Hypertension

Not so essential after all

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Disclosures

Disclosure of financial relationships: NONE

Off-label usage: NONE

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Case 1

42 year old WM with hypertension for 10 years
BP 160/100 mm Hg on no meds.
24 hour ABPM average is 164/98 mm Hg. Non dipper
Normal weight. Non smoker
No caffeine or alcohol use
Good nutrition and exercise
FHx is negative for hypertension
PMHx negative
PE shows mild hypertensive retinopathy, S3 gallop, 2/6 systolic murmur
Lab is normal except for FBS of 102 mg %
EKG: Left ventricular hypertrophy
Plasma renin activity (PRA): 3.2 pg/ml/hr (normal is <0.65)
MNT micronutrient deficiencies: Mg, CoQ 10 and vitamin B 6
What is your treatment plan?

#1 Cause of Death Worldwide[1]

CVD has been the #1 COD since 1920

- 2200 deaths EVERY DAY from CVD & CVA[2]
- Equivalent to four 747s crashing every day!
- 2 out of 3 men will die of CVD
- 1 out of 2 women will die of CVD

We were doing BETTER! - Between 2000-2011

- Heart related mortality ↓'d 3.7% per year
- Stroke mortality ↓'d 4.5% per year

1. American Heart Association 1/17DS11775, 2017
2. NEJM 2011;365:2098

CVD is Expensive!

- Nation's **most expensive disease**[1]
- $1 Billion a day in medical costs & lost productivity[2]
- 2014 - stroke and heart failure were the most expensive chronic conditions in the Medicare fee-for-service program[1]
- CVD **Expenses are expected to "soar"** in the coming years[1]
- It will surpass cost estimates for other chronic diseases (diabetes & Alzheimer's)[1]

1. American Heart Association 1/17DS11775, 2017
2. CDC Foundation, April 29, 2015

#1 Cause of Death Worldwide[1]

We WERE getting better, but…

- CVD is now growing faster than our ability to combat it
- 2015 - CHD death rate increased by 1% for the first time since 1969
- 2015 – prevalence was 41.5%
  - Wasn't predicted to occur until 2030[2]
  - 15 years early!
- By 2035, nearly 50% of the US Population will have CVD

1. American Heart Association 1/17DS11775, 2017
2. Medpage Today/AHA February 15, 2017

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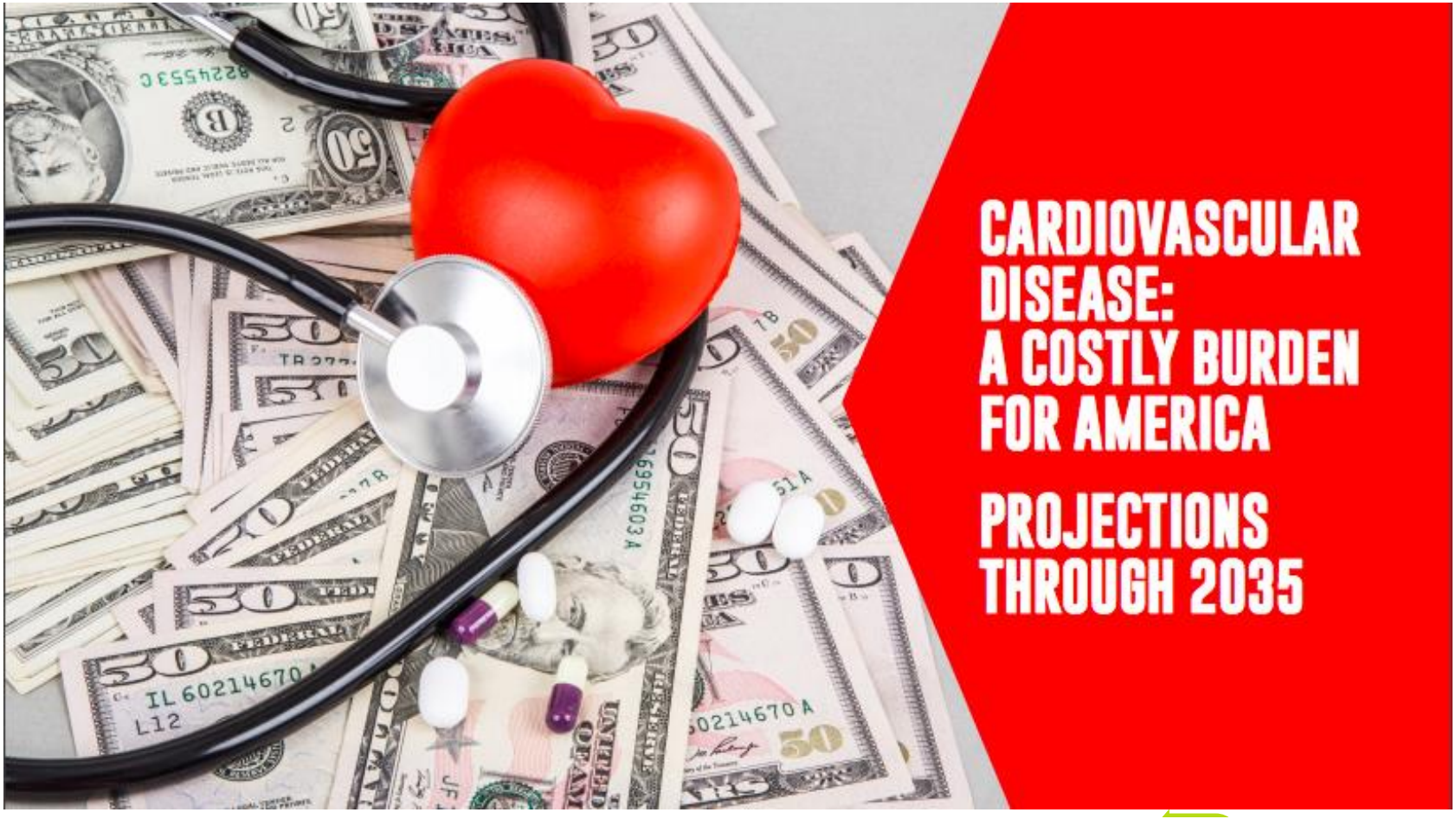

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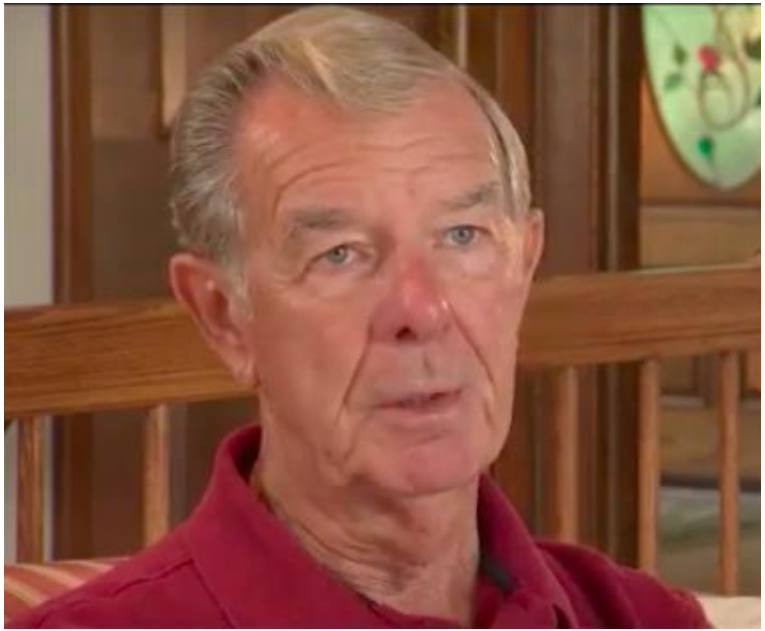
Million Hearts - John's Story

"I thought it would be nearly impossible for me to have a heart attack. But, I did…"

- Hx HTN (on meds)
- +FHx
- Frequent cholesterol checks
- Passed stress tests "with flying colors" (before his MI)
- "*He's the kind of patient we want to see. We want to see people while they have serious issues but before they have irreversible damage*." – His heart surgeon
- 5 vessel CABG



1. https://youtu.be/8DQo3uCK5_Y

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Top 5 Risk Factors

1. Hypertension
2. Hyperlipidemia
3. Tobacco
4. Diabetes
5. Obesity

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Hypertension, CVD, and CKD

Hypertension is

- #1 cause of CVD in the US
- one of the leading causes of CKD in the US

CVD is the **#1 cause of death** in the US (36% of all deaths)

<u>CVD costs</u>:

- 2009 - > $475 Billion dollars
- 2020 – projected > $800 billion

ASH Definition of Hypertension

“Hypertension is a progressive cardiovascular syndrome arising from complex and inter-related etiologies, which features early markers that are often present before blood pressure elevation is sustained.”

