in aldosterone-infused rats. The treatment with spironolactone significantly reduced NAD(P)H oxidase subunits mRNA expression. Losartan and apocynin decreased on NAD(P)H oxidase subunits mRNA expression in aorta and kidney from aldosteroneinfused rats. *P< 0.05 vs. control rats; †P<0.05, vs. aldosterone-infused rats.

Role of p47phox in vascular oxidative stress and hypertension caused by ang II

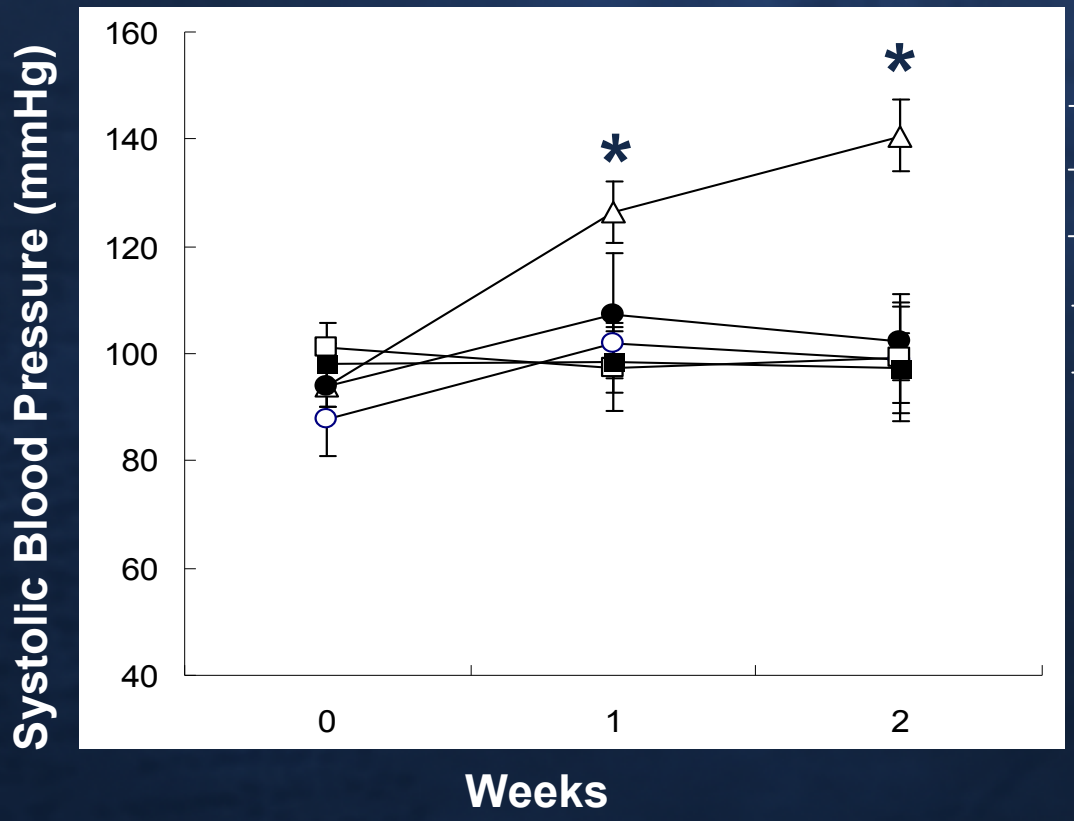


In situ dihydroethidium staining



Landmeser U…Harrison D. Hypertension. 2002;40:511-5.

