

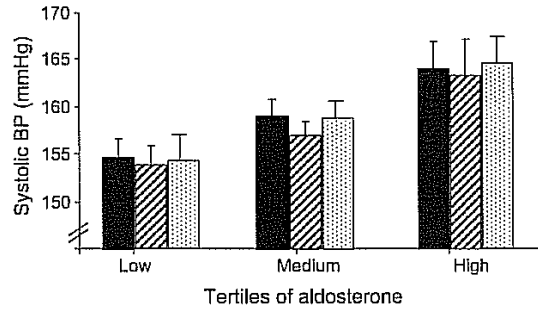


Aldosterone and “Essential” Hypertension

Theodore A. Kotchen, MD
Professor Emeritus, Department of Medicine
Associate Dean for Clinical Research

- Genest J et al. Human arterial hypertension: a state of mild chronic hyperaldosteronism? *Science* 1956
- Grim CE. Low renin “essential” hypertension: a variant of primary aldosteronism? *Arch Intern Med* 1975

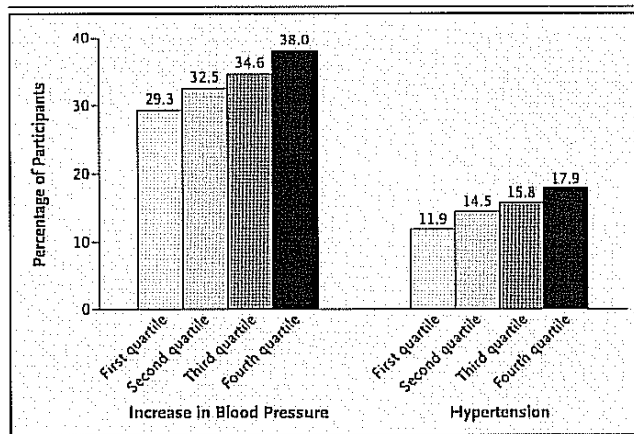
Systolic Blood Pressure by Tertile of Plasma Aldosterone



Black solid bar—after dex
 Striped bar—no drug
 Dotted bar—after ACTH

Reynolds et al, Hypertension, 2009;53:932-936

Blood Pressure Outcomes at 4 Years by Serum Aldosterone



Vasan RS et al, NEJM, 2004;

Subjects for Inpatient Protocol

Inclusion criteria:

- African American (age 18-55 yrs)
- Hypertension: Screening BP >140/90 mmHg, or on antihypertensive meds
- Normotension: Screening BP in lower tertile of population based distribution

Exclusion criteria:

- serum creatinine >2.2 mg/dl
- diabetes
- BMI >36 kg/m²
- substance abuse
- recent MI or stroke

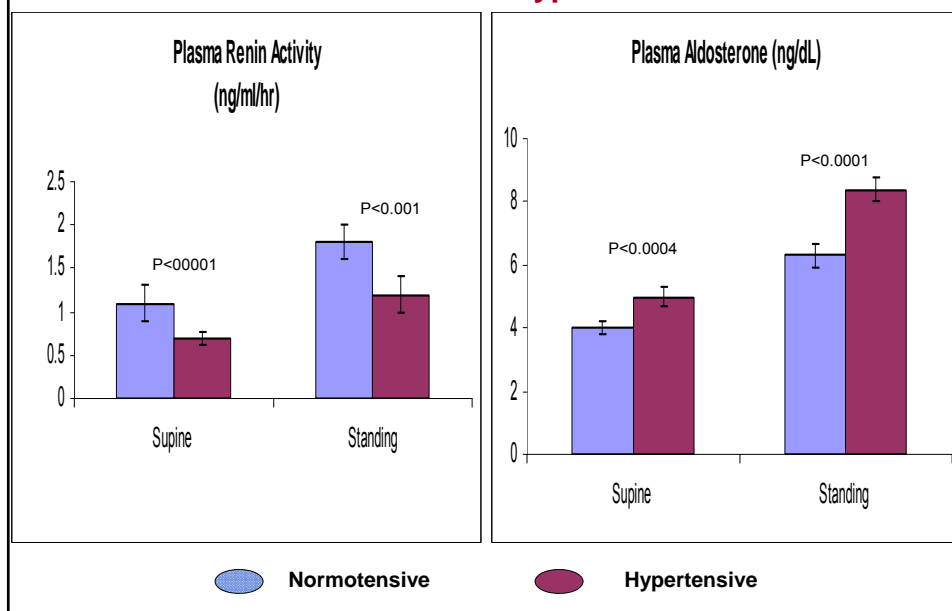
Study conditions:

