Hypertension

Ιωάννης Γ. Γριβέας, MD, PhD

athens-NEPHROLOGY

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Review

The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics

Richard J. Johnson,[1] Miguel A. Lanaspa,[1] L. Gabriela Sánchez-Lozada,[2] and Bernardo Rodriguez-Iturbe[3]

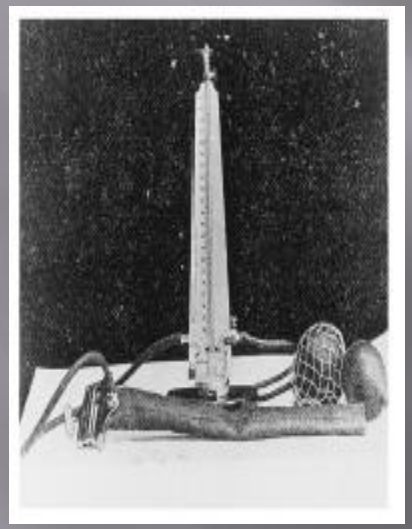
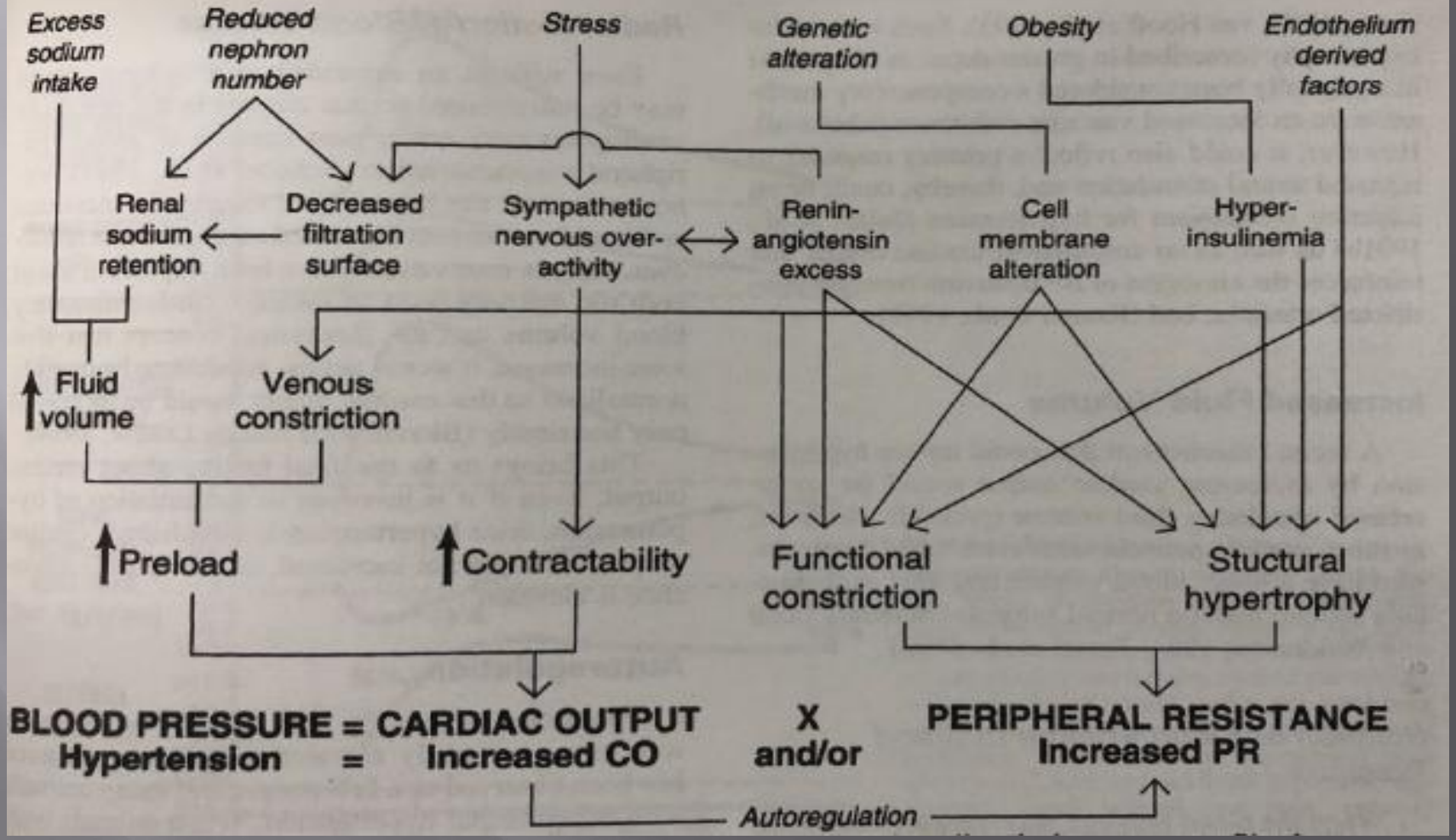
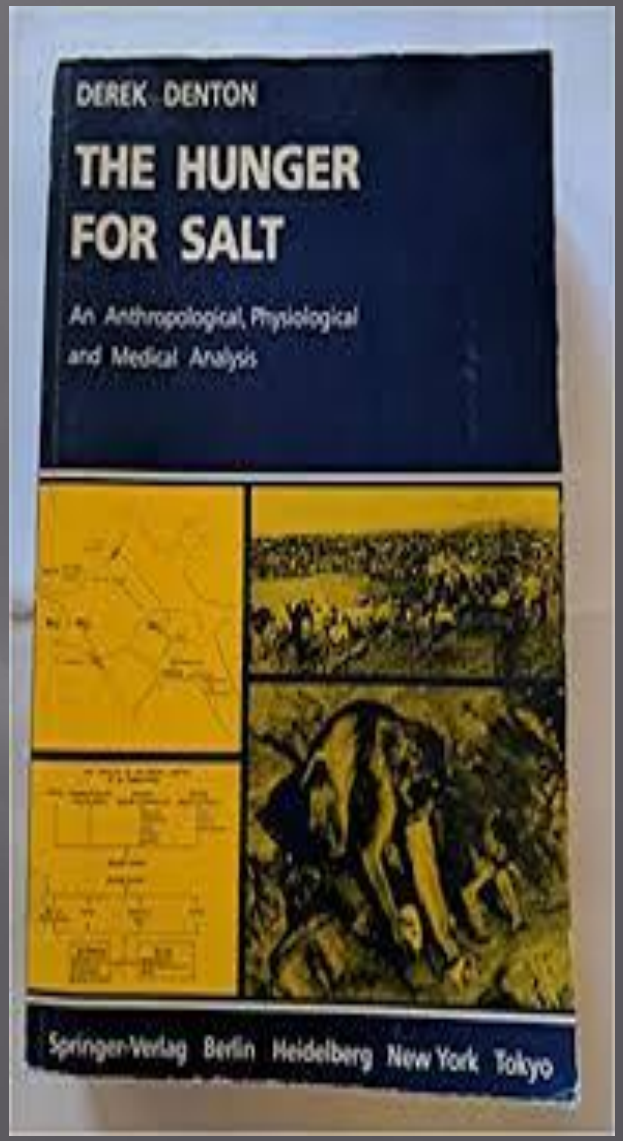


Fig. 1. Scipione Riva-Rocci (*left*) described a practical method of determining systolic blood pressure using a mercury manometer and an inflatable cuff (*middle*) to determine the pressure (mmHg) needed to occlude the brachial artery and thus suppress the radial pulse. The photograph of Scipione Riva-Rocci (unknown photographer, 1896) is in the public domain according to the Danish Consolidated Act Copyright of 2010 (Danish National Archive). Nicolai Korotkoff (*right*) described the appearance and disappearance of sounds "just below the cuff" using a stethoscope, thus allowing for the measurement of diastolic pressure. He stated that "the absence of pulsations is not indicative that the artery is completely occluded. In this respect, our hearing is a better guide" (90, 132). The photograph of Nicolai Korotkoff (unknown photographer, 1900) is in the public domain according to article 1256 of the Civil Code of the Russian Federation. The photograph of the manometer is in the public domain because its copyright has expired; the original source is Korotkoff NS, *Experiments for Determining the Strength of Arterial Collaterals*. St. Petersburg, Russia: Imperial Military Medical Academy, 1910. Dissertation.


Excess sodium intake
Reduced nephron number
Stress
Genetic alteration
Obesity
Endothelium derived factors
Renal sodium retention
Decreased filtration surface
Sympathetic nervous over-activity
Renin-angiotensin excess
Cell membrane alteration
Hyper-insulinemia
Fluid volume
Venous constriction
Preload
Contractability
Functional constriction
Stuctural hypertrophy
BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE
Hypertension = Increased CO and/or Increased PR
Autoregulation

"There are good grounds but by no means a proven case for suspecting excess salt intake, probably associated with reduced potassium intake , in the aetiology of hypetensionn in Western-Type communities "



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Sodium and Potassium in the Pathogenesis of Hypertension

Horacio J. Adrogué, M.D., and Nicolaos E. Madias, M.D.

N Engl J Med 2007;356:1966-78.

potassium. Isolated populations that eat natural foods have an individual potassium intake that exceeds 150 mmol per day and a sodium intake of only 20 to 40 mmol per day (the ratio of dietary potassium to sodium is >3 and usually closer to 10).[6,8,10] By contrast, people in industrialized nations eat many processed foods and thereby ingest 30 to 70 mmol of potassium per day and as much as 100 to 400 mmol of sodium per day (the usual dietary potassium:sodium ratio is <0.4).[3,10]

Hypertension affects less than 1% of people in isolated societies but approximately one third of adults in industrialized countries.[3,10] Differ-