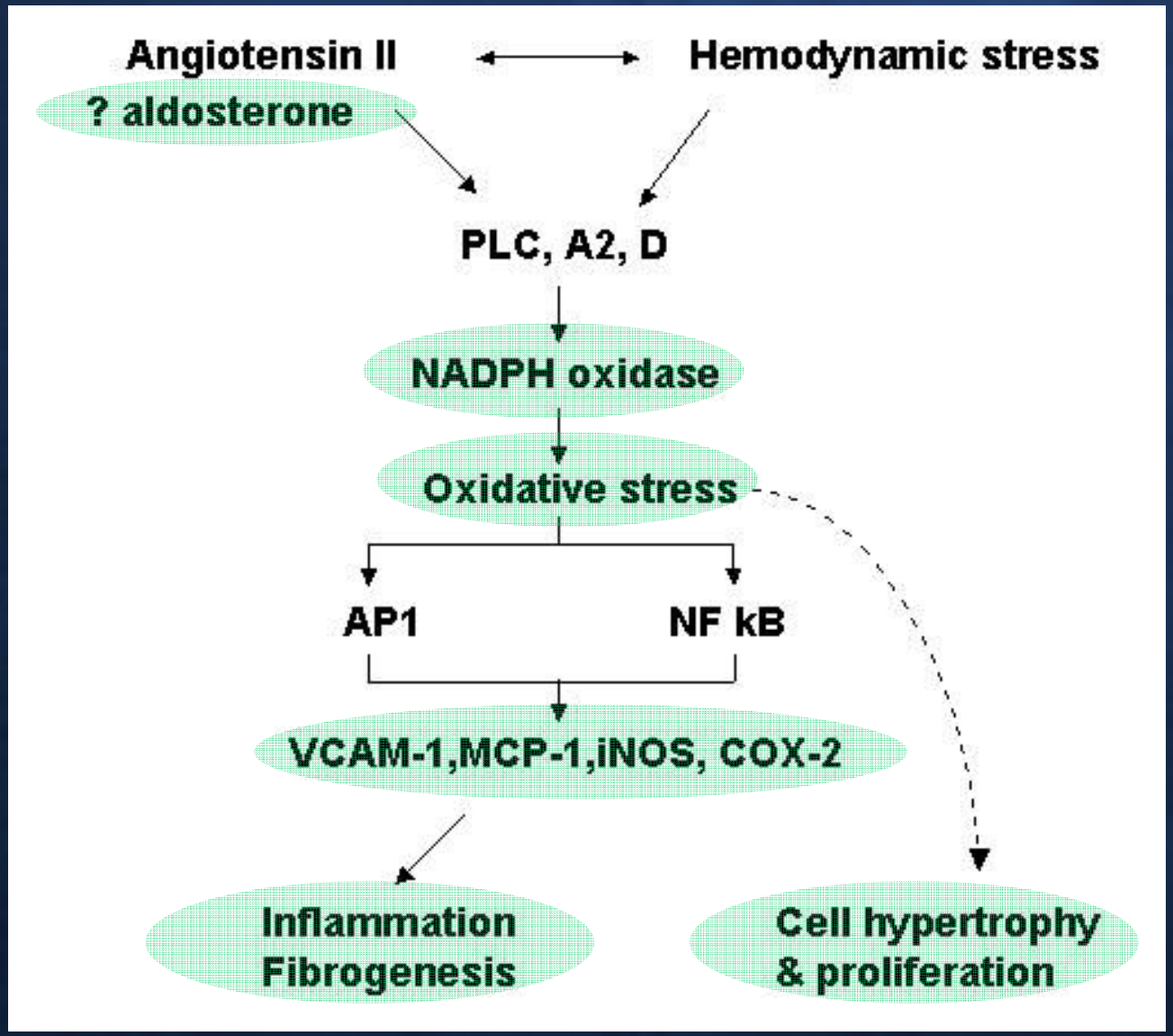
Role of a p47*phox*-containing NADPH oxidase in aldosterone-induced vascular oxidative stress and hypertrophy in mice