- Off antihypertensive meds >1 week
- Off lipid lowering meds >4 weeks

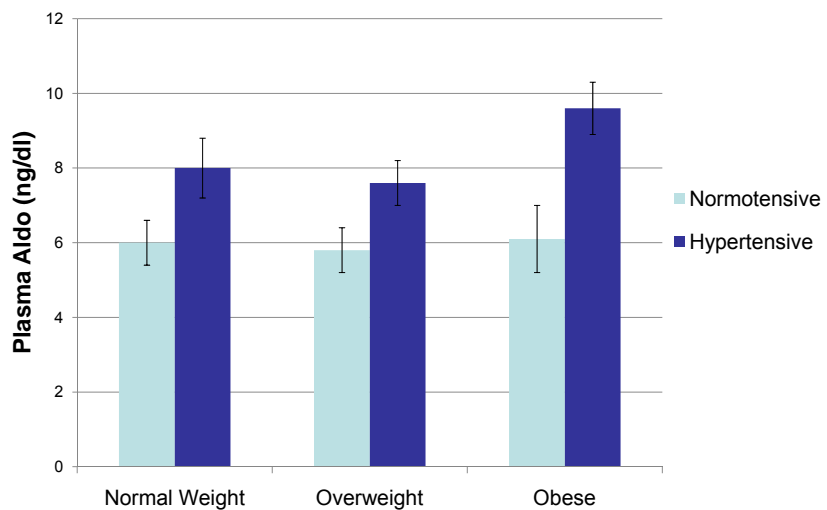
	Normotensives (n=231)	Hypertensives (n=231)
Age (yrs)	42.4	45.4*
% Female	53	46
Day BP (mmHg)	116/70	146/88
Night BP (mmHg)	110/65	139/83
BMI (kg/m ²)	27.8	29.6*
Waist Circum (cm)	87.7	94.2*
Glucose (mg/dl)	88	90
Insulin (uU/ml)	11.8	13.2*
HOMA-IR	1.5	1.7*
Triglycerides (mg/dl)	90	110*
Cholesterol (mg/dl)	175	185*
HDL (mg/dl)	49	45*
LDL (mg/dl)	109	118*

	Normotensives	Hypertensives
Creat. Clear. (ml/min)	147 ± 4	139 ± 4
Na ⁺ excretion (mEq/24 hr)	195 ± 6	185 ± 6
Microalb excretion (mg/24 hr)	12.4 ± 0.9	13.7 ± 0.9
Renal Blood flow (mL/min/1.73m ²)	2046 ± 109	1694 ± 86*
Renal Vasc Resis. (units/1.73m ²)	3760 ± 160	6320 ± 320*
Cardiac index (L/min/m ²)	2.22 ± 0.07	2.23 ± 0.09
TPR (dynes/sec/cm ⁻⁵ /m ² (MAP/CI) x80	3556 ± 143	4932 ± 199*
Vasc Compliance (ml/m ² /mmHg)	0.91 ± 0.03	0.62 ± 0.03*

