

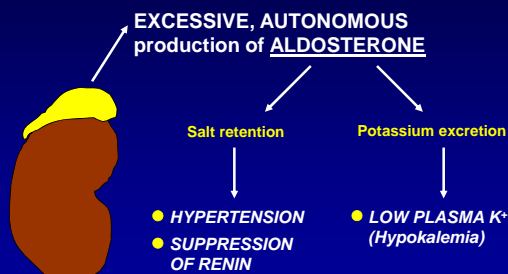
The "Aldosterone Renaissance"

Bench to bedside evidence for the expanding role of aldosterone excess as a cause of hypertension and cardiovascular disease, and importance of detection and management

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PRIMARY ALDOSTERONISM (PAL)



SUBTYPES OF PRIMARY ALDOSTERONISM

BILATERAL ADRENAL HYPERPLASIA (BAH) ~70%
- both adrenals overproducing aldo

ALDOSTERONE-PRODUCING ADENOMA (APA) ~30%
- benign adrenal tumor overproducing aldo

ALDOSTERONE-PRODUCING CARCINOMA
- malignant adrenal tumor overproducing aldo

FAMILIAL HYPERALDOSTERONISM TYPE I
- rare, genetic form of PAL that runs in families (glucocorticoid suppressible hyperaldosteronism)

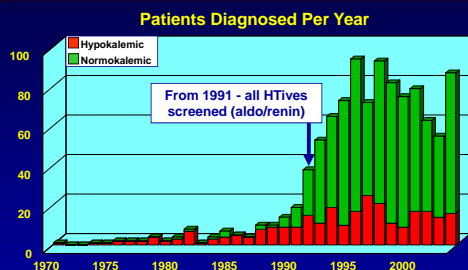
Harrison's Principles of Internal Medicine, 1991

"...primary aldosteronism accounts for less than 1% of all patients with hypertension..."

Clinical Hypertension, 1994

"...the search for primary aldosteronism need only be undertaken in those with hypokalemia..."

PRIMARY ALDOSTERONISM - Greenslopes Hospital (1970-) and Princess Alexandra Hospital (2000-)



- Total number of patients with PAL = 1414
- Total number undergoing unilateral ADX for APA = 352

Gordon RD, et al. Lancet 1992
Stowasser M, et al. Mol Cell Endocrinol 2004

PRIMARY ALDOSTERONISM - GREENSLOPES HOSPITAL

- Out of 199 normokalemic patients referred to the HT Unit without the diagnosis of PAL in mind:
- 19 had PAL (9.5%)

Gordon RD, et al. Clin Exp Pharm Physiol 1994

- Out of 52 patients with HT who volunteered for antihypertensive drug trials:

- 6 had PAL (12%)

Gordon RD, et al. Clin Exp Pharm Physiol 1993

PREVALENCE OF PAL - SINCE 1997

Units reporting increased prevalence:

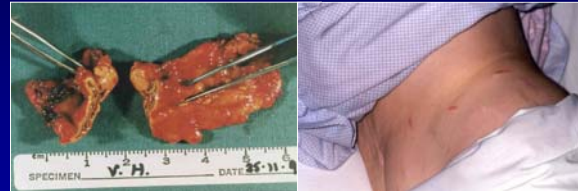
Fardella, et al (Chile)	Loh, et al (Singapore)
Widimsky, et al (Czech Rep)	Rayner, et al (Sth Africa)
Douma, et al (Greece)	MacDonald, et al (UK)
Benchetrit, et al (Israel)	Young Jr, et al (USA)
Rossi, et al (Italy)	Gallay, et al (USA)
Mulatero, et al (Italy)	Calhoun, et al (USA)
Nishikawa, et al (Japan)	Schwartz, et al (USA)

● **Prevalence rates:** mostly 5 - 15%

● **Proportion normokalemic:** 59 - 100%

TREATMENT OF PRIMARY ALDOSTERONISM DUE TO ALDO-PRODUCING ADENOMA

UNILATERAL LAPAROSCOPIC ADRENALECTOMY



- HT cured in 50-60%, improved in all the remainder
- Marked improvement in quality of life