*, p<0.001, WT+Aldo vs others

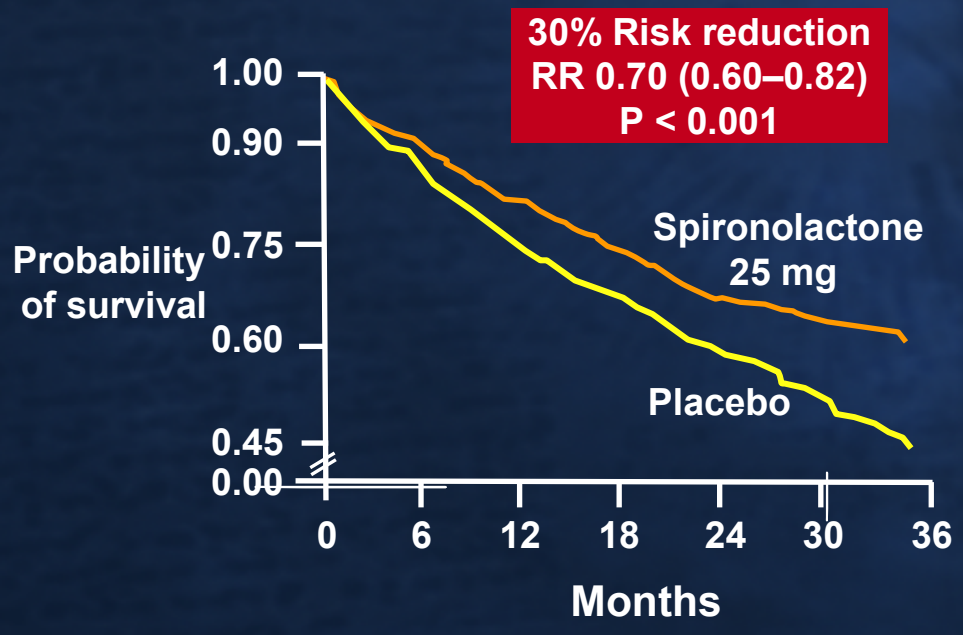
2007 unpublished, Park YM and Park JB

Relationship between aldosterone, and oxidative stress, inflammation, fibrosis

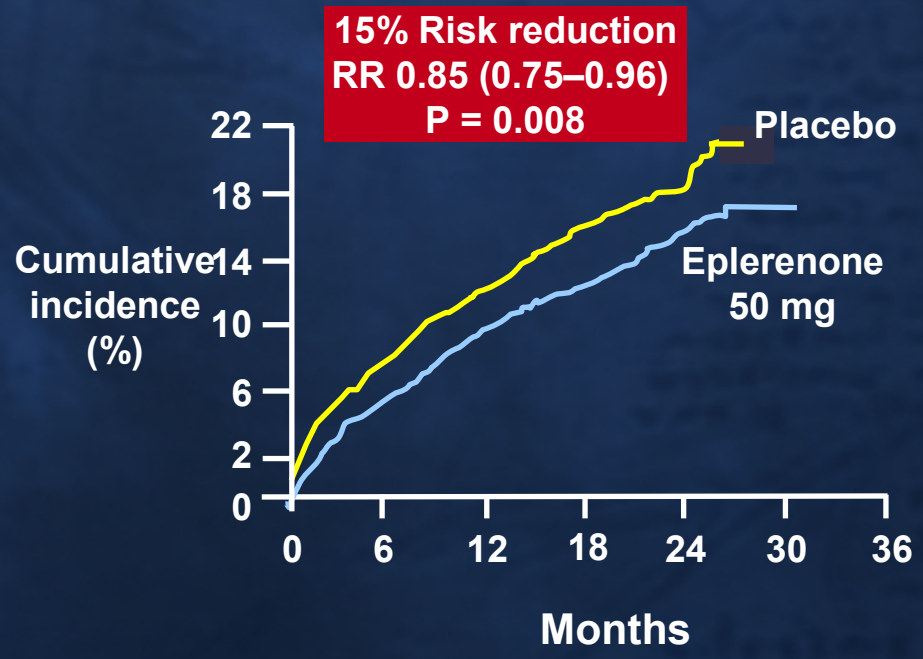