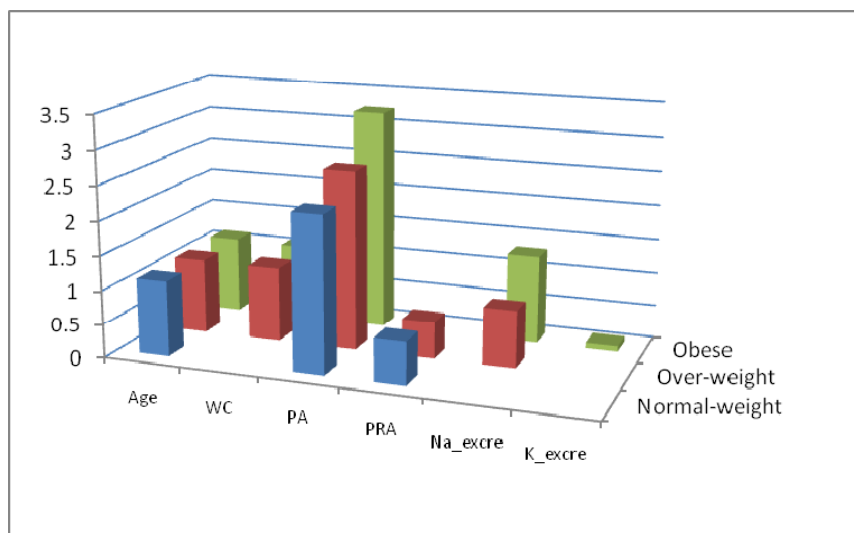
Plasma Renin Activity and Plasma Aldosterone in Normotensives and Hypertensives



Plasma Aldo by Body Weight and BP Status



Odds Ratio for Hypertension in Normal Weight, Overweight, and Obese Subjects

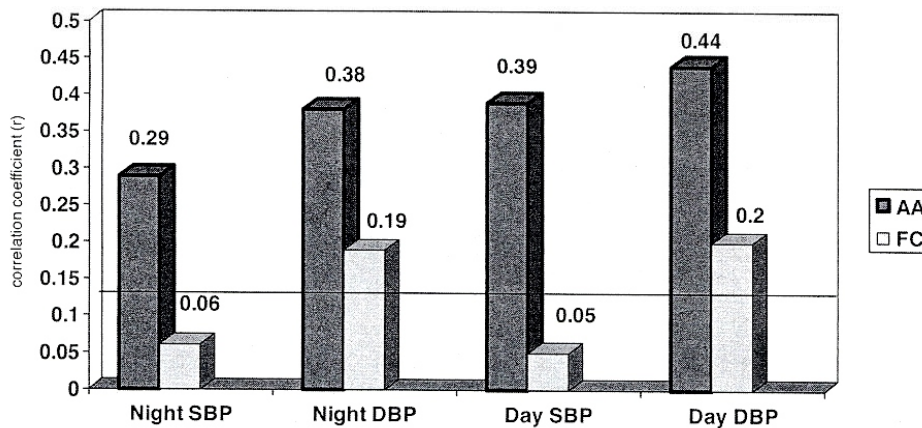


Comparison of Aldo and PRA by Ethnicity and BP Group

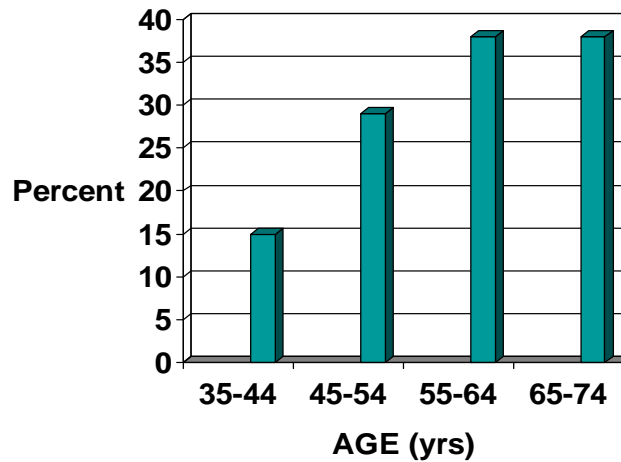
	African Americans		French Canadians	
	Normotensive (n=233)	Hypertensive (n=233)	Normotensive (n=150)	Hypertensive (n=129)
Plasma Aldo (ng/dl)	6.1 ± 0.4	8.4 ± 0.4*	6.2 ± 0.3	7.6 ± 0.4*
PRA (ng/ml/hr)	2.0 ± 0.2	1.0 ± 0.2*	2.3 ± 0.3	1.8 ± 0.1*
Aldo/PRA	12.8 ± 2.0	30.8 ± 3.0*	4.5 ± 0.5	8.0 ± 1.2*