-American Society of Hypertension definition

1. J of Hypertension 2006;8:5-14

Hypertension is NOT a disease!

- marker for endothelial and vascular dysfunction.
- “correct” but chronic dysregulated response
- Vascular system is the innocent bystander.

HTN is a Vasculopathy

Characterized by:

1. Vascular Inflammation
2. Vascular oxidative stress
3. Vascular autoimmune dysfunction

Abnormal vascular biology with:

1. Endothelial Glycocalyx dysfunction
2. Endothelial dysfunction
3. Vascular smooth muscle dysfunction (VSMD)

Leads to:

1. Structural remodeling
2. Increased arterial stiffness

Initially these processes are adaptive to the increased BP, but then become maladaptive leading to a bi-directional contributing factors.
Endothelial dysfunction and vascular smooth muscle dysfunction **precede the development of hypertension by decades**.

1. Curr Opin Nephrol and Hypertension 2012;21:119-121
2. J of Hypertension 2012;30:2440

Vascular Biology

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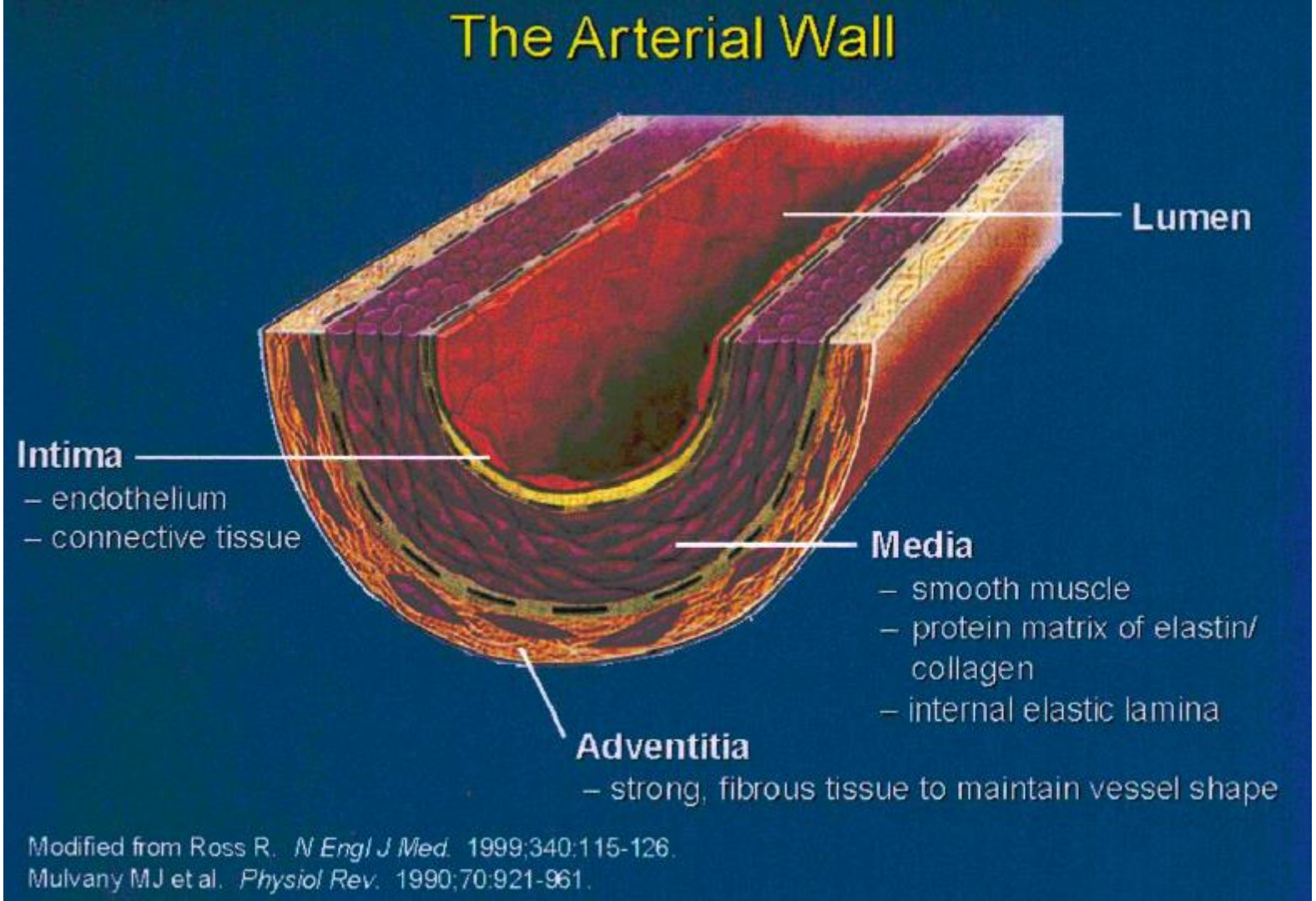
The Arterial Wall



Modified from Ross R. *N Engl J Med.* 1999;340:115-126.
Mulvany MJ et al. *Physiol Rev.* 1990;70:921-961.

Vascular Disease is a Balance

Vascular Injury
Nitric oxide vs angiotensin II endothelin and aldosterone

VS

Vascular Repair
Endothelial Progenitor Cells (EPC's)

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Infinite Insults – these are just the top 25

1. Hypertension
2. Dyslipidemia
3. Hyperglycemia
4. Obesity
5. Smoking
6. Hyperuricemia
7. Renal Disease
8. Increased Fibrinogen
9. Increased ferritin
10. Trans fatty acids & refined carbs
11. Low dietary Omega-3 fatty acids
12. Low dietary K^{+} & Mg^{++} w/ high Na^{+}
13. Inflammation: ↑ hsCRP
14. Increased oxidative stress & decreased oxidative defense
15. Increased immune dysfunction
16. Lack of sleep
17. Lack of exercise
18. Stress, anxiety, & depression
19. Hyperhomocysteinemia
20. Subclinical hypothyroidism
21. Hormonal imbalance (men and women)
22. Chronic clinical or subclinical infections
23. Micronutrient deficiencies
24. Heavy metals
25. Environmental pollutants

Your vessels are under attack!

