Vascular disease and the kidney
Renal disease causes hypertension

Hypertension causes renal disease

Hypertensive arterionephrosclerosis

Case 1

- A 28 yo B M presents with acute low back pain following weekend basketball game
- Has no other complaints; states he was told of HBP during college sports Px but never followed up on this.
  You treat the acute low back pain and ask the patient to return for a more thorough evaluation of CV status.
- BP: 148/90 mm Hg (first reading)
  - 146/88 mm Hg (second reading- end exam)
  - Height: 6'0"; weight: 218 lb; BMI: 29.6 kg/m²

BP on return visit when patient feels well is 150/92 and repeat is 148/90 mm HG.

- Family Hx is significant for HBP in both parents.
- Laboratory findings: BUN 13 mg/dl creatinine 0.9 mg/dL;
  Fasting glucose: 96 mg/dL
  - U/A 2+ prot, 0 heme
  - Cholesterol 170 mg/dL, LDL-C: 102 mg/dL, HDL 48 mg/dL, TG 100 mg/dL
  - CXray wnl, EKG borderline LVH.
Hypertension Affects Approximately 65 Million Americans: 28% of Adults

Prevalence of Hypertension Increases With Age: NHANES 1999-2000 Data

- **Men (age, years)**
  - 18-39
  - 40-59
  - ≥60

- **Women (age, years)**
  - 18-39
  - 40-59
  - ≥60

*Hypertension defined as a BP of ≥140/90 mm Hg or reported use of antihypertensives. Error bars indicate 95% confidence intervals. Data are weighted to the US population. Adapted from Hajjar I, Kotchen TA. *JAMA.* 2003;290:199-206.

The Most Common Causes of ESRD

Primary Diagnosis for Patients Who Start Dialysis

- **Diabetes** 50.1%
- **Hypertension** 27%
- **Glomerulonephritis** 13%
- **Other** 10%

*No. of dialysis patients (thousands)*

- **1984**: 243,524
- **1996**: 281,355
- **2000**: 520,240

*Projected data: r²=99.8%*

Case 1

- Lifestyle modifications alone may be sufficient for a 28 yo patient with mild hypertension and no other CV risk factors,
- If lifestyle modifications do not achieve goal BP within 3-6 months, pharmacologic therapy can be prescribed (speaker’s opinion)
- Excellent clinical trial outcome data prove that lowering BP with several classes of drugs, including ACEIs, ARBs, β-blockers, CCBs, and thiazide-type diuretics, will reduce the complications of hypertension

JNC 7: Lifestyle Modifications to Prevent and Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mm Hg/10 kg</td>
</tr>
<tr>
<td>DASH diet</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Sodium reduction</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>

DASH = Dietary Approaches to Stop Hypertension.
Chobanian AV et al. JNC 7: Complete Report.
Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.
Walking the dog

Case 1

- Patient education is:
  - An integral component of successful management of hypertension
  - Critical to establish adherence to a treatment regimen
- Emphasize to patients that lifestyle modifications and medications not only lower BP numbers but also reduce the incidence of CV events

Chobanian AV et al. JNC 7: Complete Report. Available at: http://hyper.ahajournals.org/cgi/content/full/42/6/1206.
Pathology of hypertensive kidney disease
(arterionephrosclerosis)
Hypertension and the kidney

Renal disease causes hypertension

Hypertension causes renal disease

Clinical features of hypertensive arterionephrosclerosis

Most patients are asymptomatic

A minority develop chronic renal failure, with/without proteinuria
Arterionephrosclerosis:
Bilateral, small kidneys, granular surface

Uniform thinning of cortex
Arterionephrosclerosis

- Arteriolosclerosis/hyalinosis
- Segmental and global glomerulosclerosis
- Patchy tubular atrophy and Interstitial fibrosis

Arteriolar sclerosis and hyalinosis: = Insudated plasma proteins and degenerating medial myocytes
Arterionephrosclerosis-Glomerular changes

- Glomerulomegaly
- Global sclerosis
- Perihilar FSGS

Case 2:

- 60 yo BM with Severe Hypertension presents to ER with severe head aches over last few weeks, and chest pain and SOB of 2 hrs duration.
- He is found in the ER to have a BP of 190/130 mm HG, P84, R 18/min, blurring of disc margins on eye exam, S4G, Rales at both bases, and no edema.
- Lab: Bun 38 mg/dl, creatinine 2.4 mg/dl, U/A 2+ prot, 2+ heme 10-15 rbc no casts. CXray cardiomegaly. EKG shows LVH + evidence of an acute inferior MI.
- BP is controlled with IV labetalol, he is given ASA and plavix, and of bare-metal cardiac stent is placed in his R coronary artery.
- Over next few days BP is controlled with a beta blocker, ACE inhibitor and diuretic. He feels much improved, but BUN and creatinine only change slightly.
- USG shows 10 cm echogenic kidneys.
Case 2