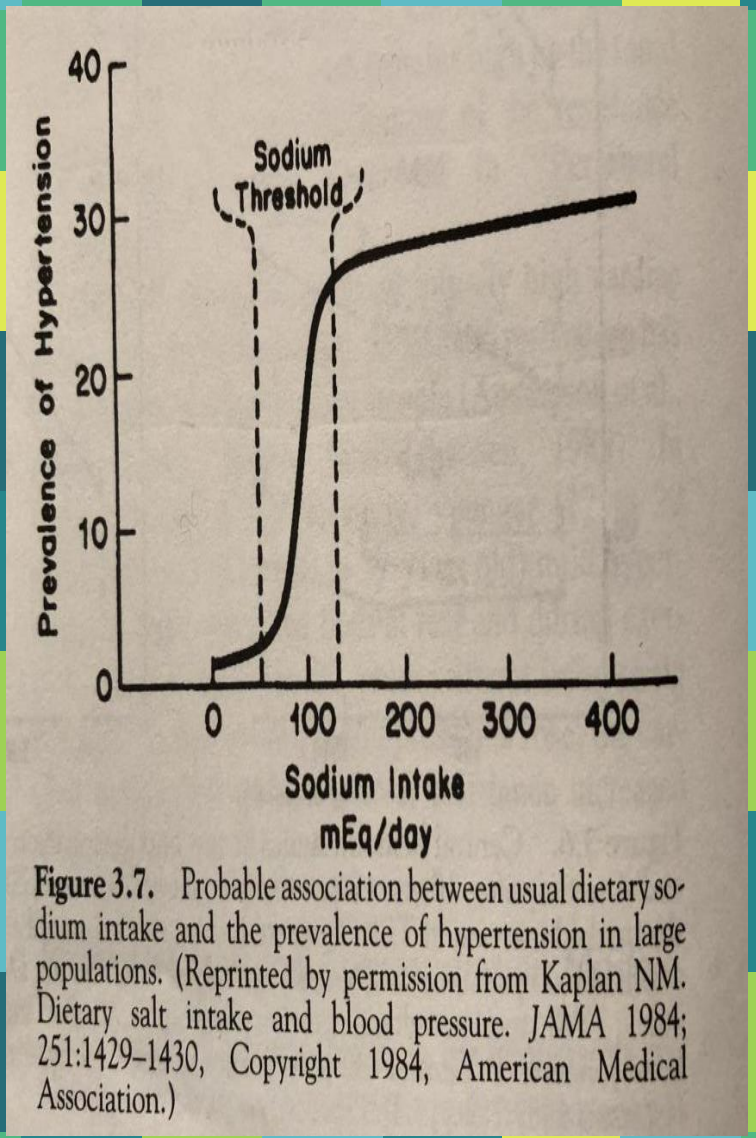
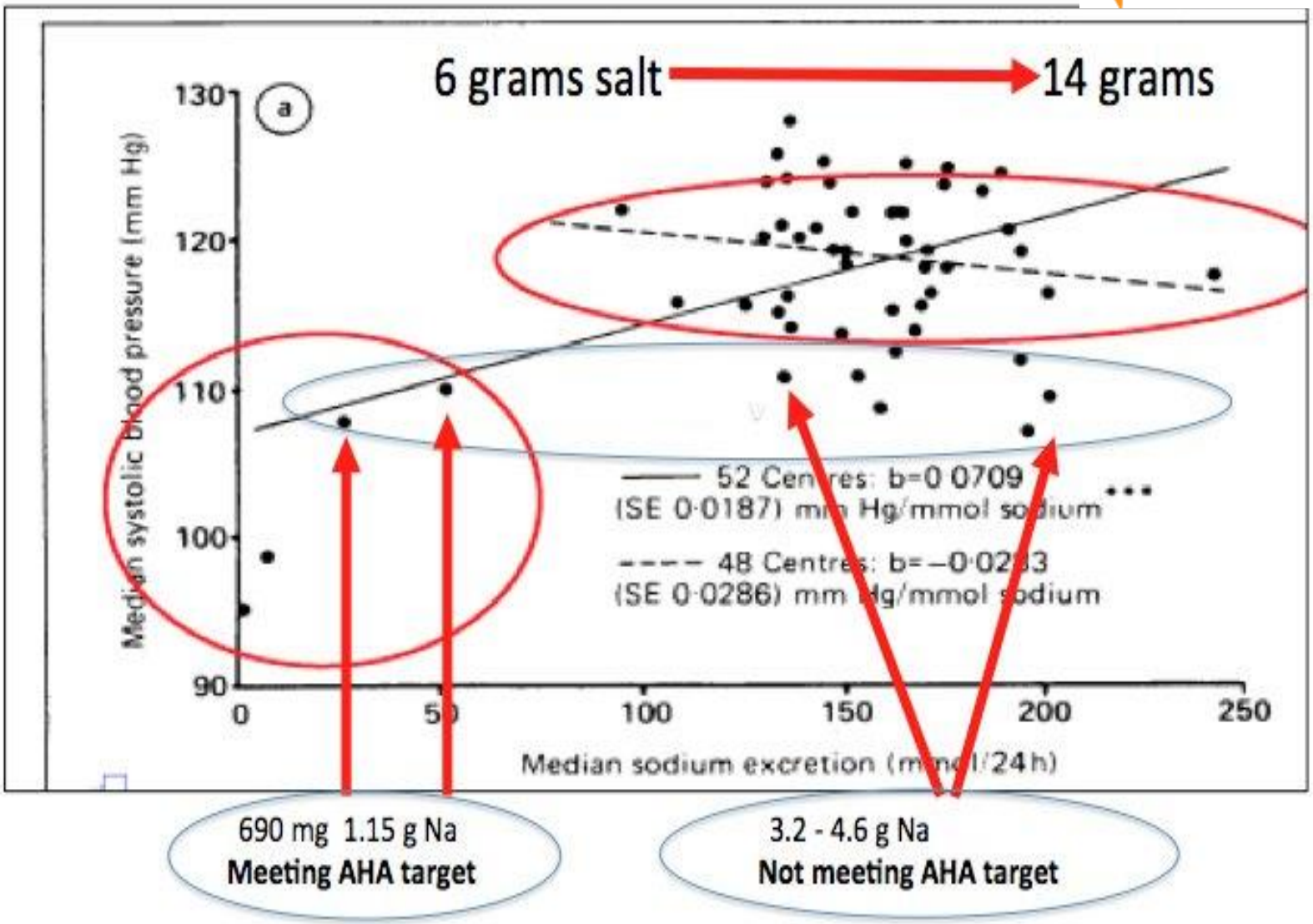
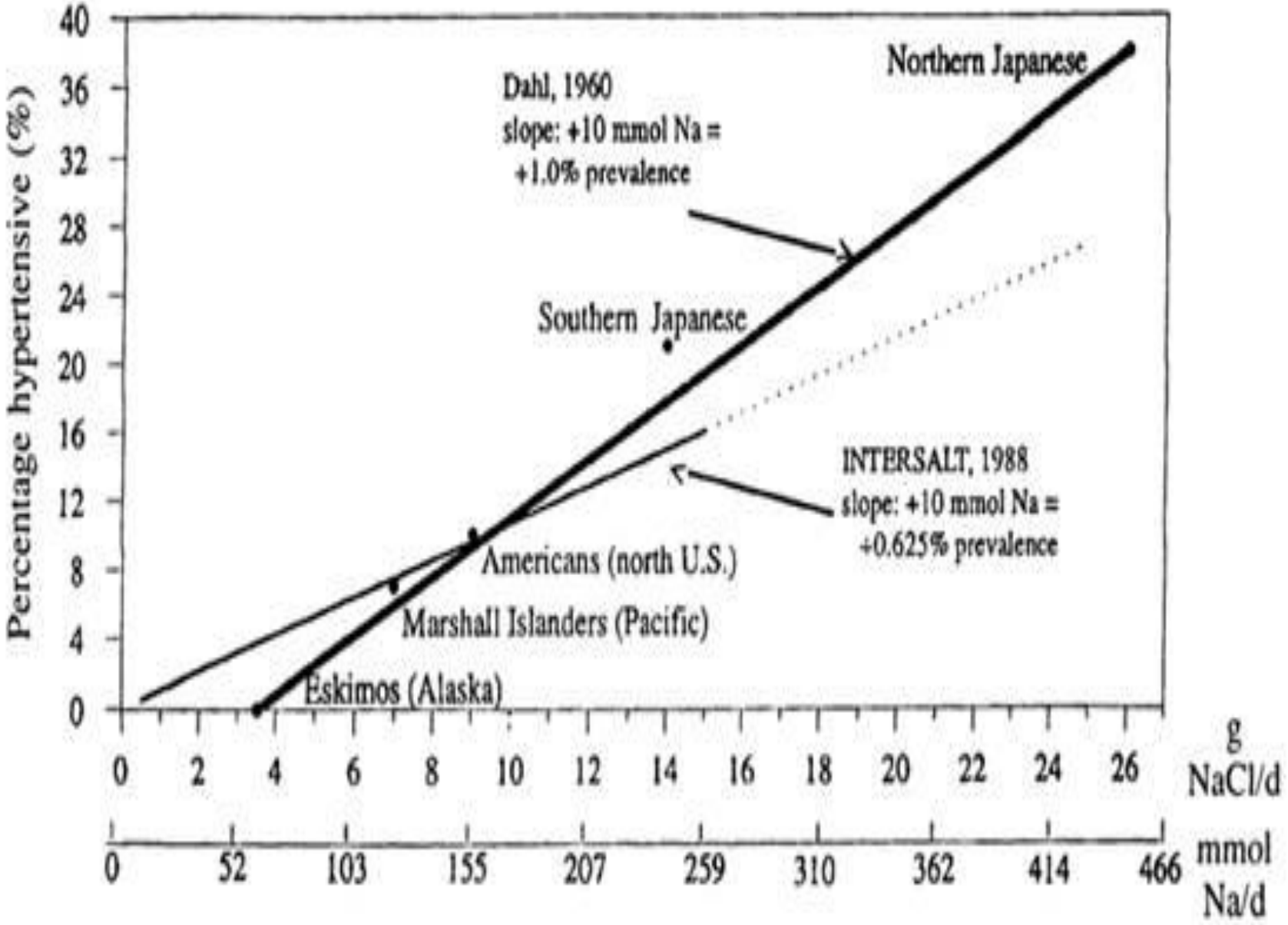


Figure 3.7. Probable association between usual dietary sodium intake and the prevalence of hypertension in large populations. (Reprinted by permission from Kaplan NM. Dietary salt intake and blood pressure. *JAMA* 1984; 251:1429–1430, Copyright 1984, American Medical Association.)