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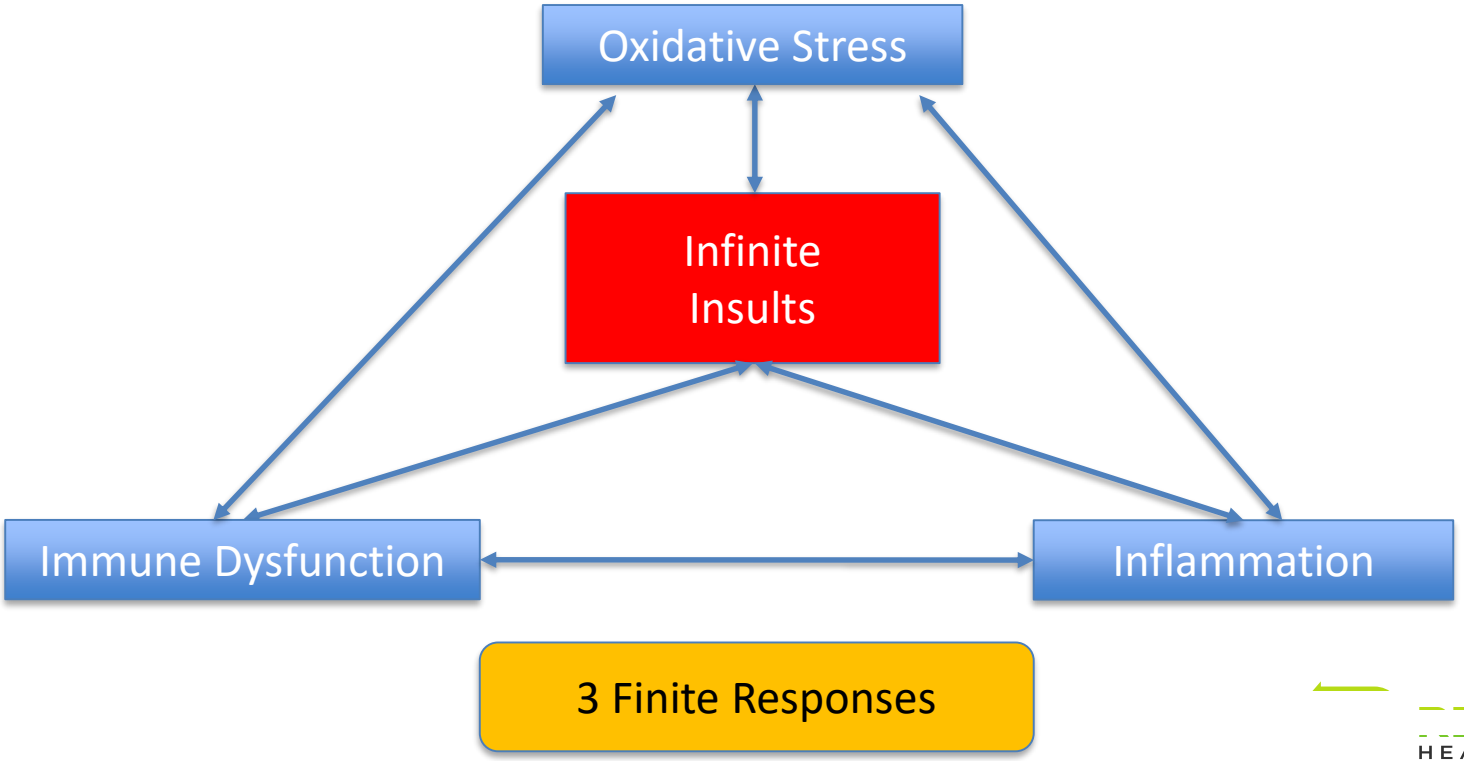
Infinite Insults



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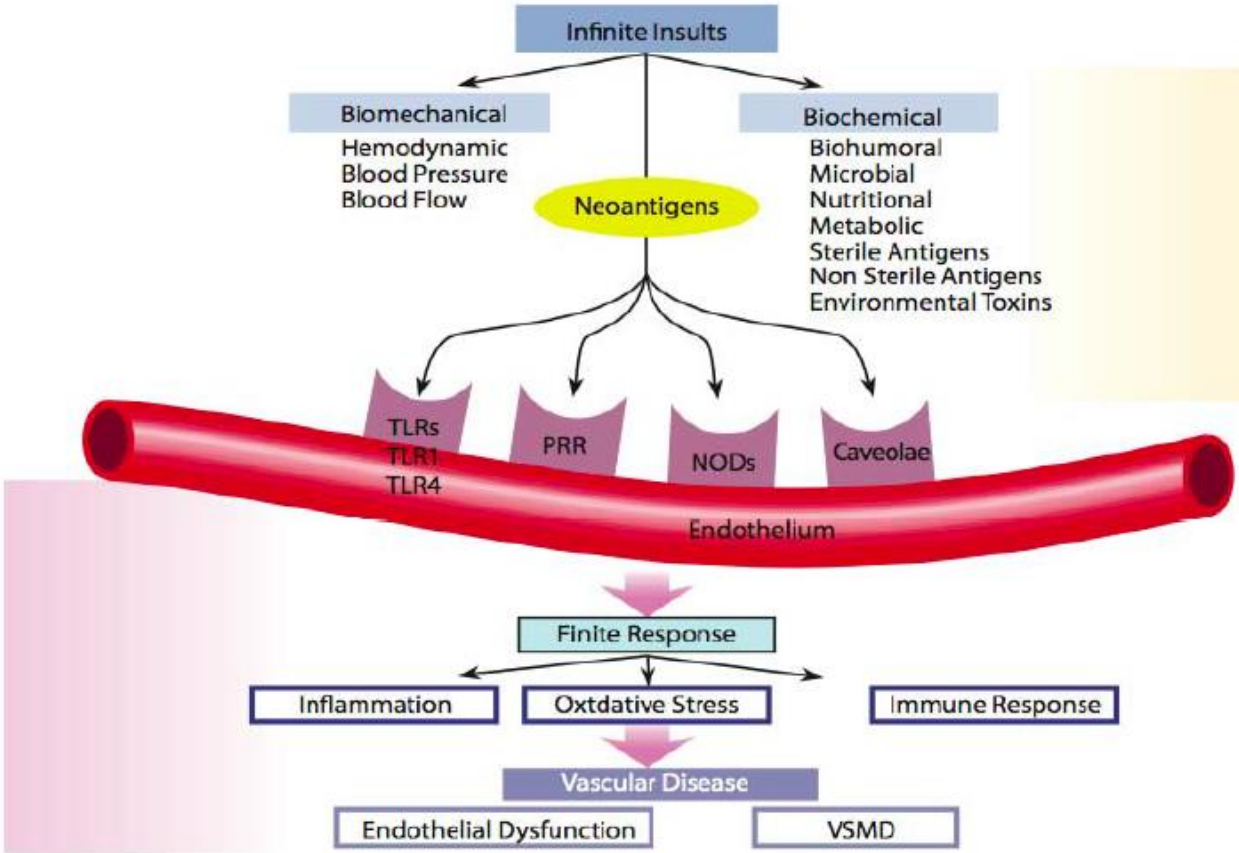
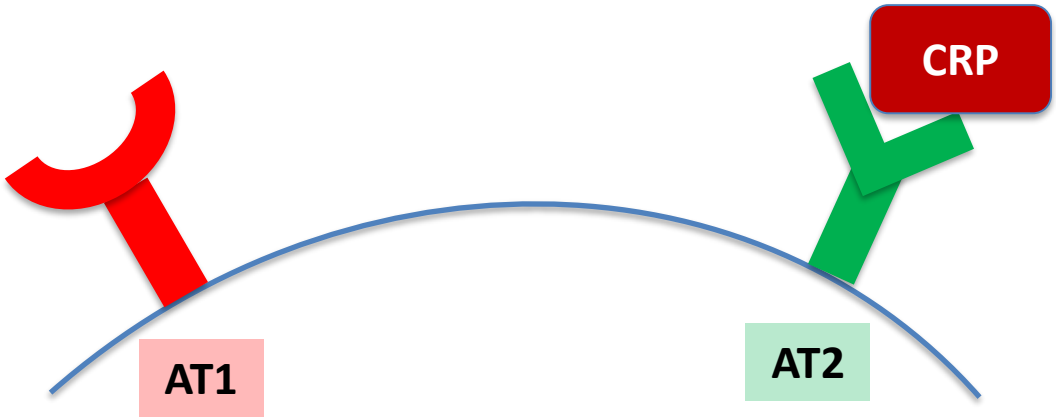
Infinite Insults



- Angiotensin II
- Endothelin
- Aldosterone
- oxLDL
- AGTR1 AA

- Nitric Oxide



- Vasoconstriction
- Na^+ & H_2O Retention
- Growth Stimulation
- Disease Progression
- Increased oxidation

- Vasodilation
- Anti-oxidant
- Anti-inflammatory
- Anti-thrombotic
- Growth inhibition

Endothelium

- barrier and primary sensor of physiological and chemical changes
- “air traffic controller” for the vasculature.

The endothelium acts as an inflammatory, oxidative stress and immune cell.