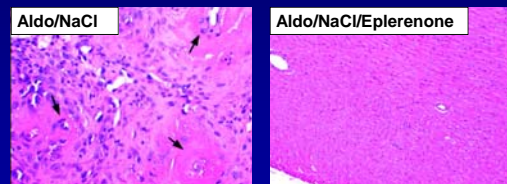
TREATMENT OF PRIMARY ALDOSTERONISM DUE TO BILATERAL ADRENAL HYPERPLASIA

SPECIFIC MEDICAL TREATMENT

- Aldosterone receptor blockers - spironolactone, eplerenone
- Epithelial sodium channel inhibitors - amiloride
- Improved control of hypertension (often marked)

ALDO + SALT = INFLAMMATION & FIBROSIS

- 1990 Karl Weber aldo+salt, rats, myocard fibrosis
- 2002 Ricardo Rocha aldo+salt, rats, coronary vasculitis



Rocha et al, Am J Physiol 2002

CARDIAC ABNORMALITIES IN PRIMARY ALDOSTERONISM

Compared with matched essential hypertensives:

- ↓ myocardial perfusion at rest on thallium-201 scanning (M Abe, et al)
- ↑ exercise-induced myocardial ischemia on MIBI-SPECT and echocardiography (C Napoli, et al)
- ↑ LVMI, ↓ Diastolic function (GP Rossi, et al)
- ↑ Myocardial backscatter (M Kozakova et al)
- ↓ Flow-mediated vasodilatation (M Nishikawa et al)
- ↑ Strokes, AMIs, AF (P Milliez et al and C Catena, et al)

CARDIOVASC ABNORMALITIES IN PAL - CCRE STUDY 1

Relationship of aldo levels to cardiac abnormalities in primary aldosteronism

Subjects

- 60 patients with primary aldosteronism (PAL)
 - mean age 54 ± 12 y SD; 48% males
- 33 normotensive controls (CTRL)
 - mean age 47 ± 13 y SD; 58% males

CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 1

	PAL (n=60)	CTRL (n=33)	P value
Serum Aldo (ng/dL)	23.3 ± 14.2	11.8 ± 7.8	<0.001
24h Amb SBP (mmHg)	148 ± 19	125 ± 11	<0.001
24h Amb DBP (mmHg)	87 ± 11	75 ± 8	<0.001
PWV (m/s)	14.9 ± 4.1	12.4 ± 3.3	<0.01
LVMI (g/m²)	113 ± 28	81 ± 14	<0.001

Results expressed as means ± SD

M Stowasser & T Marwick, et al

CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 1

	PAL (n=60)	CTRL (n=33)	P value
<u>Function</u>			
Strain Rate (s⁻¹)	-1.25 ± 0.21	-1.53 ± 0.28	<0.001
Cyc Var of Integrated Backscatter (dB)	8.5 ± 2.9	10.8 ± 2.9	<0.001
<u>Structure</u>			
Integrated Backscatter (dB)	-24 ± 11	-31 ± 6	<0.01

Results expressed as means ± SD

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Multivariate Analyses (PAL only)

<u>Strain Rate</u>	b value	P value	<u>CVIB</u>	b value	P value
Age	-0.30	n.s.	Age	-0.10	n.s.
Gender	-	n.s.	Gender	-	n.s.
24h SBP	0.12	n.s.	24h SBP	-0.37	0.051
24h DBP	-0.41	0.05	24h DBP	0.16	n.s.
ALDO	-0.35	<0.05	ALDO	-0.45	<0.01
PIIINP	-0.02	n.s.	PIIINP	0.03	n.s.
LVMI	-0.08	n.s.	LVMI	0.48	<0.05

n = 40

r² = 0.23

n = 40

r² = 0.40

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CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 2

Assessment of cardiac structure and function in normotensive subjects with primary aldosteronism

- 8 subjects with an inherited form of primary aldosteronism (Familial Hyperaldosteronism Type I, FH-I) detected by genetic testing, whose blood pressure levels were still normal, compared with 24 normotensive age- and sex-matched controls (3 for each subject with FH-I):
 - 24h ABPM
 - Aldo, renin, ARR levels
 - Echo

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CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 2

	FH-I (n=8)	CTRL (n=24)	P value
Age (y)	26 ± 14	26 ± 12	n.s.
Females (%)	5 (63%)	15 (63%)	n.s.
24h Amb SBP (mmHg)	120 ± 10	118 ± 10	n.s.
24h Amb DBP (mmHg)	71 ± 11	70 ± 5	n.s.
Serum Aldo (ng/dL)	20.3 ± 15.1	11.1 ± 7.8	<0.05
PRA (ng/ml/h)	1.8 ± 2.6	2.3 ± 2.9	n.s.
Aldo/renin	79 ± 117	7 ± 5	<0.01