INTERSALT 1988 – 48 populations




Percentage hypertensive (%)
40
36
32
28
24
20
16
12
8
4
0
Dahl, 1960
slope: +10 mmol Na =
+1.0% prevalence
Northern Japanese
Southern Japanese
INTERSALT, 1988
slope: +10 mmol Na =
+0.625% prevalence
Americans (north U.S.)
Marshall Islanders (Pacific)
Eskimos (Alaska)
0 2 4 6 8 10 12 14 16 18 20 22 24 26
g NaCl/d
0 52 103 155 207 259 310 362 414 466
mmol Na/d

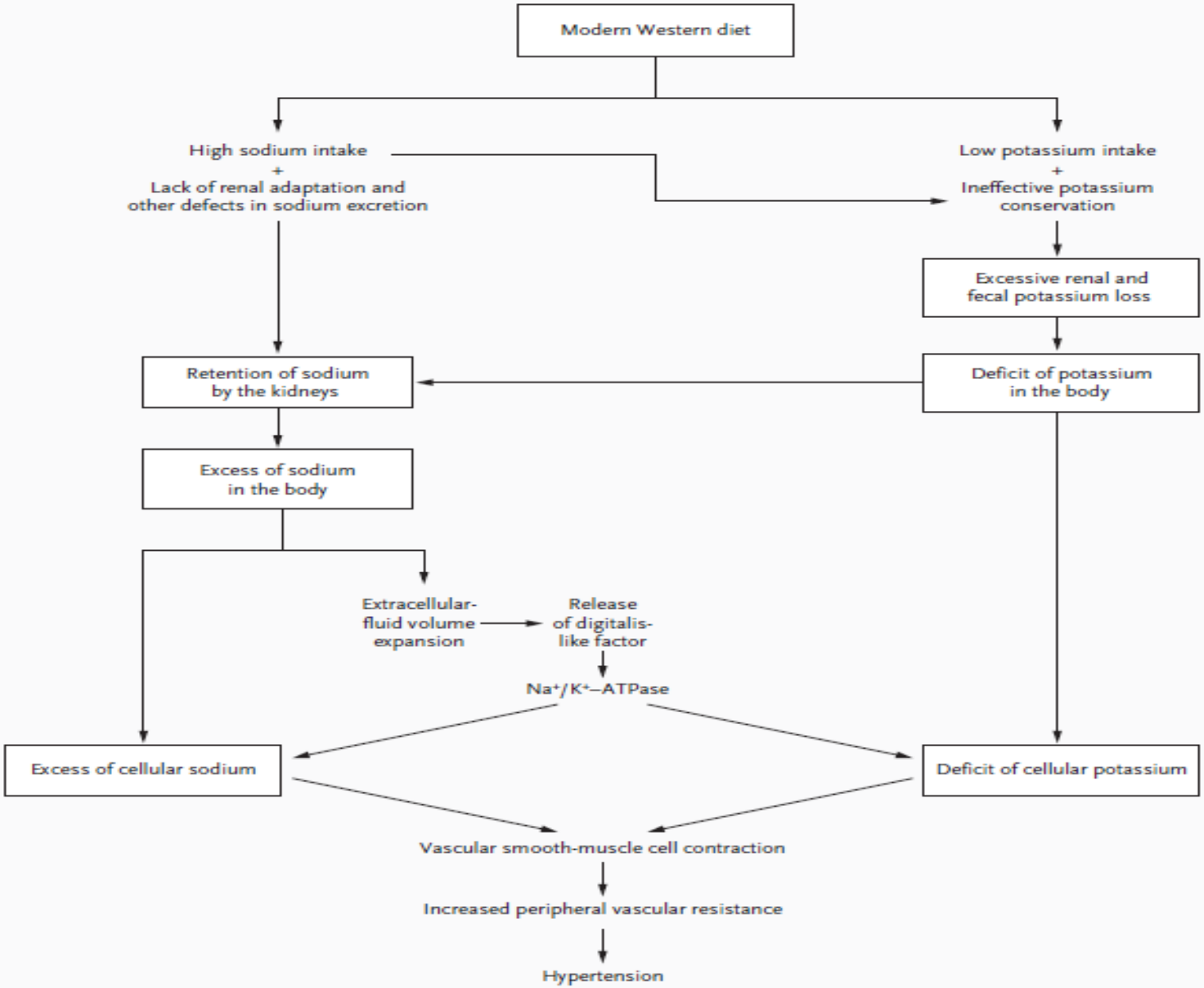


Figure 1. Interaction of the Modern Western Diet and the Kidneys in the Pathogenesis of Primary Hypertension.
The modern Western diet interacts with the kidneys to generate excess sodium and cause a deficit of potassium in the body; these changes increase peripheral vascular resistance and establish hypertension. An initial increase in the volume of extracellular fluid is countered by pressure natriuresis.

Ελληνική Νεφρολογία 2012; 24 (3): 167 - 173

Ανασκόπηση

Σηματοδοτικές οδοί της ενδογενούς ουαμπαΐνης και νατριούρηση

Ι. Γριβέας[1]
Π. Πασαδάκης[2]
Ν. Παπαγαλάνης[3]

Περίληψη

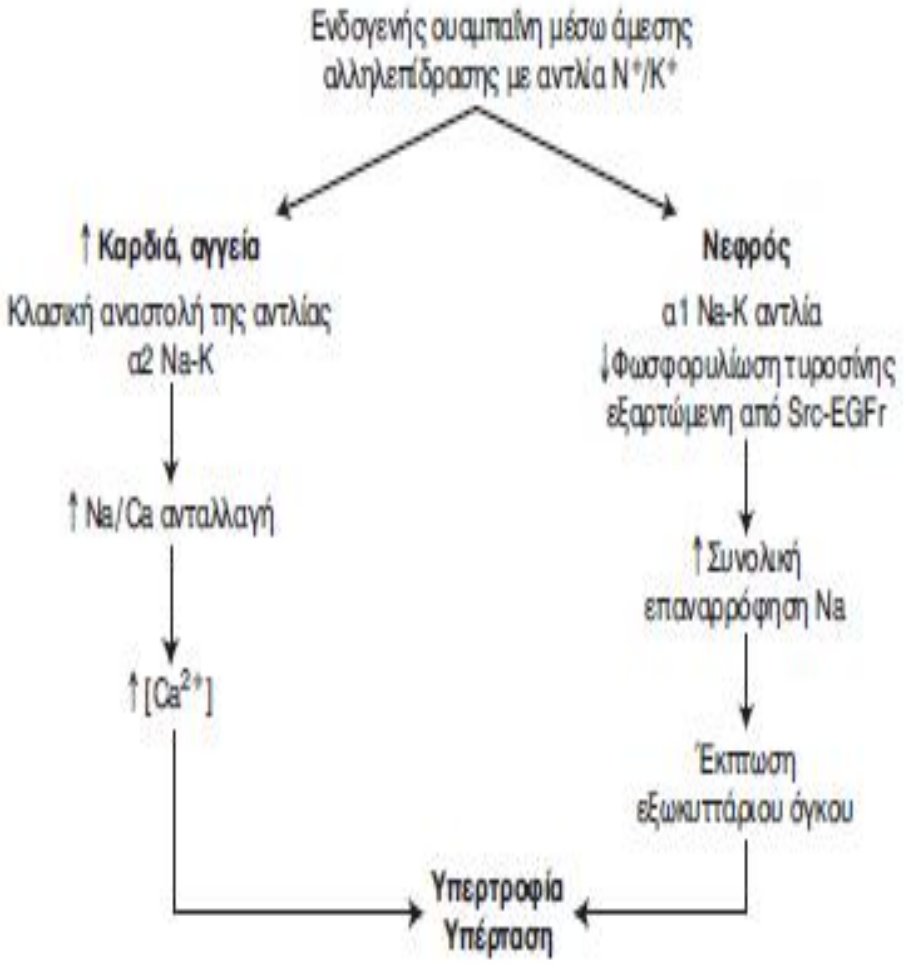
Η παρούσα ανασκόπηση αναφέρεται στην ενδογενή ουαμπαΐνη (ouabain), η οποία ανήκει στα ενδογενή καρδιοτονωτικά στεροειδή (endogenous cardiotonic steroids, CTS), ομάδα γνωστή και ως παράγοντες παρόμοιοι με δακτυλίτιδα (digitalis-like factors), ή αναστολέας της Na^+/K^+-ATPάσης. Τα CTS αποτελούν σύνδεσμο της διατροφικής πρόσληψης NaCl και των καρδιαγγειακών και νεφρικών παθήσεων. Αν και η ύπαρξη και η σημασία των παραγόντων αυτών αποτέλεσε αντικείμενο διαμάχης, αξιοσημείωτη είναι η πρόοδος που έχει επιτευχθεί κατά τα τελευταία 15 χρόνια. Υπάρχουν σε υψηλά επίπεδα στο πλάσμα στο 40% περίπου ασθενών με ιδιοπαθή υπέρταση. Οι παράγοντες αυτοί προκαλούν κατακράτηση άλατος μέσω αύξησης της δραστηριότητας και της έκφρασης της νεφρικής αντλίας νατρίου. Μελέτες τα τελευταία 10 χρόνια έχουν διευκρινίσει πολλές και σημαντικές πρωτεϊνικές αλληλεπιδράσεις της Na^+-K^+-ATPάσης οι οποίες σηματοδοτούν την έναρξη μιας καινούργιας εποχής. Ας σημειωθεί ότι γνωρίζουμε μέχρι σήμερα λίγα για τη συσχέτιση μεταξύ της μεταφοράς ιόντων με βάση τη λειτουργία της Na^+-K^+-ATPάσης και των μηχανισμών της σηματοδότησης στη ρύθμιση των λειτουργιών των κυττάρων.

Λέξεις κλειδιά: *αντλία Na^+, ουαμπαΐνη, υπέρταση.*

Εισαγωγή

Η παρούσα ανασκόπηση αναφέρεται στην ενδογενή ουαμπαΐνη (ouabain), η οποία ανήκει στα ενδογενή καρδιοτονωτικά στεροειδή (endogenous cardiotonic steroids, CTS), με ομάδα γνωστή και ως παράγοντες παρόμοιοι με δακτυλίτιδα (digitalis-like factors), ως αναστολέας της Na^+/K^+-ATασης[1]. Τα CTS αποτελούν σύνδεσμο μεταξύ της διαιτητικής πρόσληψης άλατος (NaCl) και καρδιαγγειακής και νεφρικής νόσου. Αν και η ύπαρξη και η σημασία, των παραγόντων αυτών αποτέλεσε αντικείμενο αντιπαράθεσης στην διεθνή επιστημονική κοινότητα, αξιοσημείωτη πρόοδος έχει επιτευχθεί κατά τα τελευταία 15 χρόνια. Υψηλά επίπεδα των CTS παρατηρούνται στο πλάσμα στο 40% περίπου των ασθενών με ιδιοπαθή υπέρταση, που δεν λαμβάνουν θεραπεία και συσχετίζονται άμεσα με την τιμή της αρτηριακής πίεσης. Οι παράγοντες αυτοί προκαλούν κατακράτηση νατρίου μέσω αύξησης

[1] Νεφρολογικό Τμήμα, 401 Γενικό Στρατιωτικό Νοσοκομείο Αθηνών
[2] Ιατρική Σχολή Δημοκρίτειου Πανεπιστημίου Θράκης
[3] Νεφρολογικό Τμήμα, Γενικό Νοσοκομείο Αθηνών «Κοργιαλένειο-Μπενάκειο»



Εικ. 4. Οι οδοί της ενδογενούς ουαμπαΐνης.