Endothelial Dysfunction

Definition: the potential for vascular endothelium to undergo phenotypic modulation to a nonadaptive state, characterized by the loss or dysregulation of critical homeostatic mechanisms normally operative in healthy endothelial cells.

Key & earliest event in vascular disease

Present with only risk factors but no atherosclerosis.

ED = loss of Nitric Oxide

Correlates with future CV events (MI, PCTA, CABG, sudden death).

Endothelial Dysfunction Predicts CVD

Very accurate predictor of**:**

- **future cardiovascular events** (CVD)
- target organ damage (TOD) such as CHD, MI, CVA, CRF and CHF

For each 1% increase in Endothelial Function there was an 8% decrease in CVD

This is particularly true in low risk hypertensive patients and less so in the late stages of CV TOD.

1. J of Hypertension 2014;32:2393

How to Measure Endothelial Dysfunction

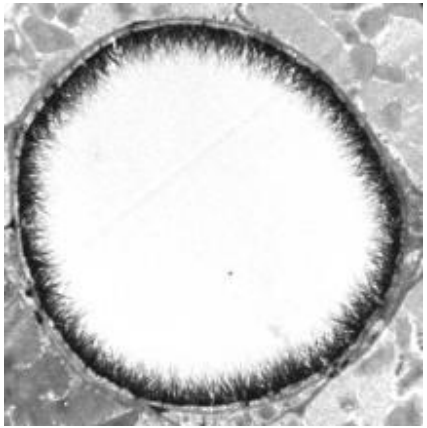
- EndoPAT, Endothelix
  - Measures reactive hyperemia and endothelial dysfunction
  - FDA approved
  - About $25,000
- 5 minute occlusion of brachial artery with BP cuff
- Digital measurement for ED-FMD as increase in signal amplitude
- Measure pre and post occlusion ratio index
- Index of 1.67 (EndoPAT) has
  - sensitivity of 82%
  - specificity of 77% to diagnose coronary endothelial dysfunction and highly correlates to brachial artery FMD (r=0.33 to 0.55).
- Predicts hypertension and CHD.

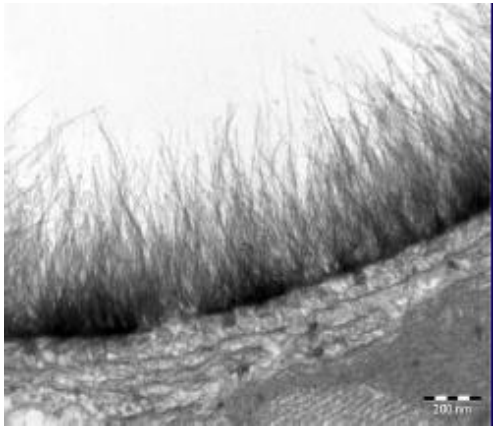
1. JACC 2010;55:1688
2. JACC 2004;44:2137
3. Circulation 2008;117:2467

Endothelial Glycocalyx

The Endothelium's "First Line of Defense"

- Microscopically thin gel-like layer
- coats the entire luminal side of the vascular endothelium
- provides a nonadherent shield.





van den Berg, Vink & Spaan, Circulation Research (2003), 92: 592-594

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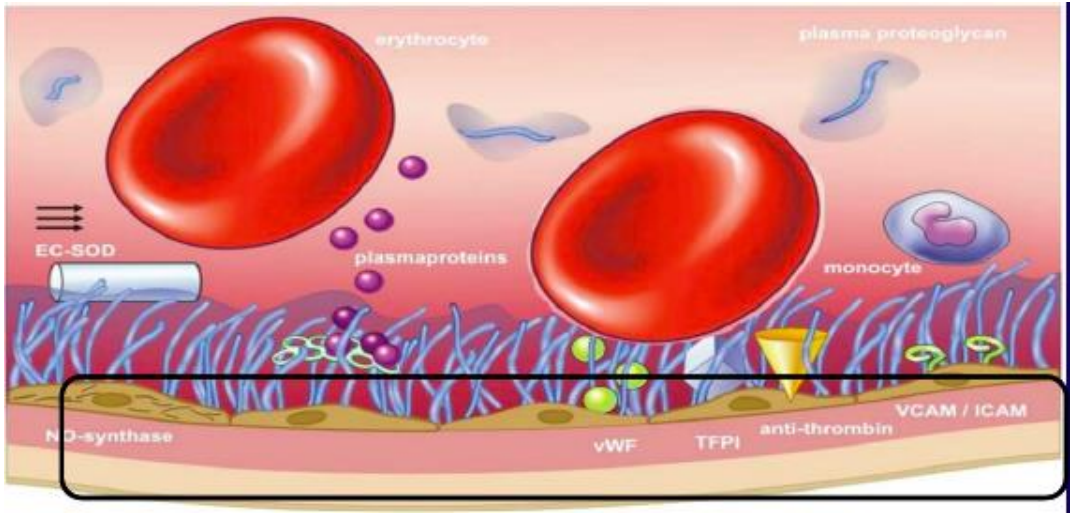
Functions of a Healthy Glycocalyx

- Triggers shear induced nitric oxide, ↓s ED, ↓s BP, and ↓s ASCVD
- Shear stress sensors
- Houses extra-cellular superoxide dismutase (ec-SOD)
- Vascular permeability (electrostatic charge, size and steric hinderance)
- Maintains colloid osmotic gradient of the vascular barrier
- Anti-thrombosis. Harbors coagulation regulatory factors
- Inhibits platelet adherence
- Prevents leukocyte adhesion & diapedesis



- Mediation of fibroblastic growth factor (FGF), AT-III, heparin cofactor, thrombomodulin, tissue factor inhibitor (TFI)
- Inhibits inflammation, oxidative stress, & vascular immune dysfunction
- Forms an interface between the blood and the endothelium