Results expressed as means ± SD

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CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 2

	FH-I (n=8)	CTRL (n=24)	P value
<u>Wall thicknesses</u>			
IVS (mm)	9.4 ± 1.2	7.9 ± 0.9	<0.001
PW (mm)	9.2 ± 1.7	7.7 ± 1.0	<0.01
RWT	0.29 ± 0.03	0.24 ± 0.02	<0.001
LVMI (g/m ²)	82 ± 21	70 ± 14	n.s.
<u>Diastolic function</u>			
E wave (m/s)	0.74 ± 0.10	0.90 ± 0.16	<0.05
E/A ratio	1.6 ± 0.2	2.1 ± 0.4	<0.01
Em (cm/s)	8.3 ± 1.8	10.3 ± 2.6	<0.05

Results expressed as means ± SD

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CARDIOVASC ABNORMALITIES IN PAL – CCRE STUDY 3

Assessment of cardiac response to surgical and medical treatment of primary aldosteronism

- Comparison of pre-treatment versus at least 6 months post-treatment (lap adrenalectomy or commencement of spironolactone):
 - 24h ABPM, No. of Drugs
 - Echo

Unilat Adrenalectomy Group

n = 19 with APA (10 M, 9 F)
Age = 50.7 ± 10.2 y

Whole PAL Cohort

n = 40 (21 M, 19 F)
Age = 53.1 ± 9.7 y

Spironolactone-Treated Group

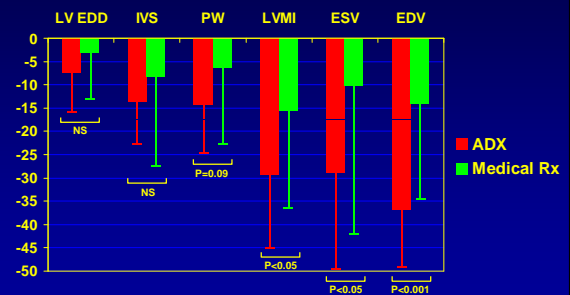
n = 21 with BAH (11 M, 10 F)
Age = 55.3 ± 8.8y

CV EFFECTS OF ADRENALECTOMY VS SPIRONOLACTONE CHANGES DURING FOLLOW UP (mean 17 mo)

	ADX-treated (n = 19)	Spiro-treated (n = 21)	P value
Δ 24h SBP (mmHg)	-15.3 ± 14.1**	-11.6 ± 18.8*	NS
Δ 24h DBP (mmHg)	-8.9 ± 10.2**	-6.4 ± 10.0*	NS
Δ No. Drugs	-0.8 ± 1.2*	0.3 ± 0.9	< 0.01
Δ IVS (mm)	-0.17 ± 1.3***	-0.12 ± 0.22*	NS
Δ PW (mm)	-0.17 ± 0.14***	-0.09 ± 0.18	NS
Δ LVM (g)	-87.1 ± 54.8***	-44.3 ± 58.1**	<0.05
Δ LVMI (g/m ²)	-43.2 ± 26.4***	-23.0 ± 32.6**	<0.05
Δ ESV (mL)	-13.3 ± 10.2***	-5.5 ± 12.6	<0.05
Δ EDV (mL)	-44.3 ± 18.6***	-15.6 ± 24.7*	<0.001

* P<0.05, ** P<0.01 and *** P<0.001 for pre- vs post-treatment

CV EFFECTS OF ADRENALECTOMY VS SPIRONOLACTONE PERCENT FALL DURING FOLLOW UP



CONCLUSIONS

- 1) PAL is much more common than previously thought, accounts for 5-10% of HTives, with most patients normokalemic, and is the commonest potentially curable/specifically treatable form of HT
- 2) Among patients with PAL, aldo levels predict impaired LV systolic function independently of BP. Furthermore, compared with matched normotensive controls, normotensive subjects with PAL (due to FH-I) and raised aldo levels demonstrate thicker LV walls and evidence of reduced diastolic LV function. These findings are consistent with aldo excess having direct adverse effects on the heart independently of, and possibly even predated, its effects on raising BP
- 3) Unilateral adrenalectomy (in APA) and, to a lesser extent, spironolactone (in BAH), leads to marked reductions in LV dimensions

These findings highlight the importance of detecting patients with PAL who may then benefit not only from the BP lowering effects, but also from reversal of non-BP dependent adverse effects of aldo excess, by the institution of specific surgical or medical treatment.

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