*p < 0.05 (or less) in same ethnic group

Correlation Coefficients of Plasma Aldosterone with Blood Pressure in African Americans and French Canadians



Percent of Hypertensives(n=287) with Elevated Aldo/Renin Ratio*, by Age

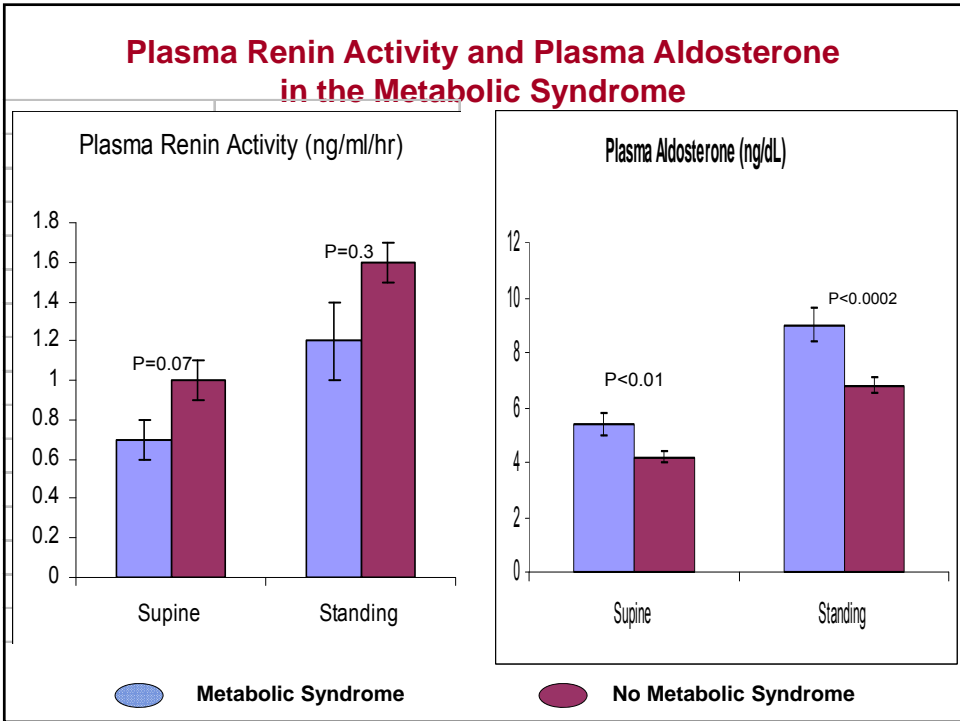
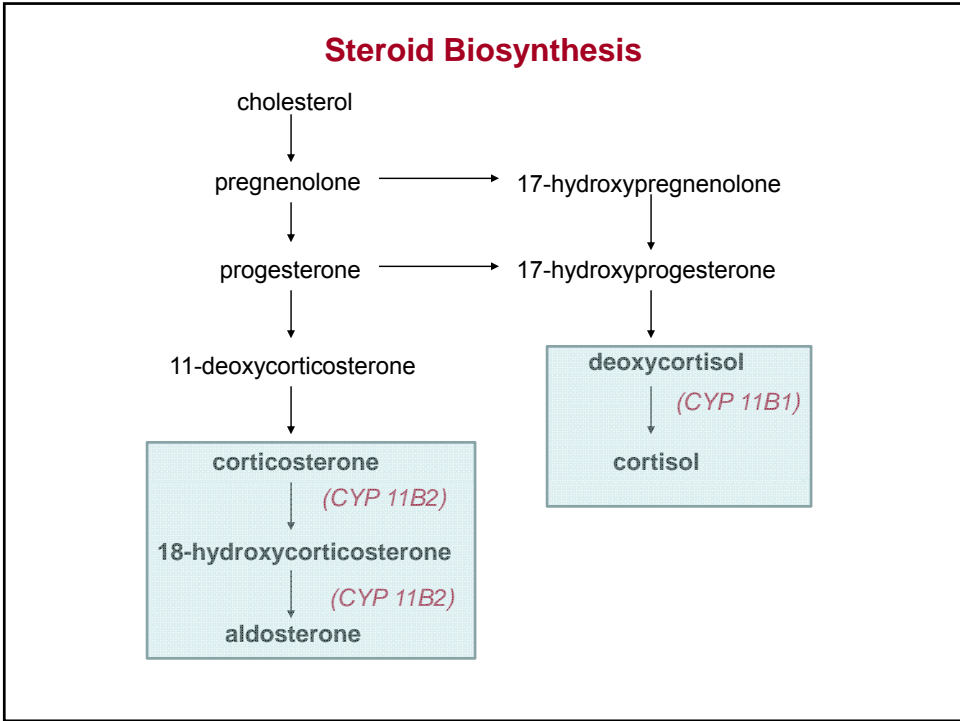