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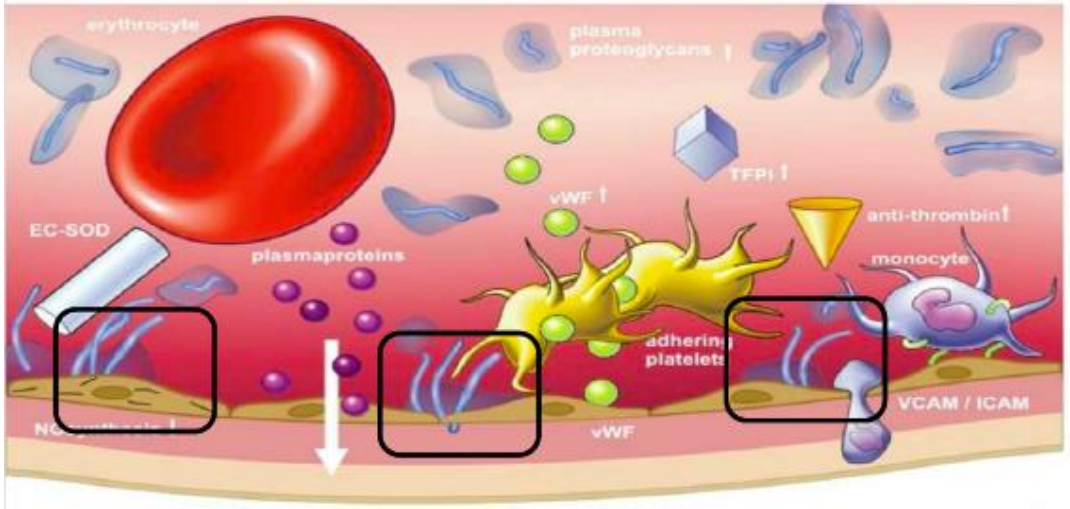
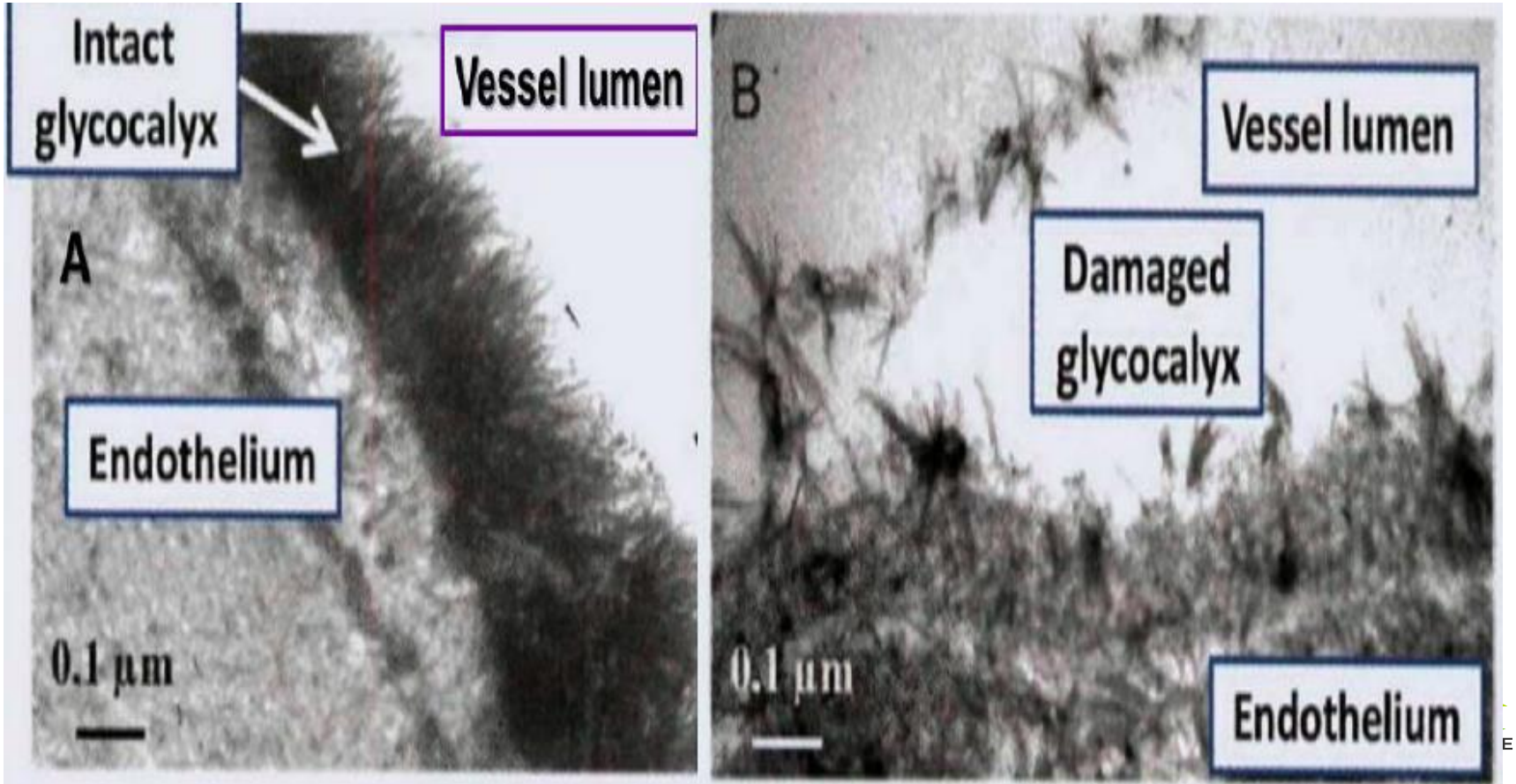
Compromised Endothelial Glycocalyx

Damage to the EGC precedes damage to the endothelium

- ↓'d NO production
- ↑'d oxidative stress
- ↑'d macromolecule leakage
- DM complications
- Ischemia-reperfusion injury
- ↑'d platelet adherence
- ↑'d thrombin generation
- ↑'d leukocyte adhesion & diapedesis
- CHD and atherosclerosis



Normal vs. Damaged Glycocalyx



Known Causes of EGC Degradation

- Hyperglycemia/DM
- oxLDL stimulates leukocyte CAMs and immobilization on the endothelial lining and induces anionic charges
- ↑ LDL and ↑ TG
- Thrombin
- TNF-alpha and other cytokines
- Inflammation
- Oxidative stress
- Immune vascular dysfunction
- Hypervolemia
- Low fluid shear stress
- Hyaluronidase
- Matrix metalloproteinases (MMP)
- Ischemia reperfusion
- Atrial natriuretic peptide (ANP)
- Endotoxins

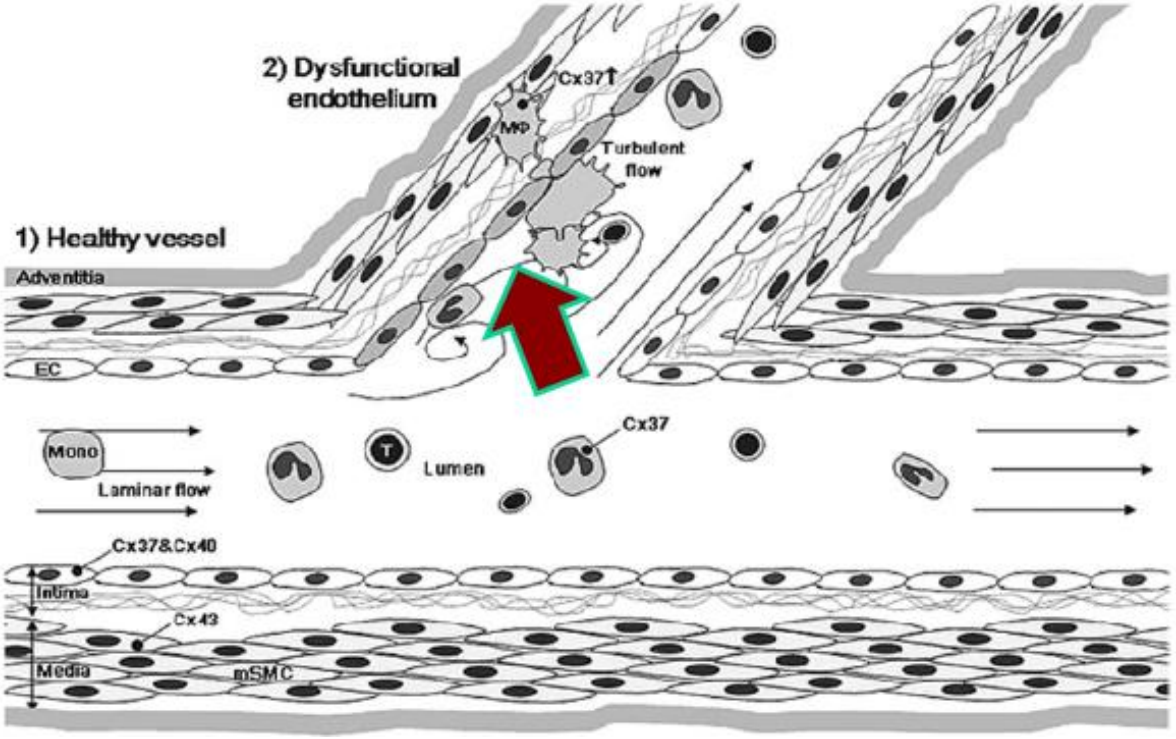
Spatial Variation of EGC Thickness

Significantly decreased at atheroprone locations (branches, bifurcation, & curvatures).