Aldosterone blockade and AT_1R blockade: Trials in post-MI LV dysfunction and HF

RALES

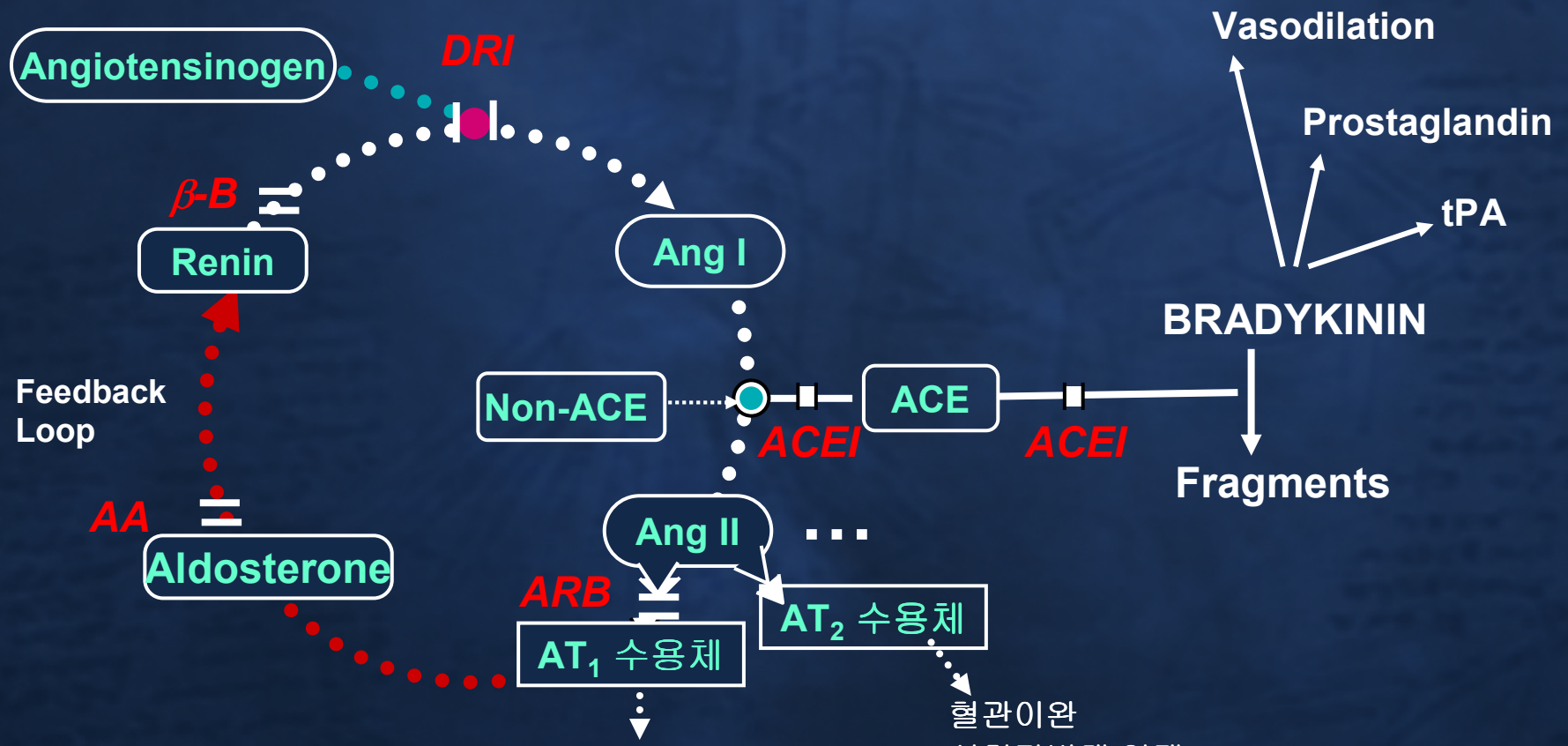


EPHESUS



Pitt B et al. *N Eng J Med*. 1999;341:709-17.
Pitt B et al. *N Eng J Med*. 2003;348:1309-21.