* >50 ng/dl/ng/ml per hr

Olivieri et al, JCEM 2004;89:4221-4226

Hypothetical Mechanisms for Relatively High Aldosterone, Despite Low Renin, in Hypertensives

- a. aldosterone stimulating factor in visceral adipose tissue
- b. other aldosterone stimulating factors
- c. secretion of aldosterone by adipocytes
- d. decreased NO bioavailability
- e. "autonomous" aldosterone production
- f. variation in aldosterone synthetase (*CYP11B2*)



Sex-Specific Correlation Coefficients of Plasma Aldosterone

	Women	Men
SBP	0.31***	0.20**
BMI	-0.05	0.21**
Waist Circ	0.11	0.17*
Trig	0.06	0.14*
HDL	0.00	-0.15*
Insulin Resis	0.00	0.30***

Phenotypic Correlates of Serum Aldosterone

- Hemodynamic
 - 24-hour blood pressure ***
 - Vascular compliance **
 - Renal vascular resistance *
- Cardiac
 - LV mass index ***
 - Post wall thickness **
 - Interstitial thickness *
- Anthropometric
 - BMI *
 - Waist circumference **
 - Insulin resistance *

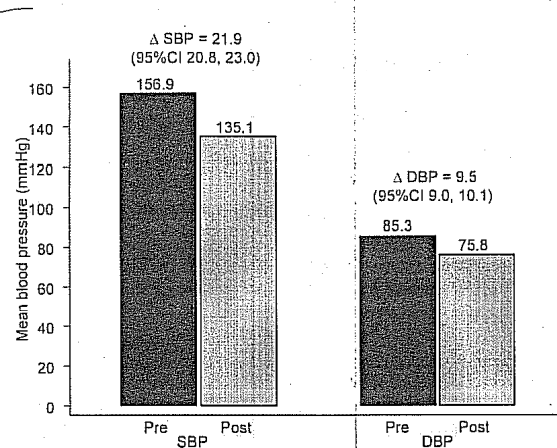
Cardiac Dimensions in Hypertensive African Americans and French Canadians

	African Americans (n=109)	French Canadians (n=73)
LVMI (gm/m ²)	123 ± 5	86 ± 2*
PWT (mm)	11.7 ± 0.2	8.8 ± 0.1*
IST (mm)	12.1 ± 0.3	9.6 ± 0.2*

Correlation Coefficients of Plasma Aldosterone with Cardiac Mass

	African Americans (n=109)	French Canadians (n=73)
LVMI	.36***	-.06
PWT	.33**	-.08
IST	.26**	.03