These locations are characterized with disturbed blood flow patterns including reversed, oscillatory, and turbulent flows associated with low shear stress

Gouverneur, et al., Journal of Internal Medicine (2006), 259: 393-400

High Risk of Plaque at Bifurcations



Anne Brisset, et al. Connexins in Vascular Physiology and Pathology (2008), Antioxidants & Redox Signaling 11(2):267-82

The EGC as Focus for CVD Intervention

CVD starts with Endothelial dysfunction

Endothelial glycocalyx is the primary protector of the endothelium

- MULTIPLE functions essential to CV health

A healthy Endothelial Glycocalyx may be **one of most important targets** for prevention of CVD

How to fix the Endothelial Glycocalyx

- Hydrocortisone
- Calcium channel blockers
- Glycemic control: Metformin, Sulodexide
- Sulodexide
- Statins
- Reduction of inflammatory mediators: hydrocortisone, anti-TNF
- Antagonizing enzyme-mediated glycocalyx injury: doxycycline
- Nitric oxide
- NAC (N acetyl cysteine)
- Glycocalyx regenerating compounds (GRCs): hyaluronan, antithrombin III, heparin, **special sulfated polysaccharides (SSP)**, and protein C

Buffering System of Vasculature

- In systole there is rapid infusion of stroke volume
  - 20 – 30% is forward flow
  - 70 – 80% is stored in large conduit (capacitive) arteries, then released to periphery during diastole (maximizes CV efficiency)
- Converts pulsatile flow in aorta to continuous flow in capillaries (Windkessel effect)
- Loss of buffering with ↓ arterial compliance (AC)
  - ↓'d continuous flow
  - ↑'d pulsatile flow to precapillary & capillary vasculature
  - Induces small vessel & end organ damage
- ↑ pulse wave velocity - PWV
  - Faster & distorted pressure wave
  - Reflected wave
  - Augmentation index (systole)
  - Augments Central SBP
- Artery stiffness - marker for CVD and events

1. World J of Cardiology 2015;7(11):742

Arterial Compliance - Overview

Functional & structural alterations of the arterial wall precede atherosclerosis & CV events.

- **Endothelial dysfunction is the earliest marker**
- **Arterial stiffness is 2nd**

HTN Tx (pharmacologic) has ↓'d CVA to predicted levels
BUT… CHD reduction has been sub-optimal.
"**CHD GAP**" due to lack of therapeutic response in improving:

1. Endothelial dysfunction (ED)
2. Arterial compliance (AC)
3. Concomitant risk factors
4. Hemodynamic and hypertension dysfunction

Endothelial Dysfunction effects Arterial Compliance via NO

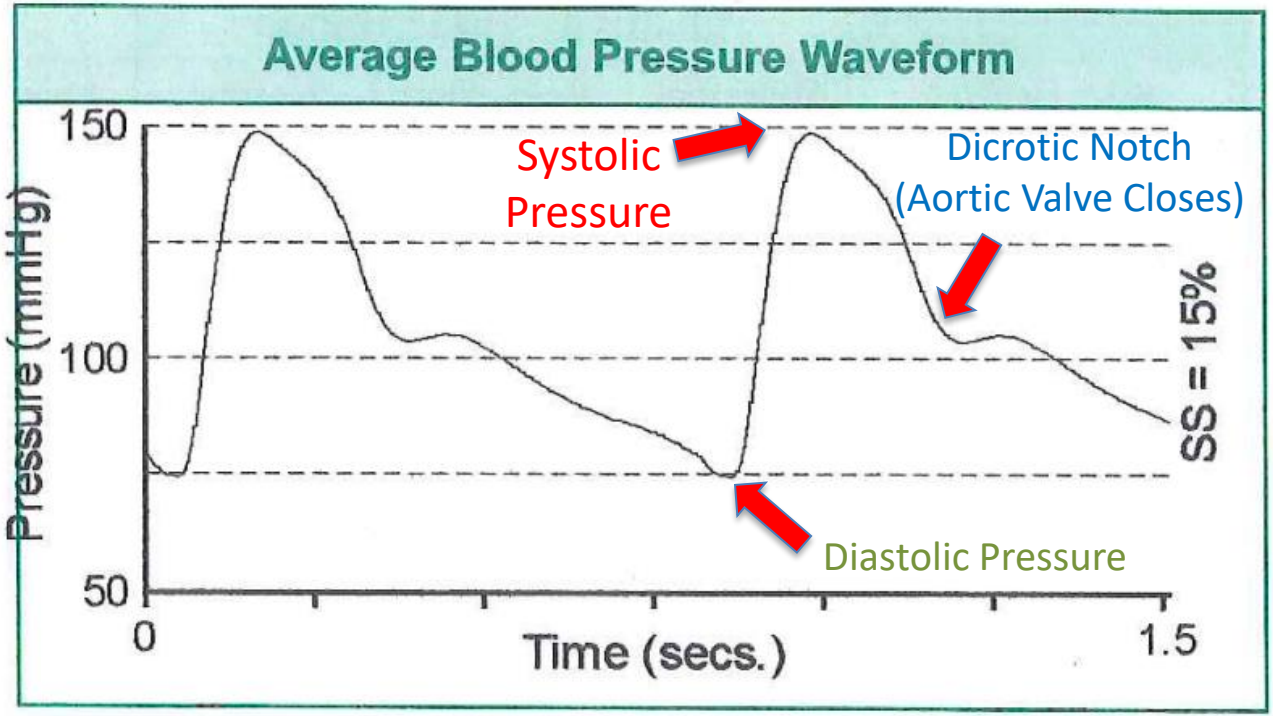
Arterial Compliance – Artery Types

- Conduit (Capacitive): C1 (store blood in systole) (buffer) (thin endothelium with thick elastin and collagen), less VSM
- Branch (Oscillatory): C2 (pressure oscillations/reflected waves) (intermediate structure)
- Arterioles (Resistance): C2 (control blood flow), VSM + endothelium primarily with minimal elastin or collagen, NO dependent.
    - Early marker for vascular disease (HBP, HLP, DM)

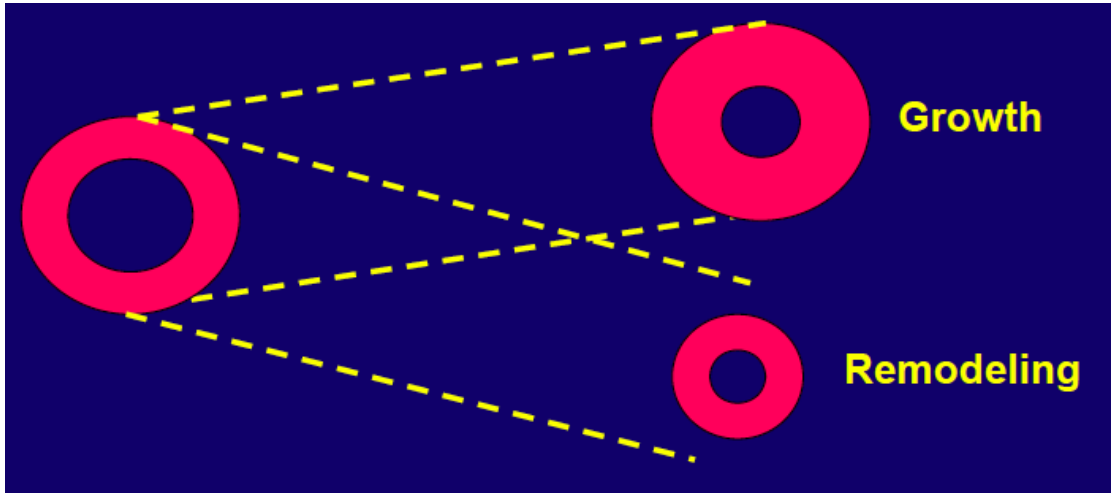
Endothelial role greatest in thin wall vessels – C2 vessels

ED occurs earlier & greatest in C2 vessels.

Blood Pressure Waveform



Vascular Remodeling



Hypertrophic Remodeling: Increased Media Lumen Ratio (MLR). Typical with HLD, DM, CKD, & other 2^{o} causes. Vascular SM Hypertrophy.

Eutrophic Remodeling: Increased Media Lumen Ratio (MLR). Inward growth. Markedly ↑'d tensile strength. Typical of "Essential" HTN.

Hypertensive patients have:

- abnormal microvasculature (eutrophic remodeling)
- ↑ vascular resistance
- ↑ MLR
- ↓'d maximal organ perfusion
- ↓ flow reserve
- CFR (coronary flow reserve) in the heart

1. J of Hypertension 2017;35:914
2. J of Hypertension 2011; 29:896-905
3. Journal of Hypertension 2018;36:2148-2156

Blood Pressure Evaluation

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Blood Pressure Evaluation

"Standard BP measurements are not adequate,
are often misleading,
& may not accurately reflect CV risk."