Nephrol Dial Transplant (2008) 1 of 7
doi: 10.1093/ndt/gfn325

NDT
Nephrology Dialysis Transplantation

Editorial Comment

Role of endogenous cardiotonic steroids in sodium homeostasis

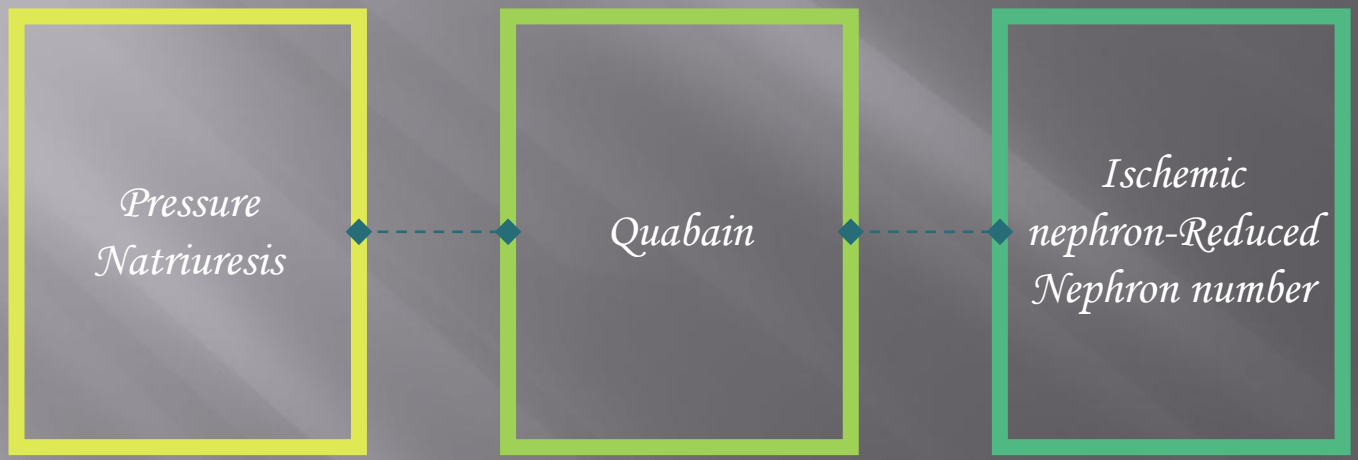
Wilhelm Schoner and Georgios Scheiner-Bobis

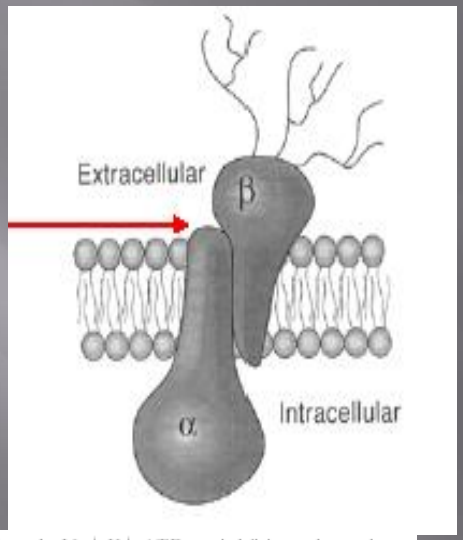
Institute of Biochemistry and Endocrinology, Justus-Liebig-University Giessen, Frankfurter Str. 100, D–35392 Giessen, Germany

It is evident now that long-term excessive sodium consumption stimulates, in addition to other known mechanisms, the generation of arterial hypertension via the release of various endogenous cardiac glycosides. A long-lasting rise of

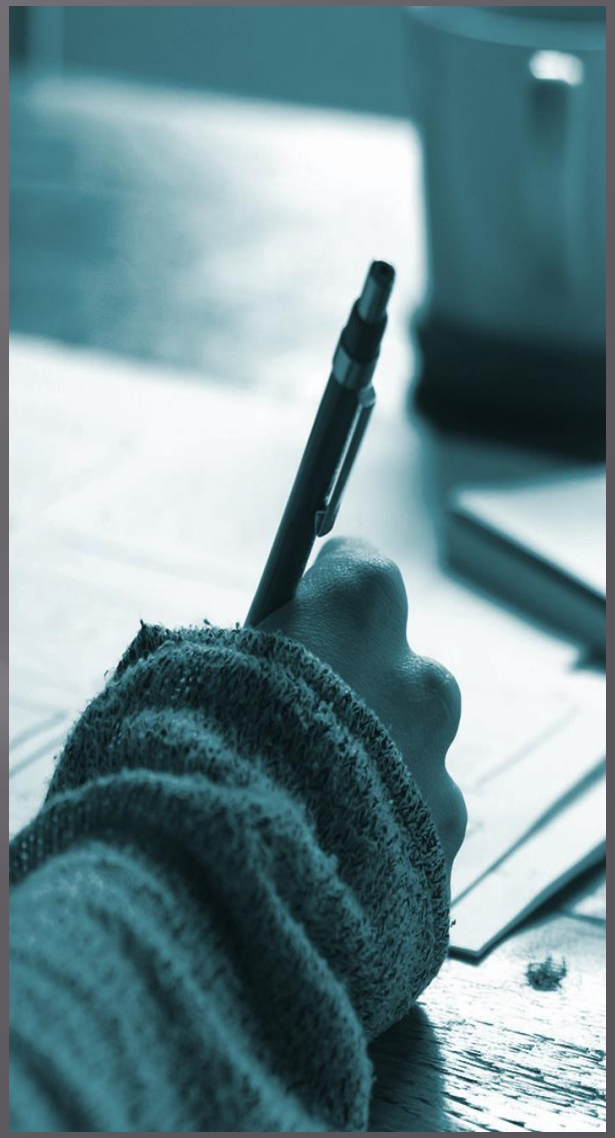
ous endogenous cardiac glycosides. A long-lasting rise of this new type of steroid hormone in blood plasma, and especially that of ouabain and marinobufagenin, leads to arterial hypertension, natriuresis and finally, via altered gene expression patterns, to remodelling of the heart, arterial wall and kidneys. In particular, a prolonged increased secretion

Renal Sodium Retention





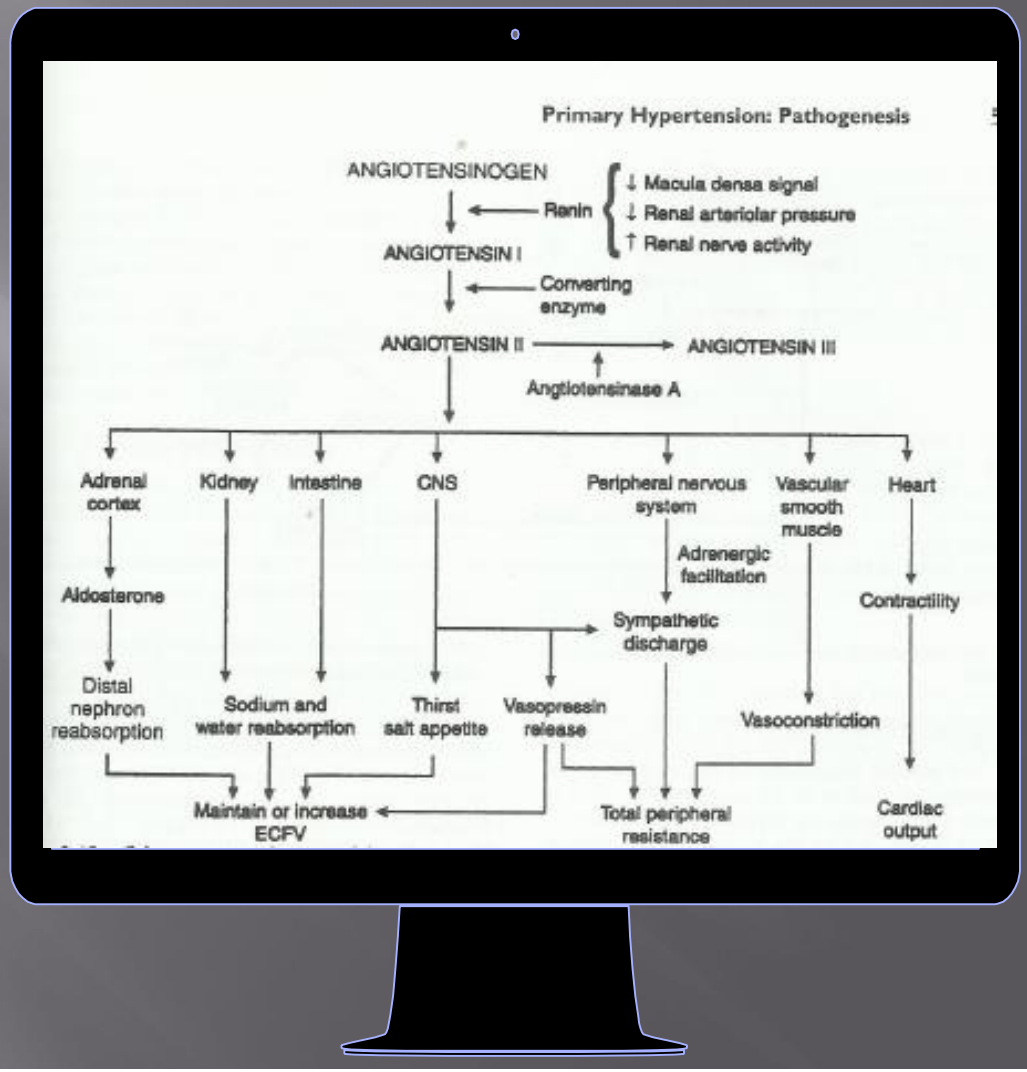
And beyond the confines of nephrology: if such Na^+-K^+-ATPase inhibitors have been conserved during evolution so long—from foxglove to *Homo sapiens*—it is difficult to believe that the only reason why nature preserved them was to make life difficult for nephrologists. The substance must obviously have more basic physiologic regulatory functions that so far escape us. The future will hopefully give the answer to the question of what role it plays in normal physiology.



The inextricable role of the kidney in hypertension

Steven D. Crowley[1] and Thomas M. Coffman[1,2]

The renin-angiotensin system (RAS) is a powerful modulator of blood pressure, and dysregulation of the RAS causes hypertension. Pharmacological blockade of the RAS with renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers effectively lowers blood pressure in a substantial proportion of patients with hypertension (19), reflecting the important role for RAS activation as a cause of human hypertension. Similarly, in rodent models, deletion of RAS genes lowers blood pressure whereas overexpression causes hypertension (20).



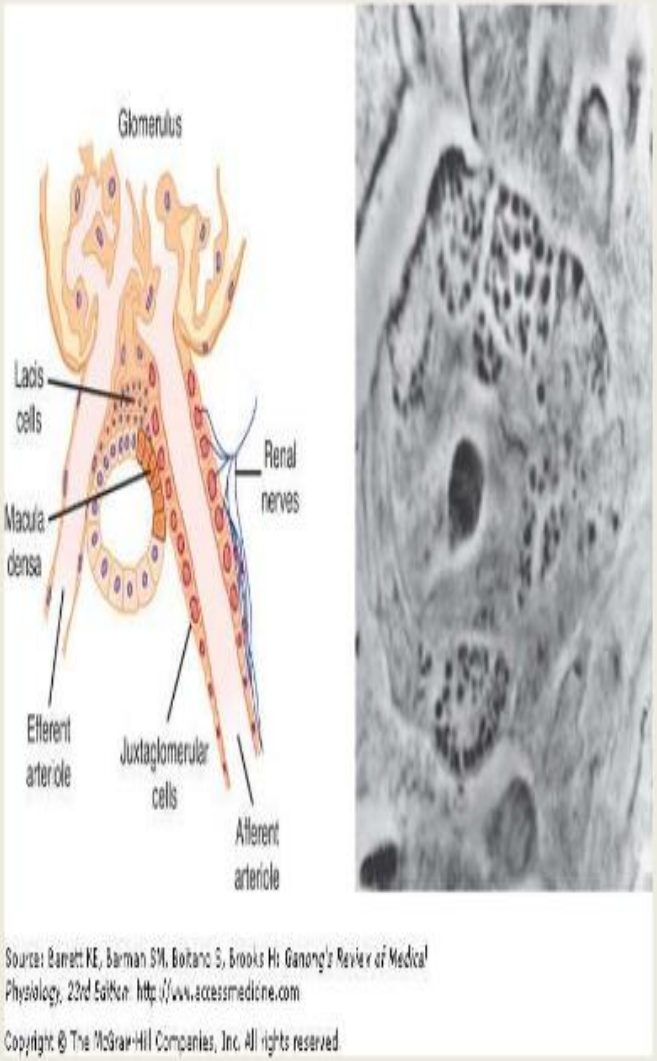
J Clin Invest. 2014;124(6):2341-2347. https://doi.org/10.1172/JCI72274.