• What are the consequences of severe (accelerated, malignant) HBP?
• What is likely to happen to his kidney function if he stops his BP medications after hospital discharge?
• What is likely to happen to his kidney function if he stays on BP medications?
• How many BP medications will it take to control his hypertension?
• If this patient had died from his myocardial infarct, what would his kidneys likely show at autopsy?
Many Patients in the US Are Not at JNC-Recommended BP Goals


<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Goal BP (mm Hg)</th>
<th>% Not at Goal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hypertensives</td>
<td>&lt;140/90</td>
<td>57% 26%</td>
</tr>
<tr>
<td>African American</td>
<td>&lt;140/90</td>
<td>60% 32%</td>
</tr>
<tr>
<td>Mexican American/Hispanic</td>
<td>&lt;140/90</td>
<td>63% 30%</td>
</tr>
<tr>
<td>Older patients (≥60 yr)</td>
<td>&lt;140/90</td>
<td>71% 9%</td>
</tr>
<tr>
<td>Symptomatic CHD</td>
<td>&lt;140/90</td>
<td>47% 4%</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>&lt;130/85†</td>
<td>81% 24%</td>
</tr>
</tbody>
</table>


**MRFIT: Effect of Systolic BP and Diastolic BP on Age-Adjusted CHD Mortality**

CHD death rate per 10,000 person-years

Diastolic BP (mm Hg)  
Systolic BP (mm Hg)

BP=blood pressure, CHD=coronary heart disease, MRFIT=Multiple Risk Factor Intervention Trial. Age-adjusted CHD death rates per 10,000 person-years by level of systolic and diastolic BP for men in MRFIT. Adapted with permission from Neaton JD and Wentworth D. Arch Intern Med. 1992;152:56-64. ©1992, American Medical Association.
HOT Study: Fewer Major CV Events in Patients With Diabetes Randomized to Lower BP Goal

N = 18,790.
HOT = Hypertension Optimal Treatment.

<table>
<thead>
<tr>
<th>Target DBP (mm Hg)</th>
<th>Stroke, MI, or CV Death (per 1000 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤80</td>
<td>0</td>
</tr>
<tr>
<td>≤85</td>
<td>5</td>
</tr>
<tr>
<td>≤90</td>
<td>10</td>
</tr>
</tbody>
</table>

*Syst-Eur: Adjusted Relative Hazards for Active Therapy vs Placebo*

<table>
<thead>
<tr>
<th></th>
<th>Diabetic Patients (N=492)</th>
<th>Nondiabetic Patients (N=4203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>0.45</td>
<td>0.94</td>
</tr>
<tr>
<td>Mortality from CV causes</td>
<td>0.24</td>
<td>0.87</td>
</tr>
<tr>
<td>CV events</td>
<td>0.31</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.27</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>0.37</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Adjusted relative hazard

Summary of Studies on Nephropathy Progression

**SBP (mm Hg)**

- 130
- 134
- 138
- 142
- 146
- 150
- 154
- 170
- 180

**GFR (mL/min/yr)**

- -14
- -12
- -10
- -8
- -6
- -4
- -2
- 0

- *r=0.69; p<0.05*

- *Untreated HTN*


*Nondiabetic renal disease patients.


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**IDNT: Renal Outcome End Point—Time to Doubling of Serum Creatinine, ESRD, or Death**

<table>
<thead>
<tr>
<th></th>
<th>Months of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0  6  12  18  24  30  36  42  48  54</td>
</tr>
<tr>
<td>Irbesartan No. at risk</td>
<td>579  555  528  496  400  304  216  146  65</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>565  542  508  474  385  287  187  128  46</td>
</tr>
<tr>
<td>Placebo</td>
<td>568  551  512  471  401  280  190  122  53</td>
</tr>
</tbody>
</table>

- 20% RRR irbesartan vs placebo, *p=0.02*
- 23% RRR irbesartan vs amlodipine, *p=0.006*

IDNT: Impact of 12-Month Seated Systolic BP on Risk of Doubling of Serum Creatinine


Medication Use and BP Control in ALLHAT

Case 2: Pathology of malignant (accelerated) hypertension
Accelerated/Malignant Hypertension

WHO definition:
Severe HT plus Bilateral fundal haemorrhage & exudates

N.B. papilloedema NOT required for the diagnosis.