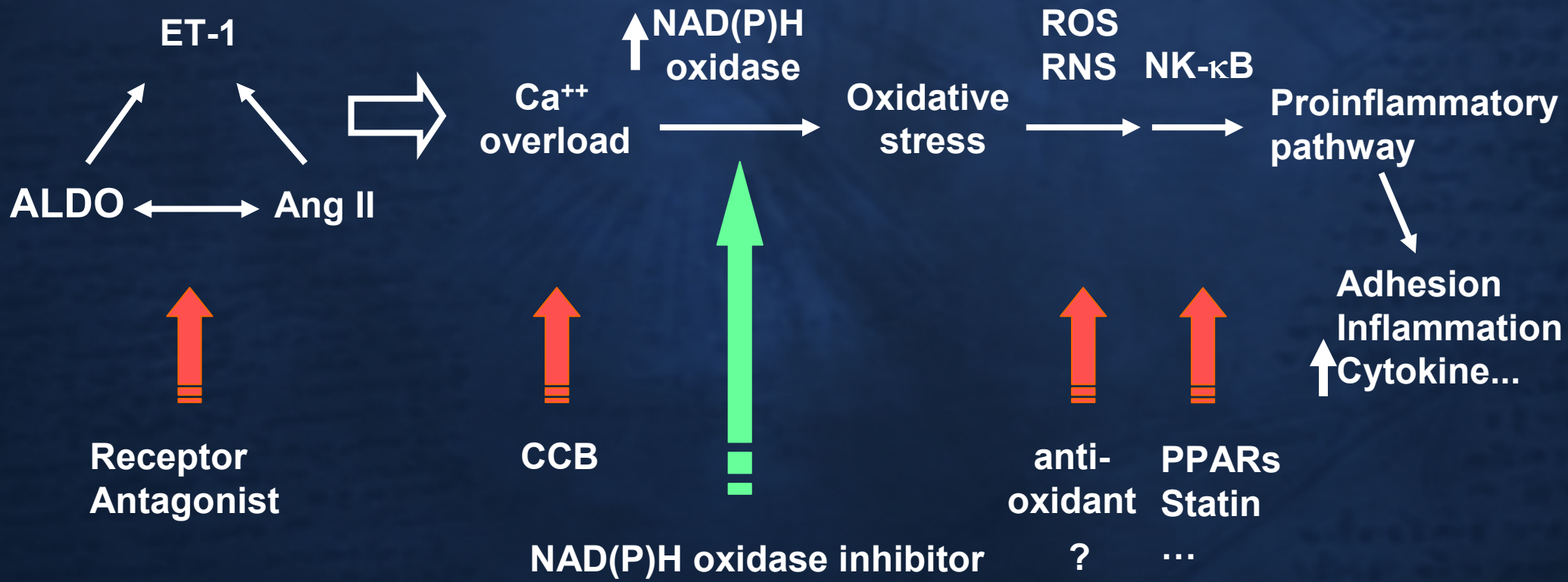
RAS blockade : where?



β-B; 베타차단제
DRI; 직접레닌억제제
ACEI; 안지오텐신 전환효소억제제
ARB; 안지오텐신수용체 (AT_1) 차단제
AA; aldosterone antagonist