Mean BP Before and During Spironolactone in Patients with Resistant Hypertension



Chapman N et al, Hypertension, 2007

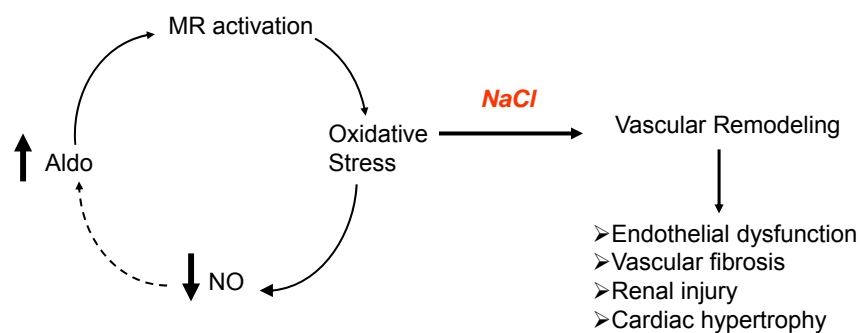
Aldosterone: Heart Disease and Proteinuria

- High plasma aldosterone on admission is associated with death in patients with acute ST-elevation MI (Beygui et al, Circ 2006)
- Spironolactone, in addition to standard therapy, reduces morbidity and mortality in patients with severe CHF (Pitt et al, NEJM 1999)
- Eplerenone, in addition to “optimal” therapy, reduces morbidity and mortality in patients with MI complicated by LV dysfunction and CHF (Pitt et al, NEJM 2003)
- Spironolactone, in addition to standard therapy, decreases proteinuria in patients with chronic renal disease (Sato et al, Am J Hypertens 2005)

Pathogenesis of Aldosterone-Induced Hypertension and Vascular Injury

- Mineralocorticoid receptors present in kidney, colon, and non-epithelial tissues (e.g., heart, blood vessels, brain)
- Activation of non-epithelial receptors causes oxidative stress, vascular inflammation, vasoconstriction, and tissue injury
- Hypertension and vascular injury potentiated by a high NaCl diet
- Mechanisms of hypertension related to
 - Na⁺ retention
 - Activation of vascular mineralocorticoid receptor

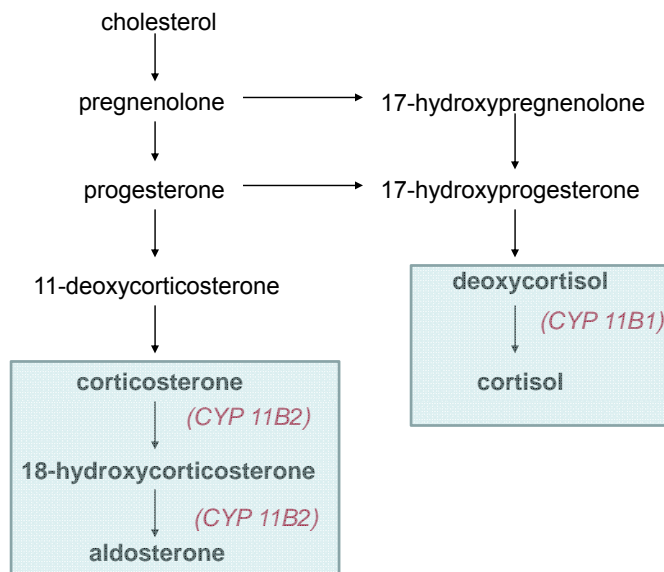
Aldosterone Induced Vascular/Tissue Injury



Monogenic “Mineralocorticoid” Hypertensive Disorders

- 17 α hydroxylase deficiency
- 11 β hydroxylase deficiency
- 11 β hydroxysteroid dehydrogenase deficiency
- Activation of mineralocorticoid receptor by progesterone during pregnancy
- Liddle’s syndrome—activation of amiloride-sensitive Na⁺ channel on distal renal tubule

Steroid Biosynthesis



Summary

- BP and hypertension are associated with relatively high aldo, despite low PRA
- Metabolic syndrome is associated with higher aldo in African American males
- Aldo induced oxidative stress leads to vascular remodeling and tissue injury
- Aldo antagonists are useful in treating CHF, post MI with CHF, resistant hypertension

Perspectives

- Is low renin “essential hypertension” a variant of mild primary aldo, particularly in African Americans?
- Most patients with “primary aldo” have bilateral adrenal hyperplasia
- There may be an expanded role for aldo antagonists in the treatment of hypertension and prevention of hypertension-related CVD in African Americans