Following may be present but not diagnostic:
- DBP usually >130 mm Hg
- Renal failure
- Microangiopathic Haemolysis

Hallmark pathology - Fibrinoid arteriolar necrosis

Malignant nephrosclerosis

Normal size kidney*
Smooth surface*
Petechial Hemorrhages

(*Unless underlying essential HTN)
Arteriole with fibrin thrombus

Schistocytes in hemolytic anemia
Severe endothelial injury leads to thrombotic microangiopathy

1. Acute renal failure
2. Microangiopathic anemia
3. Thrombocytopenia
**Von Willebrand factor**
cleaving metalloproteinase (ADAMTS13)

### Endothelial pro- and anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Procoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>Tissue factor</td>
</tr>
<tr>
<td>Thrombomodulin activation of protein C/S</td>
<td>Factor V</td>
</tr>
<tr>
<td>Antithrombin III binding by heparin-like molecules</td>
<td>Binding of</td>
</tr>
<tr>
<td>Tissue plasminogen activator tPA</td>
<td>Factor IXa, Xa</td>
</tr>
<tr>
<td><strong>Von Willebrand factor</strong></td>
<td>tPA Inhibitor</td>
</tr>
<tr>
<td>cleaving metalloproteinase (ADAMTS13)</td>
<td>von Willebrand factor</td>
</tr>
</tbody>
</table>
Accelerated HTN
Anti-phospholipid Antibody syndrome
HUS (Shiga toxin)
Allograft rejection
DIC
Vasculitis
Tumor cell emboli
Metastatic cancers
Accelerated HTN

TTP (ADAMTS13 deficiency)
Factor H mutations
Others
Anti-phospholipid Antibody syndrome

Platelets
Fibrin
Platelets
VWF
Platelets
Fibrin
Platelets
Fibrin & VWF

Thrombotic microangiopathy
Thrombocytopenia
Microangiopathic hemolysis
Dysfunction of vital organs
Case 3

- 68 yo WM retired construction worker transferred for eval vasculitis and ARF.
- Excellent health – golfer and bowler.
- 5/95 loss of appetite, fevers, temps to 102, rash on back, cough Adm Hosp
- Mild ↑ LFTs B13/Cr 1.1 WBC 2.9 Hct 33, plts 49 K. CH50 borderline, C4 low No dx disch
- 2 days later readm for temps. Hosp x 10 days Cr
  ↑ to 3.6 mg/dl, aDNA -, ANA + 1:400, ESR 68-145, U/A 2+ prot, 2+ heme, several rbc? Rbc casts?
  Urinary protein 784 mg /d
- WBC 10.0, Hct 35%, plts 142,000 LFTs wnl

Case 3

- Transfer to CUMC Px WD,WN, NAD, BP 170/84, Cor-Chest neg, Abd 2 Fb L, no edema, no rash.
- BUN 97 mg/dl Creatinine 4.0 mg/dl Palb 3.5, ALT 60 other LFTs nl
- WBC 11.2K Hct 37% plts 114 K, Pt 14 PTT 49 U/A 1+ prot +rbc no casts ANA + 1: 40 Hep B, C neg, ANCA –, CH50 and C3 nl, C4 low cryos neg,
Case 3

• What other tests should be done?
• Will a biopsy influence therapy here?
• What is a renal biopsy likely to show?
• What treatment options are available and what do we expect for outcome?
Underlying Conditions with Antiphospholipid Antibodies

- Systemic Lupus Erythematosus
- "Lupus-Like" Syndrome
- Primary Anti-phospholipid Syndrome

Clinical Manifestations Related to Anticardiolipin Antibodies

- Recurrent arterial and venous thromboses
- Placental thromboses and spontaneous abortions
- Livedo reticularis
- CNS complications
- Pulmonary Hypertension
Extrarenal Manifestations of APLS (65%)

- CNS disease 8
- Deep vein thrombosis 6
- Myocardial infarction 4
- Pulmonary embolism 4
- Livedo reticularis 4
- Adrenal disease 3
- Other (aortic thrombosis with RAS, bowel infarction, miscarriage) 3

Total 17/26

Serologies and Lab Data

- Prolonged PTT 12/26 (46%)
- Thrombocytopenia 9/23 (38%)
- +ANA 15/26 (58%)
- +AntiDNA 2/24 (8.3%)
- Low complement 7/24 (29%)
- False positive VDRL 6/11 (55%)
Clinical Presentation at Biopsy

- Hypertension: 16/26 (62%)
- Active urine sediment: 10/26 (38%)
- Serum creatinine (mg/dl): 2.0 +/- 0.22
- Proteinuria (g/day): 4.4 +/- 0.87
- Nephrotic Syndrome: 15/26 (58%)

Course of APLS Patients

- Follow up: 10 mo. - 10 yrs.
- True SLE: 1 patient
- Improved renal function: 10/19 (53%)
- Remission of N.S.: 7/10 (70%)
- Worsening renal function: 7/26 (27%)
- ESRD: 4/26 (15%)
Case 3: Antiphospholipid antibody syndrome

Pathologic findings

Glomeruli show ischemic changes (global wrinkling of glomerular basement membranes, tuft retraction, and cystic dilation of Bowman’s space)
Glomeruli show segmental intracapillary fibrin