Renin –

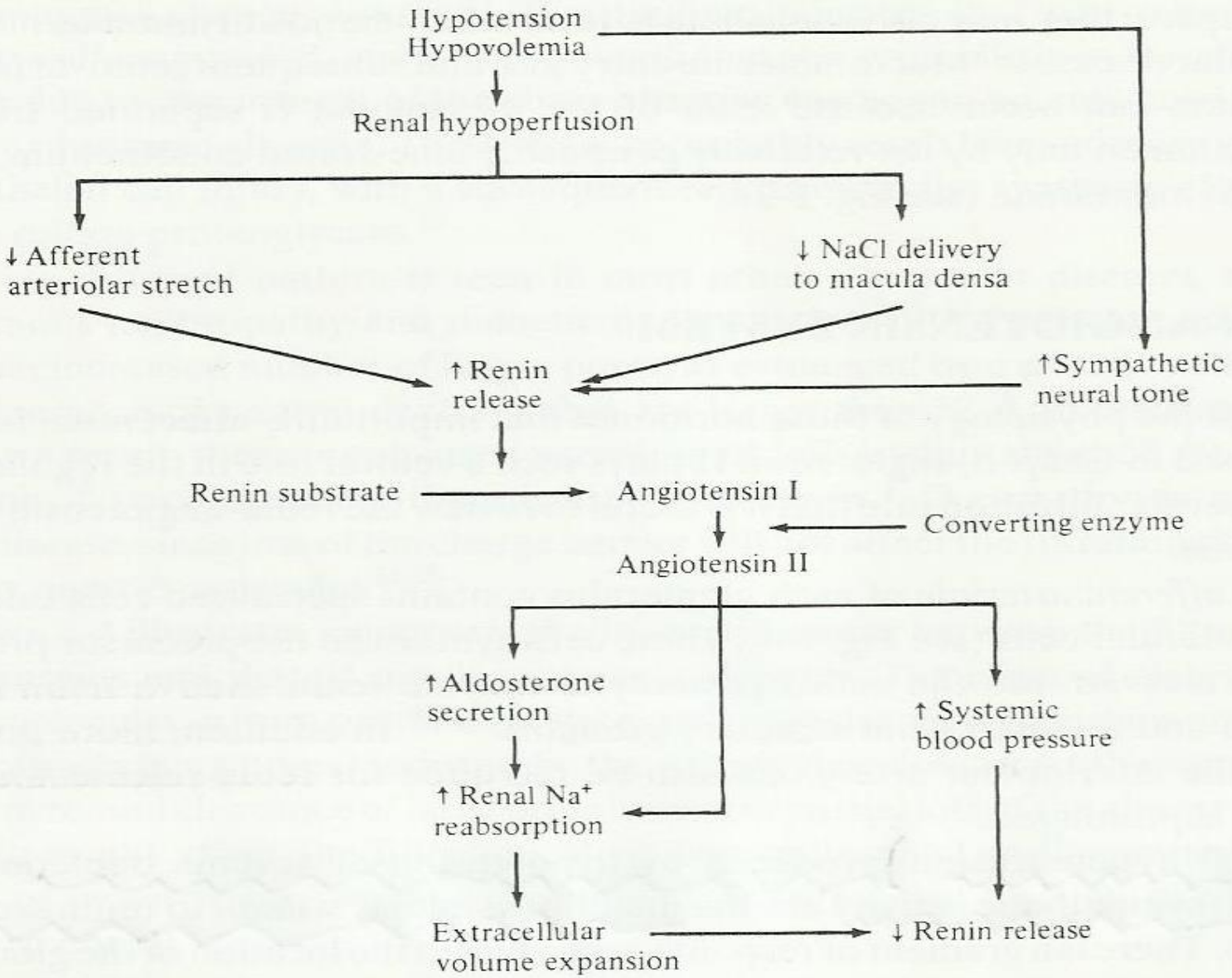
Hormonal peptide-340 AA,an enzyme .

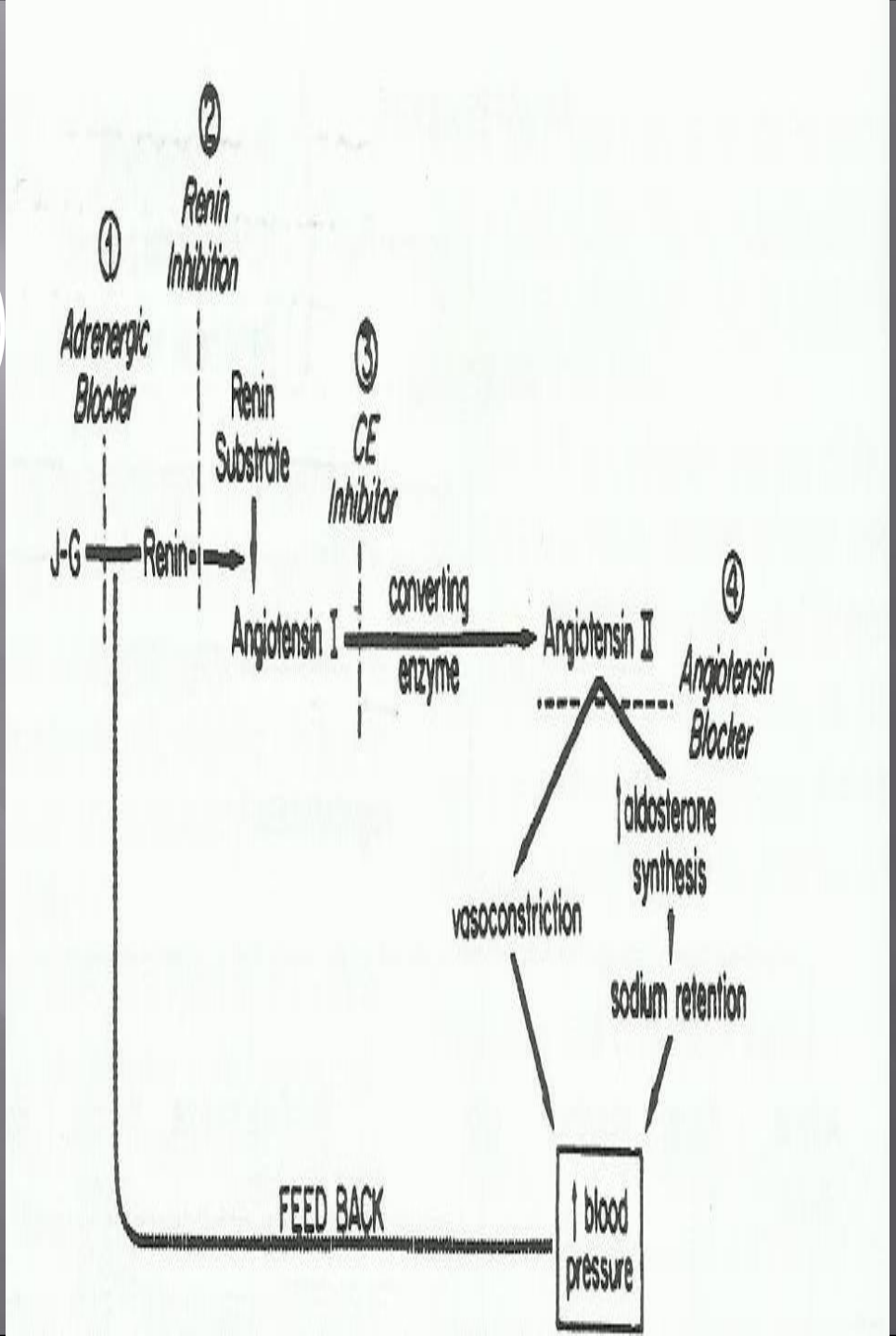
T½ -15 min ,prepared and stored in granular JG cells in kidney and also other tisuue–the main source of plasma Renin (active) and 90% in prorenin (inactive but immune reactive).it is synthesized In both constitutive and rate limiting pathway. It catalyzes the rate limiting step of RAS – attract active future target.

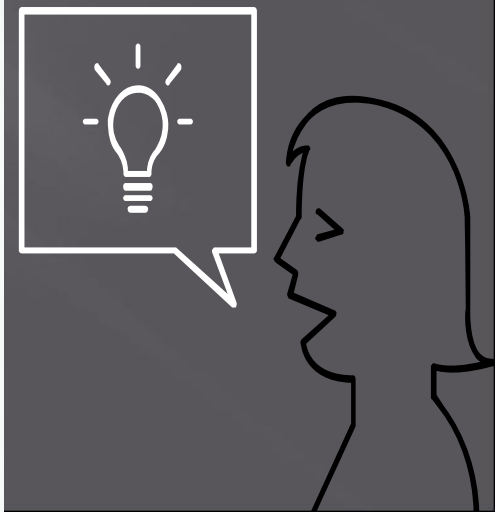
Stretch receptors(pressure sensor) in the afferent arteriole, local SNS , Na content of the tubular fluid reaching the macula Desna cell - release around JGA→Renin .