1. Hypertension. 2019;73:e35–e66

Proper BP Measurement

When checking BP:

- No caffeine within 6-8 hrs
- No exercise that morning if morning measurement
- No smoking within 4-6 hours
- Sitting (back supported, feet on the ground, legs uncrossed)
- Resting a MINIMUM of 5 minutes
- Arm level with the heart
- Appropriate Cuff size
- Deflate cuff 2 mm/Hg per second

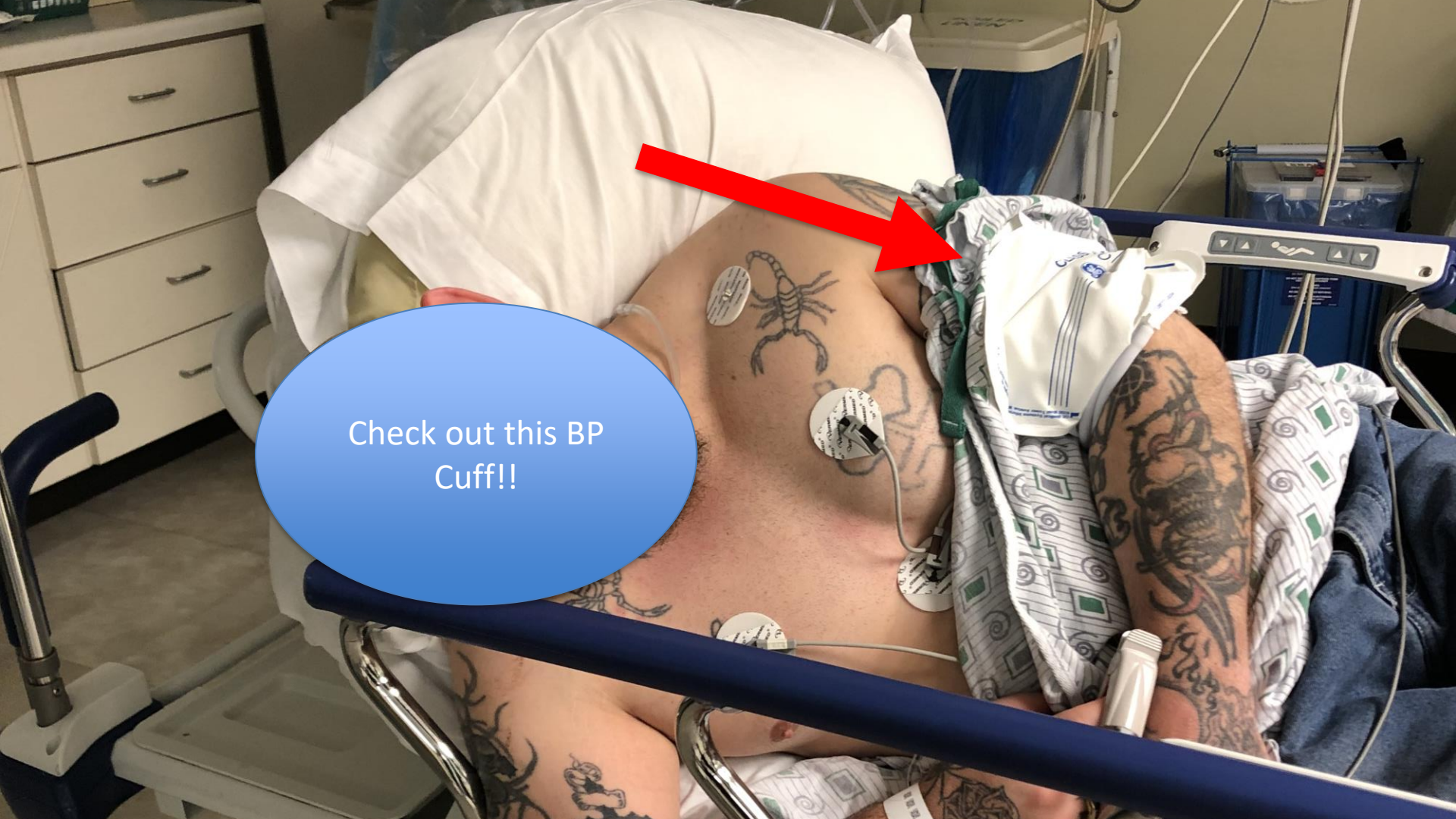
- Only use devices which are regularly recalibrated (q 2-4 wks)

1. Hypertension. 2019;73:e35–e66

BP Cuff

- Arm circumference measured ½ way between elbow (olecranon) & shoulder (acromion)
- BP cuff bladder length should be 75-100% of arm circumference
- Width should be 37.5-50% of the circumference
- Cuff on BARE SKIN
- Most common error is “miscuffing”
  - 84% use too small cuff on large arms (artificially elevated BP)

1. Hypertension. 2019;73:e35–e66


Check out this BP Cuff!!

Definitions

ACC/AHA Guidelines (2017)

- Normal = <120/80
- Elevated = 120-129/<80
- Stage 1 = 130-139/80-89
- Stage 2 = ≥140/≥90

1. Hypertension. 2019;73:e35–e66

Standard BP Evaluation is NOT Sufficient

- Need indirect arterial measurements & CV function and structure testing with noninvasive technology.
- Measure endothelial dysfunction, Augmentation Index (AI) and heart rate variability (HRV).

- Central Blood Pressure (CBP), pulse pressure (PP), augmentation index (AI)

- 24-hour Ambulatory BP Monitoring (ABPM)

- Computerized arterial pulse wave analysis (CAPWA) to assess small and large artery compliance (C1 & C2), small vessel vascular remodeling, & PWV.

- Home BP

- Improved techniques for in office BP measurements.

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Central Blood Pressure (SphygmoCor)

- Ascending Aortic BP

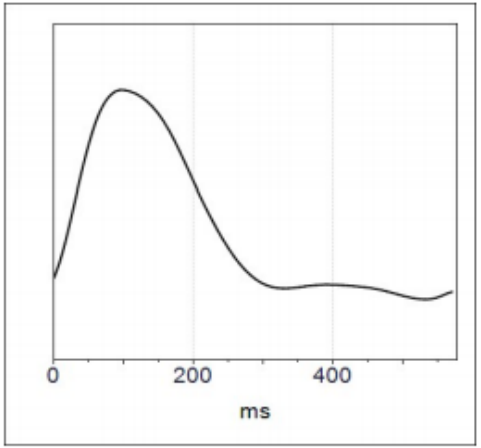
- More predictive of CVD mortality, all cause mortality, diastolic dysfunction, & LVH than brachial BP

- **Better than brachial BP measurement**
  - CBP indicates pressure exerted on heart & brain
  - CAFÉ study indicated that CVD outcome related better to CBP than brachial pressure.
  - CBP ↓'d with CCBs, ACEi, ARBs, and alpha-blockers
  - CBP ↑'d by non-vasodilating BBs and diuretics

Expert Rev Cardiovasc Ther. 2010;8:260

Central Blood Pressure (SphygmoCor)

Average Peripheral Pulse



SYS **160** mmHg

DIA **102** mmHg

PPP **58** mmHg

MAP **120** mmHg

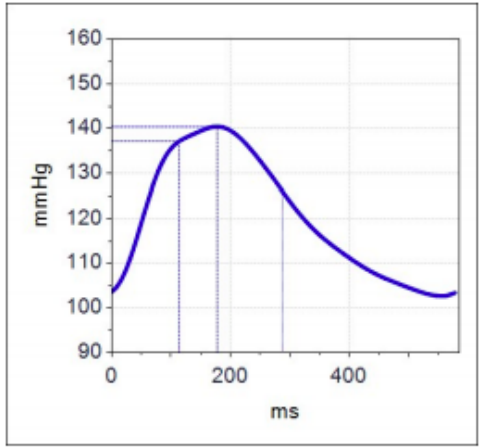
Average Aortic Pressure Pulse

SP **140** mmHg

DP **104** mmHg

PP **36** mmHg

HR **104** bpm



PP Amplification: **157 %**

Central Haemodynamic Parameters

Heart Rate, Period:	**104 bpm, 578 ms**
Ejection Duration (ED):	**288 ms, 50 %**
Aortic T2:	**178 ms**
P1 Height (P1-DP):	**34 mmHg**
Aortic Augmentation (AP):	**2 mmHg**