2007 Park JB

Aldosterone, NAD(P)H oxidase and Vascular damage and Potential intervention



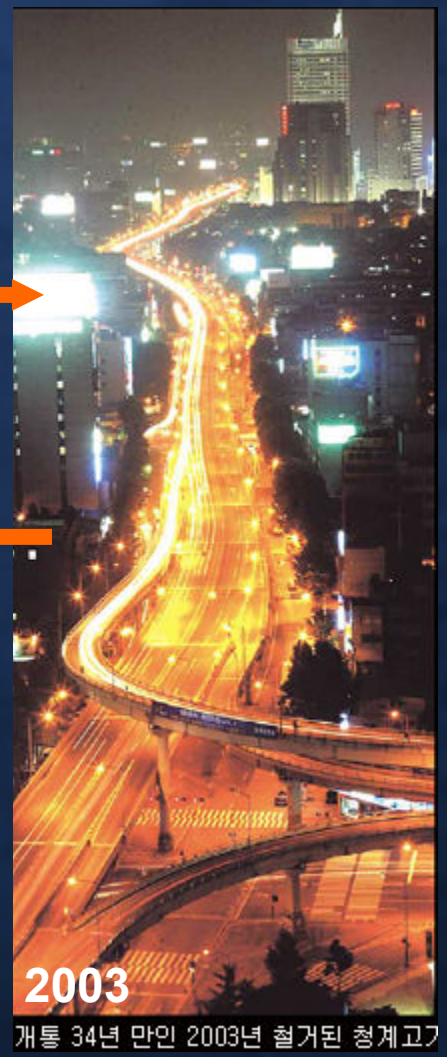
2005 Park JB

CheongGyeCheon in Seoul

▲ 1900년경 서울 수표교(현 청계천2가 **1900’**

1910년대의 오간수문 모습. **1910’**

복개를 위해 기둥을 박은 196(**1960’**



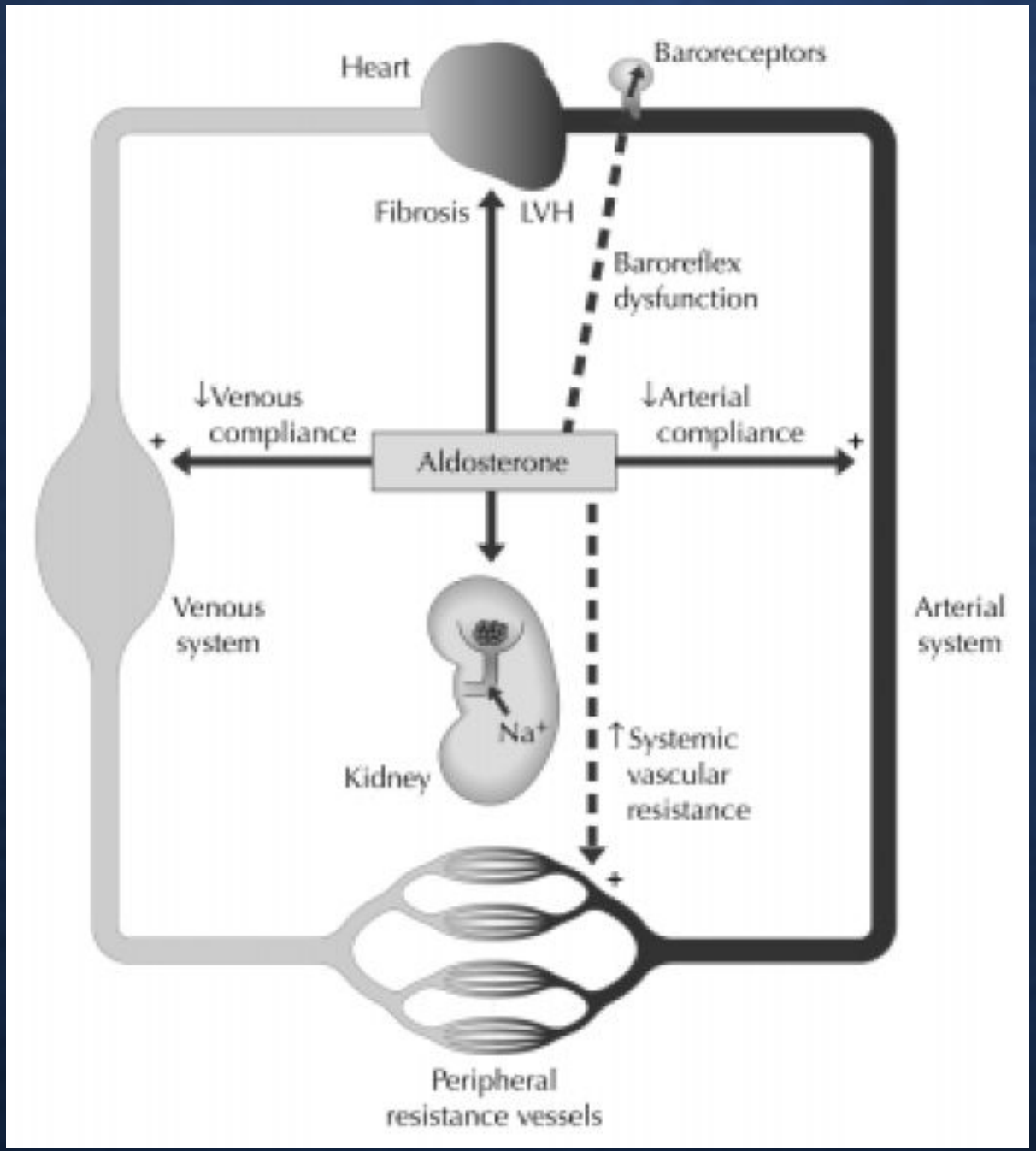
2003

개통 34년 만인 2003년 철거된 청계고가

2006

감사합니다.

Thank you!


Heart
Baroreceptors
Fibrosis
LVH
Baroreflex dysfunction
↓Venous compliance
↓Arterial compliance
Aldosterone
+
+
Venous system
Arterial system
Na+
Kidney
↑Systemic vascular resistance
+
Peripheral resistance vessels