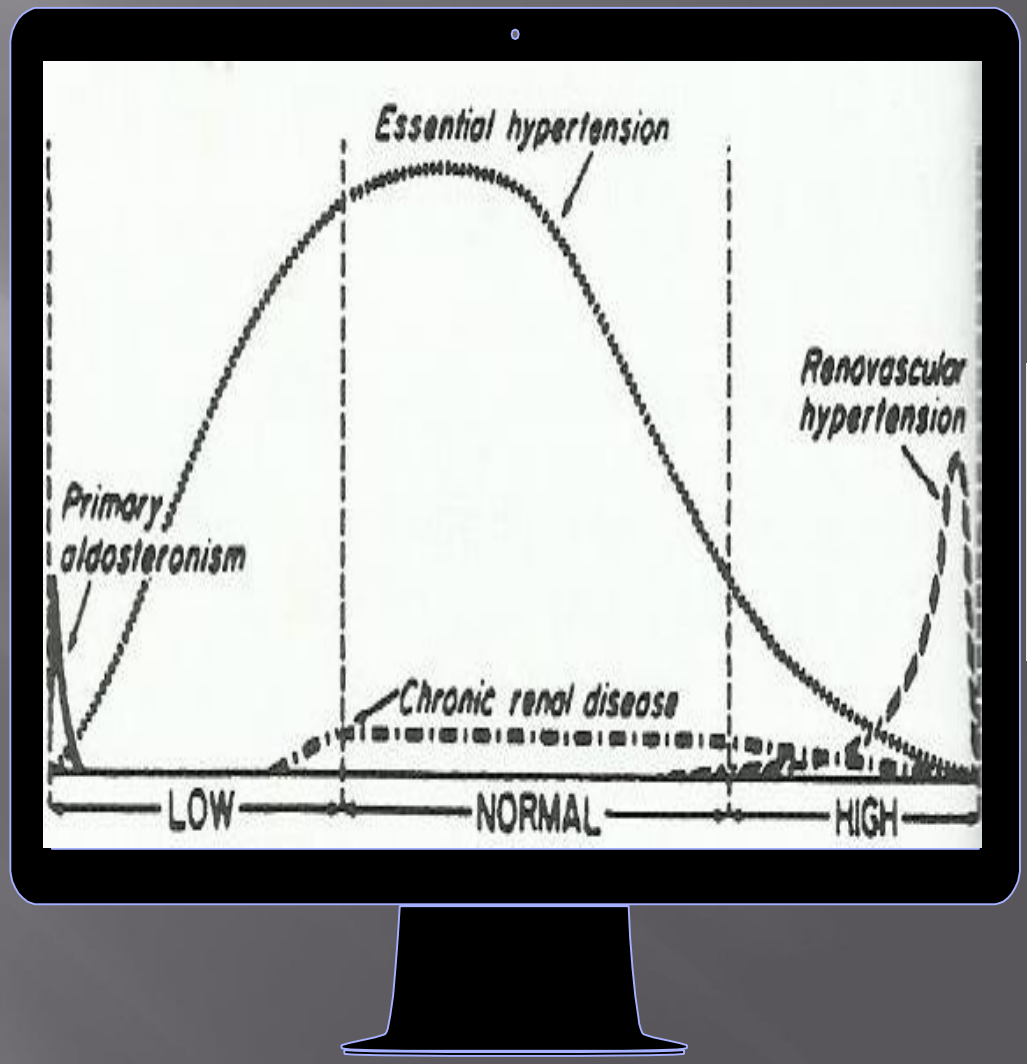
Source: Barrett KE, Barman SM, Boitano S, Brooks H: Ganong's Review of Medical Physiology, 22nd Edition http://www.accessmedicine.com

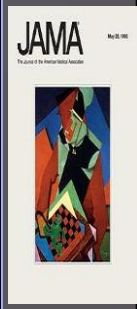

Hypotension
Hypovolemia
Renal hypoperfusion
↓ Afferent arteriolar stretch
↓ NaCl delivery to macula densa
↑ Renin release
↑ Sympathetic neural tone
Renin substrate
Angiotensin I
Converting enzyme
Angiotensin II
↑ Aldosterone secretion
↑ Systemic blood pressure
↑ Renal Na^+ reabsorption
Extracellular volume expansion
↓ Renin release


2
Renin
Inhibition
1
Adrenergic
Blocker
Renin
Substrate
3
CE
Inhibitor
J-G
Renin
Angiotensin I
converting
enzyme
Angiotensin II
4
Angiotensin
Blocker
aldosterone
synthesis
vasoconstriction
sodium retention
FEED BACK
blood
pressure



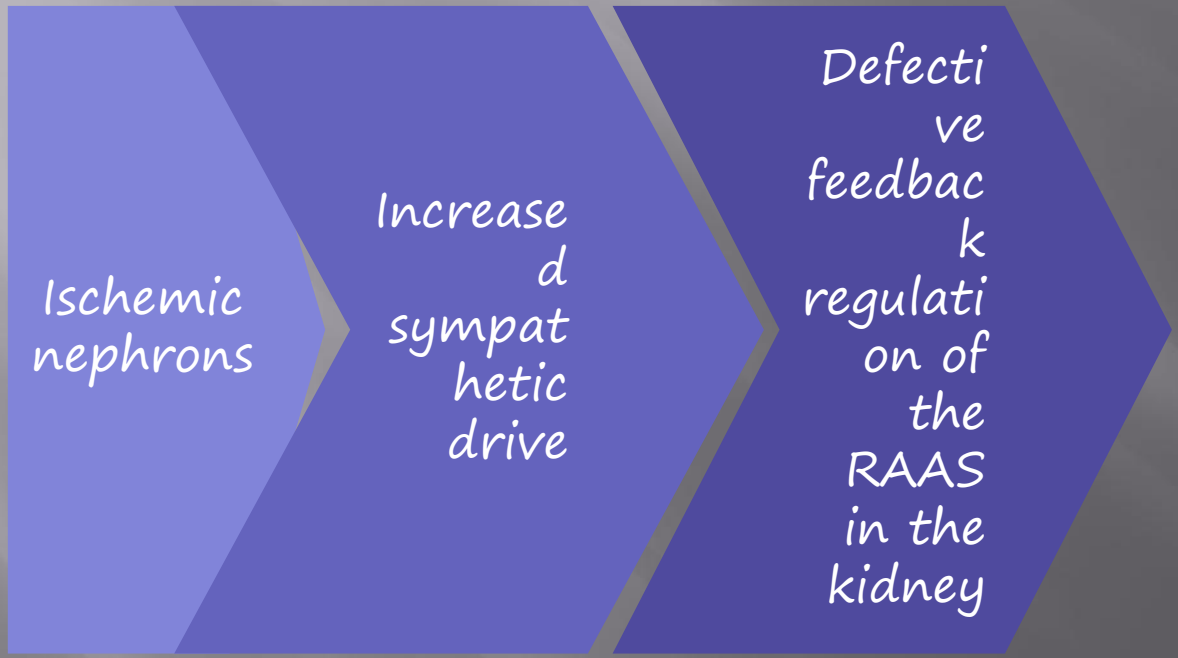
- Ασθενείς με υπέρταση τείνουν να έχουν χαμηλά επίπεδα ρενίνης σε σχέση με τους νορμοτασικούς.
- Η πλειοψηφία τους δεν έχει χαμηλά επίπεδα ρενίνης.





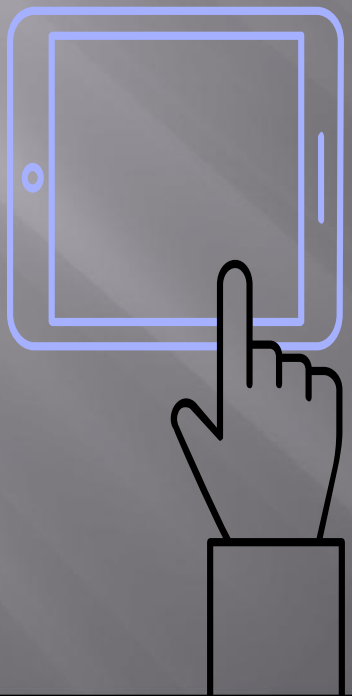
renin levels. (Reprinted with permission from Kaplan NM. Renin profiles. The unfulfilled promises. JAMA 1977;238:611–613, copyright 1977, American Medical Association.)

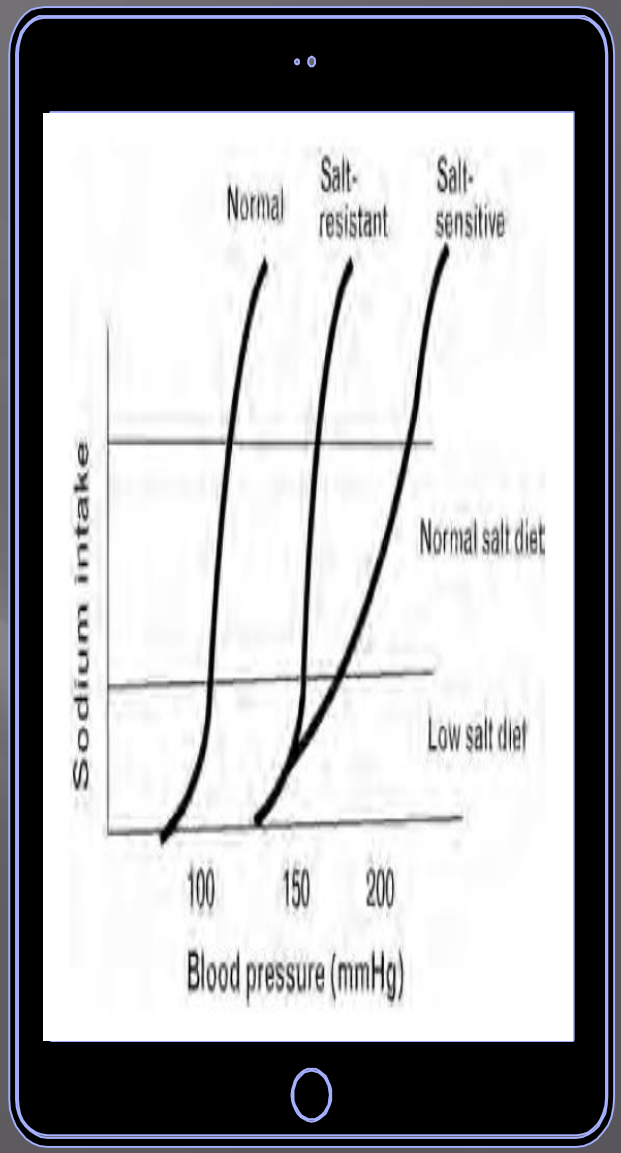
Πιθανές εξηγήσεις…



Εξήγηση του φαινομένου

Abnormally regulated and rather fixed local level of tissue AII





~1 in 3 adults have high BP in USA

49,707 deaths in 2002

contributing cause to 261,000 deaths in 2002

~40% African-Americans have high BP

30% of people with high BP don't know it

no symptoms!

2017 Guideline for High Blood Pressure in Adults

Nov 13, 2017

BP should be categorized as normal, elevated, or stages 1 or 2 hypertension to prevent and treat high BP

Normal BP is defined as <120/<80 mm Hg; elevated BP 120-129/<80 mm Hg; hypertension stage 1 is 130-139 or 80-89 mm Hg, and hypertension stage 2 is ≥140 or ≥90 mm Hg.

A 20 mm Hg higher SBP and 10 mm Hg higher DBP are each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease.

It is important to screen for and manage other CVD risk factors in adults with hypertension:

smoking,

diabetes,

dyslipidemia,

excessive weight,

low fitness,

unhealthy diet,

psychosocial stress, and

sleep apnea

Nonpharmacologic interventions to reduce BP include:

weight loss for overweight or obese patients with a heart healthy diet,

sodium restriction, and potassium supplementation within the diet;

and increased physical activity with a structured exercise program.