Arteries show widespread luminal narrowing with extensive subendothelial hyalinosis, endothelial swelling, focal myocyte dropout, focal mucoid intimal fibroplasia, and focal intramural fibrin with entrapped red blood cells.
Recanalized artery (healed thrombus)

Fibrin
Case 4

- A 4 yo girl presents with diarrhea and acute renal failure.
- Pt was in good health until 3 days PTA when went to neighbor's Bar-B-Q and had a hamburger. Over 24 hrs developed abdominal cramps, N/V, and bloody diarrhea. He became lethargic took in less fluids and his parents brought him to ER.
- BP 70/45 mm Hg, P130 /min, T 101, R22/min Cor- Chest -, Abd diffuse mild tender, no rebound, increased BS, ext- no edema, + petechiae on legs.
- WBC 12.2K, Hct 28%, plt52K, smear with schistocytes.
- BUN 45 mg/dl, creatinine 3.1 mg/dl.
- U/A 2+ prot. 3+ heme, +rbc TNTC, + rbc casts.
Case 4

- Renal disease is progressive and creatinine increases to 6 mg/dl leading to institution of dialysis.
- Would you do a biopsy?
- If yes what would it show?
- What is the diagnosis here?
- How else could you make the diagnosis?

Childhood HUS

- STx Associated
- 2.1 per 100,000 /yr peak < 5 yo
- Warm summer months
- Onset GI sx, cramps, diarrhea, n/v, fever
- 70% bloody diarrhea w/i 2 days
- E.coli 0157 3-7% sporadic, 20% epidemic
- STx – E coli in stool for wks
Role of Shiga Toxin

- Epidemics with hemorrhagic colitis +/- HUS
- Epidemics in fast food outlets
  E. coli 0157:H7
- Sporadic HUS same
- A filterable agent in stool causes Hem. Colitis & cytopathic to green monkey kidney cells (verotoxin)
- E. Coli 0157:H7 produce both STX1 and STX2

Transmission of E. Coli - STX

- E. coli in cattle (& other animals) – manure, water troughs, farms
- Transmit by food or water
- Usually beef contaminated at slaughter
- Also raw milk, fruit & veg, apple cider, apple juice
- Person to person – day care centers
Case 4: E.coli-associated HUS

Pathologic findings

Fibrin thrombi in TMA
thrombi in glomerular capillaries

Cortical necrosis
Colon: hemorrhagic necrosis

**Shigatoxin-1 and Endothelium**

- Binds to Gb3 on glomerular endothelium
- Gb3 expression equal in children vs. adults
- Mechanism for childhood susceptibility remains undetermined

Ergonul, Clayton, Fogo, Kohan, 2003
Verotoxin

- A subunit binds 60S Ribosomes, inhibit protein synthesis
- 5 B subunits binds glycolipid receptors (gb3) on surface of colonic epithelium, endothelium, and WBCs

Shiga Toxin and Cell Injury

Moake, NEJM 2002
Higher Risk HUS

- Antibiotics
- Bloody diarrhea
- Fever, vomiting
- Leukocytosis
- < 5 yo
- females

Course ARF Childhood HUS

- 50% dialysis
- 75% transfusions
- 25% Neuro sx ( CVA, sz, coma )
- 3-5% die in acute phase
- Long term renal dysfunction common
Residual Renal Disease in Childhood HUS

- 3-18% ESRD
- 10-40% low GFR, proteinuria, CRF, HBP
- Duration anuria predicts dysfunction
  - 7.5% anuria < 10 days low GFR
  - 42.5% anuria > 16 days low GFR
Thrombotic thrombocytopenic purpura (TTP)

- Familial or acquired
- Single episode, or relapsing
- F:M 3:2
- Peak in 3rd decade
- CNS, other extrarenal signs often predominate (e.g. fever; purpura; heart failure; lung edema; elevated LDH)
- Acute renal failure; microangiopathic hemolytic anemia; thrombocytopenia
ADAMTS13

- A disintegrin and metalloprotease, with TSP-1-like domains (aka vWF-clearing protease)
- Protease, normally degrades vWF multimers
- Deficiency → platelets GPIbα ↔ vWF multimers
- Mutations or autoAb
Definition of TTP Based on ADAMTS13 Deficiency

- Low ADAMTS13 activity
- Evidence of biological effects of low ADAMTS13 activity
  - ↓ proteolysis of VWF (ultra-large multimers)
- Causes
  - Genetic mutations of ADAMTS13
  - Inhibitors of ADAMTS13
  - Others?
- Propensity to microvascular thrombosis, presenting with:
  - VWF-rich thrombi in arterioles and capillaries
  - Thrombocytopenia
  - Microangiopathic hemolysis
  - Dysfunction of organs