Men should be limited to no more than 2 and women no more than 1 standard alcohol drink(s) per day.

The usual impact of each lifestyle change is a 4-5 mm Hg decrease in SBP and 2-4 mm Hg decrease in DBP; but diet low in sodium, saturated fat, and total fat and increase in fruits, vegetables, and grains may decrease SBP by approximately 11 mm Hg.

Our process is easy

The benefit of pharmacologic treatment for BP reduction is related to atherosclerotic CVD (ASCVD) risk

For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher, a BP target of <130/80 mm Hg is recommended

Follow -up

Instructions for use

Initial first-line therapy for stage 1 hypertension includes thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

Two first-line drugs of different classes are recommended with stage 2 hypertension and average BP of 20/10 mm Hg above the BP target.

Improved adherence can be achieved with once-daily drug dosing, rather than multiple dosing, and with combination therapy rather than administration of the free individual components

For adults with confirmed hypertension and known stable CVD or ≥10% 10-year ASCVD risk, a BP target of <130/80 mm Hg is recommended.

The strategy is to first follow standard treatment guidelines for CAD, HFrEF, previous MI, and stable angina, with the addition of other drugs as needed to further control BP.

In HFpEF with symptoms of volume overload, diuretics should be used to control hypertension, following which ACE inhibitors or ARBs and beta-blockers should be titrated to SBP <130 mm Hg. Treatment of hypertension with an ARB can be useful for prevention of recurrence of atrial fibrillation

Instructions for use CKD

CKD: BP goal should be <130/80 mm Hg. In those with stage 3 or higher CKD or stage 1 or 2 CKD with albuminuria (>300 mg/day),

treatment with an ACE inhibitor is reasonable to slow progression of kidney disease. An ARB is reasonable if an ACE inhibitor is not tolerated.

Pharmacotherapy for Hypertension in Patients with Diabetes

- For persons with cardiovascular or kidney disease, including microalbuminuria or with cardiovascular risk factors in addition to diabetes & hypertension, initial recommended therapy is an:
  - Angiotensin converting enzyme (ACE) inhibitor or an Angiotensin receptor blocker (ARB)

- For persons with diabetes & hypertension not included in the above recommendation, appropriate choices include (in alphabetical order):
  - ACE inhibitors
  - Angiotensin Receptor Blockers (ARBs)
  - Dihydropyridine calcium channel blockers (CCBs)
  - Thiazide/thiazide-like diuretic

Hypertension & Diabetes: Key Messages

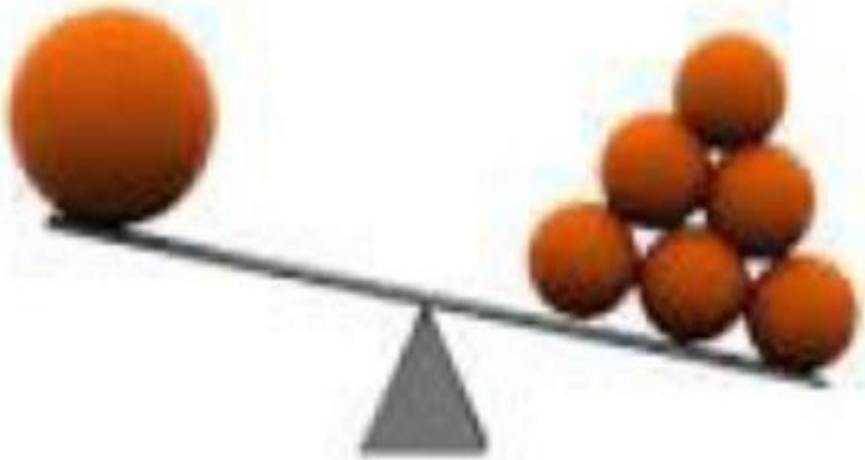
Up to 80% of people with diabetes will die of cardiovascular disease, especially stroke.

1. Ensure people with diabetes are screened for hypertension (blood pressure ≥130/80 mmHg)
2. Assess blood pressure at all healthcare visits
3. Encourage home blood pressure monitoring with approved devices
4. Pharmacotherapy and lifestyle should be initiated ***concurrently***
5. Assess and manage all other vascular risk factors
6. Enable sustained lifestyle modification and medication adherence

Conclusion is that some older patients are helped by antihypertensive medications while others are harmed. The questions for the clinician are as follows:

1. Which older patients should I treat?
2. How should I treat hypertension in the elderly?
3. What should I monitor?

A MATTER OF BALANCE



HOW SHOULD I TREAT HYPERTENSION IN THE ELDERLY?

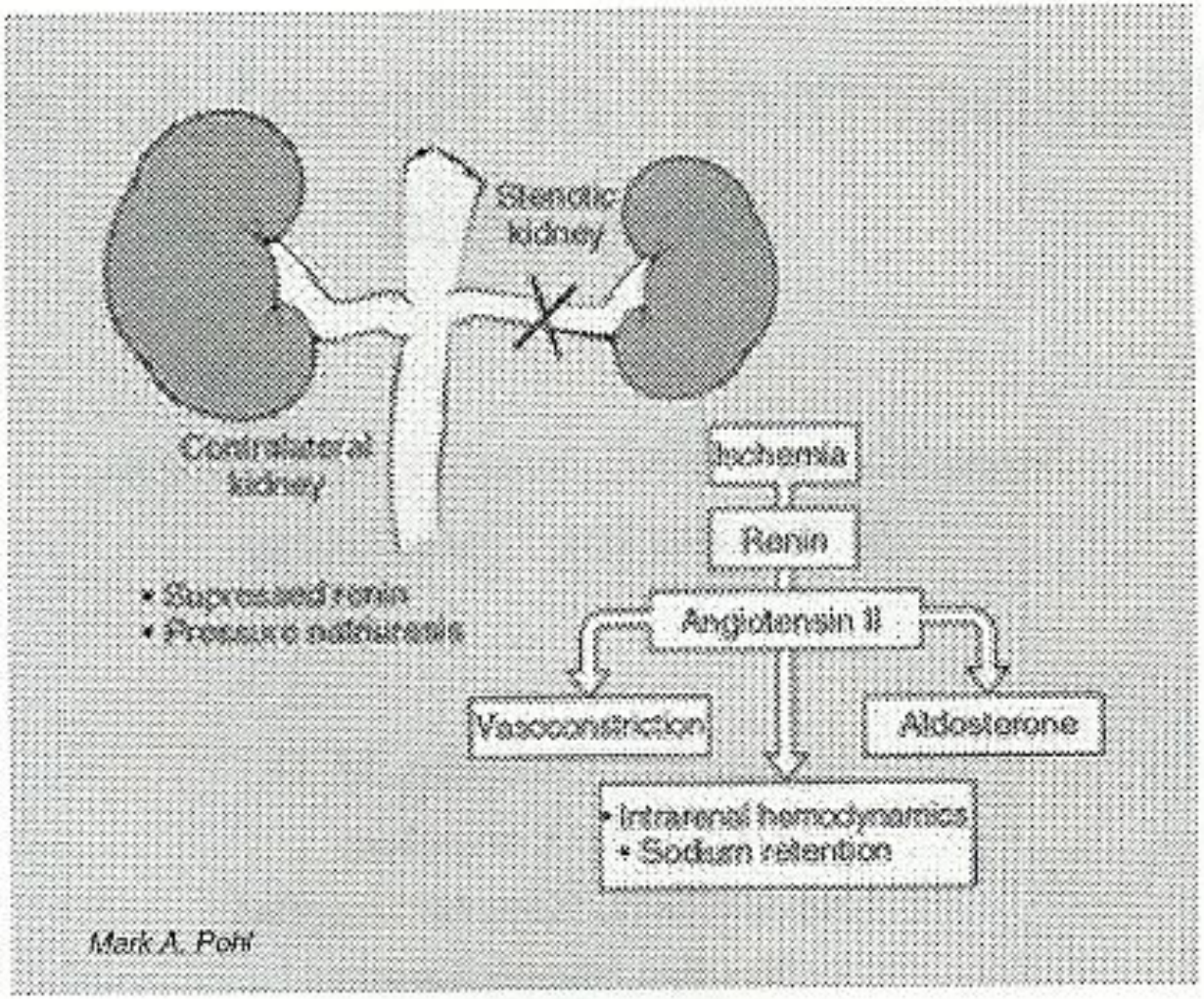
- Evidence suggests that physical activity and weight control are also effective in the elderly
- Pharmacological management:
  - Beta blockers – OUT since British-MRC trial
  - Alpha blockers- OUT since ALLHAT
  - Diuretics, ACE-I's, CCB's – IN
  - ARB's – possibly only if ACE-I not tolerated

Conclusion

- Every adult with hypertension should have a clear, detailed, and current evidence-based plan of care that ensures the achievement of treatment and self-management goals;
- effective management of comorbid conditions;
- timely follow-up with the healthcare team; and
- adheres to CVD evidence-based guidelines.
- Effective behavioral and motivational strategies are recommended to promote lifestyle modification.

Conclusion

- A structured team-based approach including a physician, nurse, and pharmacist collaborative model is recommended, along with integrating home-based monitoring and telehealth interventions.
- Outcome may be improved with quality improvement strategies at the health system, provider, and patient level.


Stenotic kidney
Contralateral kidney
• Suppressed renin
• Pressure natriuresis
Ischemia
Renin
Angiotensin II
Vasoconstriction
Aldosterone
• Intrarenal hemodynamics
• Sodium retention
Mark A. Pohl

Clinical Clues

- Onset of diastolic hypertension after age 55
- Refractory or malignant hypertension
- Development of resistant hypertension in a previously well-controlled patient
- Progressive increase in Creatinine, even if still "normal"
- Presence of atherosclerotic macrovascular disease elsewhere heightens suspicion
- Left heart failure out-of-proportion to LV dysfunction or ischemic burden
- Clinically silent RAS

Screening for Renovascular Disease

- Clinical syndrome most important in patient selection
- Various diagnostic modalities:
  - Serologic markers
  - Duplex ultrasound - in experienced hands can predict with great accuracy the presence or absence of significant RAS
  - Captopril renal scan - 10-25% false negative
  - MR angiography - rare false negatives / common false positives. Equipment/experience dependent
  - Contrast angiography

Hypertension and RAS

Among 152 patients with Unilateral or Bilateral RAS undergoing surgical revascularization:

- 90% had improvement in BP control
- Only 15% had "cure" of hypertension

Hansen et al. J Vasc Surg 1992;16;319-31.

Among 20 published series of PCI for atherosclerotic renal artery disease:

- 54% had improvement in hypertension
- 9% had "cure" of hypertension

What Are the Goals of Treatment for RAS?

- Control hypertension
- Aid in medical management
- Prevent deterioration in renal function
  - Forestall need for dialysis
  - Defer death and disability

Experimental Data supporting Stenting for Preservation of Renal Function

Watson et al. Circulation. 2000; 102:1671-1677.

- 61 vessels in 31 patients with "global" obstructive atherosclerotic renal disease
- All with chronic renal insufficiency (Creat 1.5 – 4.0)
- Stenting with non-articulated Palmaz stents
- Follow-up Renal U/S, Serum Creat , BP measurements:
  - Improvement in reciprocal slope of serum creatinine
  - Improved BP control (SBP from 170±21 Pre-stent vs. 148 ±15mmHg Post-stent; $p<0.001$)
  - Restenosis (>50%) in only 1 of 61 vessels
  - Stabilization of pole-to-pole renal dimension

Chronic Renal Insufficiency and RAS Who Benefits From Revascularization?

Novick et al. J Urol 1983; 129:907-12.

Trial of 51 patients with Creat>2.0 before revascularization with >75% Bilateral RAS:

- 67% had improvement in renal function
- 27% had stabilization in renal function
- Only 6% had worsening in renal function
- No demonstrated impact upon mortality

All that said:

We really need a randomized, well-designed trial!

CORAL

Study Design: Prospective, multi-center, two-arm randomized trial

Purpose: Medical therapy vs. Stenting for Systolic Htn + RAS

Enrollment: 1080 Patients

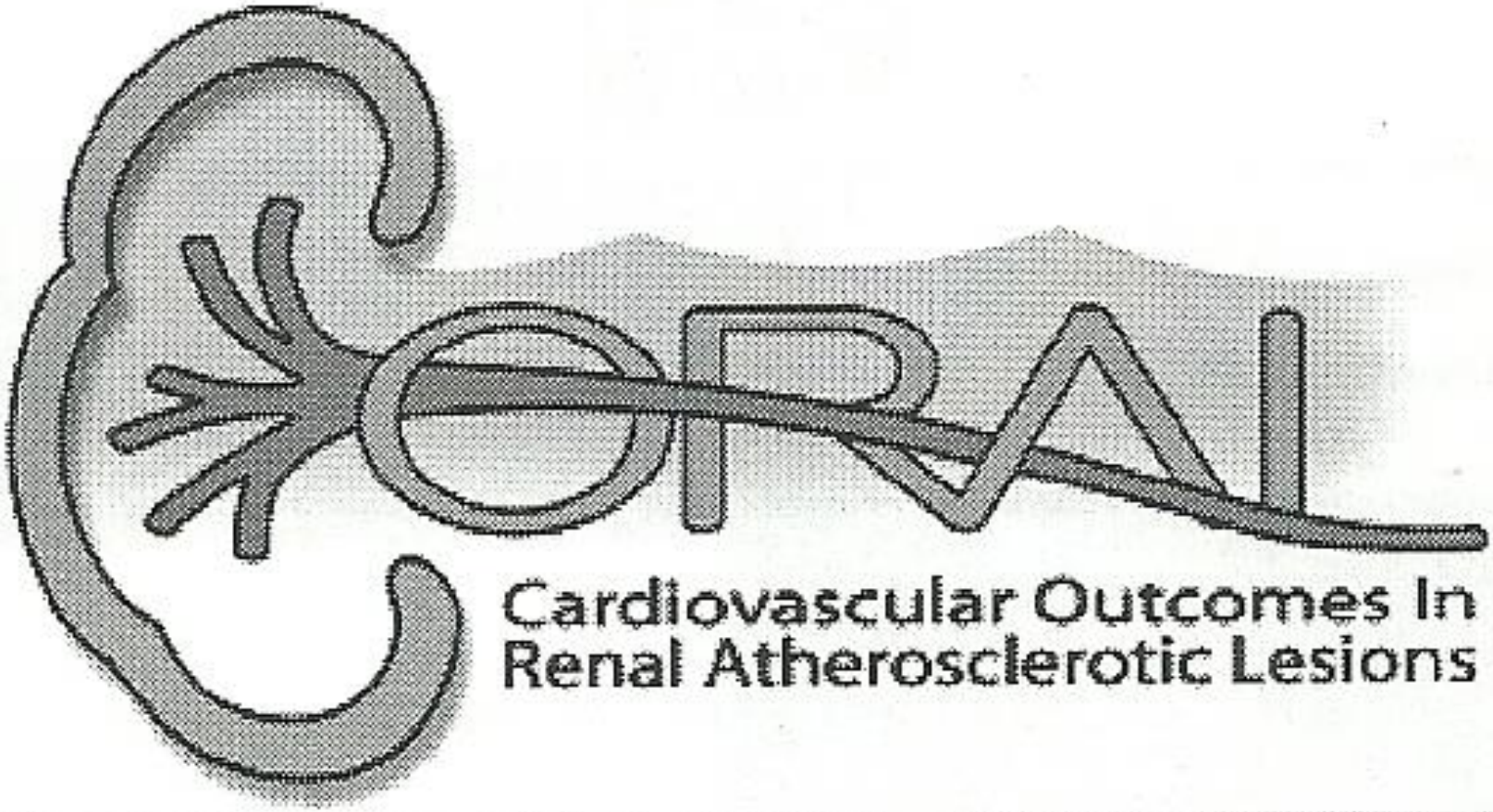
Patient Population: Systolic htn / >2 Htn Meds / >60% RAS with gradient or >80% RAS with no gradient necessary

Endpoints:

Primary – Cardiovascular/ renal death, Stroke, MI, hospitalization for CHF, progressive renal failure, need for permanent renal replacement

Seondary – Systolic BP response, Stent patency, Resistive index, all cause mortality, subgroup analysis (DM vs non-DM), Longitudinal renal fxn

National PI:	Christopher J. Cooper, M.D.	Medical College of Ohio
Site PI:	Joseph M. Garasic, M.D.	MGH
U/S Core Lab:	Michael Jaff, D.O.	MGH


CORAL
Cardiovascular Outcomes In
Renal Atherosclerotic Lesions

What are the benefits of PCI over Surgical revascularization?

- Shortened hospital stays
- Reduced post-procedural morbidity / mortality

  (J Vasc Surg 1994; 20: 76-87)

  - Early graft failure 5%
  - Peri-operative mortality 5.6%
  - 43% of patients required aortic grafting
- Comparable procedural success and improvement in renal function

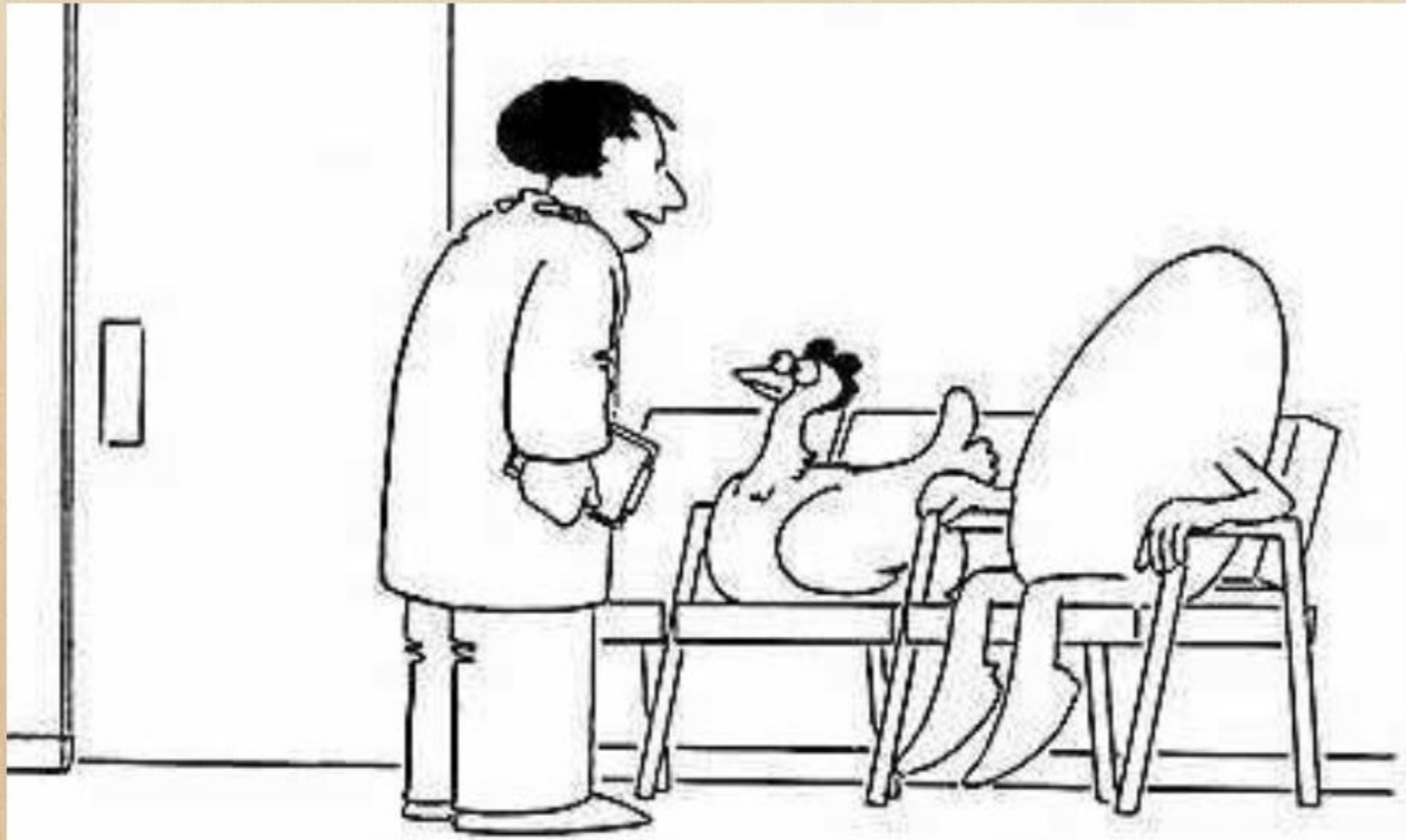
  (J Vasc Surg 1993; 18:841-52)

  - Procedural success: PTRA 83% vs. Surgery 97% (p=NS)
  - Improved or stable renal function: PTRA 83% vs. Surgery 72% (p=NS)
- Broadens pool of patients eligible for revascularization

In Summary

- Renovascular disease is an often-unrecognized contributor to:
  - Uncontrolled hypertension
  - Volume overload / CHF
  - Chronic and progressive renal failure
- Medical management of RAS involves avoidance of ACEI and use of agents commonly used in the management of CAD

  (Lipid lowering / Beta-blockade / Afterload reduction)
- Existing literature allows data-driven decision making, helping clinicians to properly manage their patients with renovascular disease. However, the optimal treatment of patients with unilateral disease or "clinically silent" disease is ill defined.
- New technologies have expanded the pool of patients eligible for percutaneous intervention, and help to limit procedural risk with renal revascularization.
- Atheroembolic distal protection devices are likely to be a mainstay of therapy in the near future.
- Vascular medicine allows cooperation and collaboration across departmental boundaries.


"Who was first?"