Aortic AIx (AP/PP, P2/P1):	**5 %, 110 %**
Aortic AIx (AP/PP) @HR75:	**19 %**
Buckberg SEVR:	**85 %**
PTI (Systole, Diastole):	**3900, 3320 mmHg.s/min**
End Systolic Pressure:	**126 mmHg**
MAP (Systole, Diastole):	**130, 110 mmHg**

24-Hour ABPM

“If you don’t do a 24-hour ambulatory blood pressure monitor you are **approaching medical malpractice**. You can’t know what drug to use, how much to give, or when to give it without a 24-hour ABPM.**”** - Mark Houston, MD

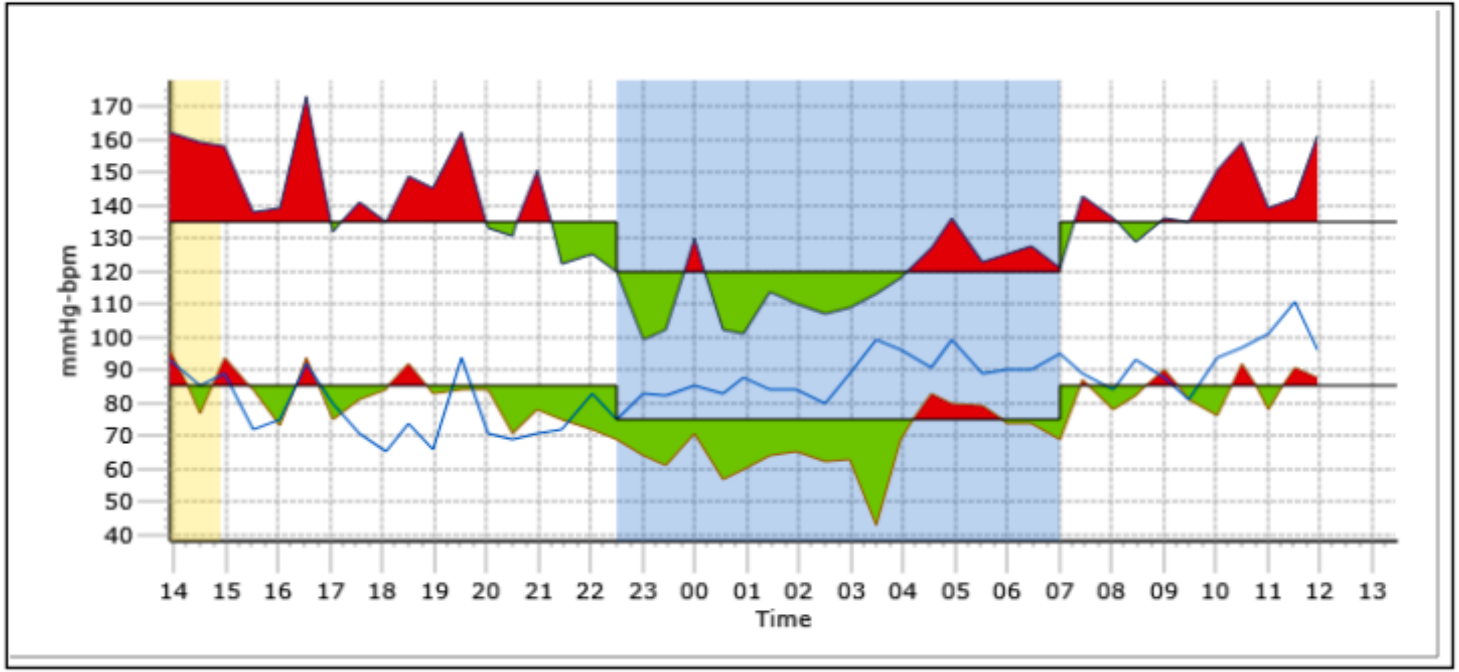
Indications for ABPM: (literally EVERYONE should have this done)

- ID white-coat HTN
- ID masked hypertension
- ID normal 24-hour blood pressure patterns (dipping, daytime/nocturnal HTN)
- Assess Tx
- Assessing HTN in the elderly, children/adolescents, pregnancy, high-risk patients
- ID ambulatory hypotension
- ID BP patterns in Parkinson’s Disease
- Endocrine hypertension

Interpretive Summary

Based upon JNC 7 and AHA recommendations, the ABPM data suggests:
- 24 hour SYS hypertension (133 mmHg) with normal 24 hour DIA pressure (77 mmHg)
- awake SYS hypertension (143 mmHg) with normal awake DIA pressure (82 mmHg)
- normal asleep SYS and DIA pressure (116/67 mmHg)

Asleep dip is 19.3 % SYS and 18.8 % DIA, Dipper (normal).



24-Hour ABPM HTN Definitions

- 24-hour average - ≥130/80
- Awake (daytime) average - ≥135/85
- Asleep (night-time) - ≥120/70
- Blood Pressure Load -

- Dipper: 10-20% is normal
- Non-Dipper: <10%
- Excessive Dipper: >20%

White Coat Hypertension (WCH)

Untreated subjects with elevated office BP ≥140/90 mmHg AND

- 24-hour ABPM <130/80 mmHg AND
- Awake ABPM <135/85 mmHg AND
- Sleep <120/70 mmHg OR
- Home BP <135/85 mmHg

7382 untreated adults. Altered cardiac structure & Fxn in WCH.

> "**The study supports the view that WCH should not be further considered a fully benign entity**."[2]

29,100 participants over 8 yrs. WCH has higher M&M but not as high as sustained HTN.[3]

1. Hypertension. 2019;73:e35–e66
2. J Hypertens. 2015 Jan;33(1):24-32
3. J Hypertens.2016 Apr;34(4):593-9

Masked Hypertension

Untreated subjects with office BP <140/90 mmHg **AND**

- 24-hour ABPM ≥130/80 mmHg AND
- Awake ABPM ≥135/85 AND
- Sleep ≥120/70 mmHg OR
- Home BP ≥135/85 mmHg

Both WCH and Masked HTN have a higher risk for sustained hypertension.

Incidence is about 12%[4]

1. Hypertension. 2019;73:e35–e66
2. J Hypertens. 2015 Jan;33(1):24-32
3. J Hypertens.2016 Apr;34(4):593-9
4. J Clin Hypertens (Greenwich). 2007 Dec;9(12):956-63

Nocturnal Hypertension

- More important than dipping status as an early marker of CV risk
- Defined as BP >120/70 during sleep
- More common than non-dipping status
- 70% of hypertensive patients
- Associated with more TOD independent of dipping/non-dipping status.
- Total mortality ↑'s 29%, all CV events ↑ 38%

MAPEC study: 2156 hypertensive patients. Bedtime administration of meds had a lower sleep-time BP, reduced non-dipping, & higher prevalence of controlled ABP.

- 5.6 yr f/u had lower RR of total CVD @ 0.39
- 17% reduction in CV risk for each 5mmHg decrease in sleep SBP
- Reduced DM2, CKD, and overall survival
- ACEi & ARBs are best therapy, CCBs less so

1. Hypertension. 2019;73:e35–e66
2. J Hypertens. 2015 Jan;33(1):24-32
3. J Hypertens.2016 Apr;34(4):593-9

Pulse Wave Analysis (CAPWA)

Computerized Arterial Pulse Waveform Analysis (CAPWA)

- Synthesize central pressure waveform from the brachial or radial waveform
- Central hemodynamics improves Dx, monitoring, prognosis
- Index of wave augmentation
  - + Arterial stiffness
  - + Wave reflection
  - + Vascular load
  - + Coronary perfusion

- Evaluate therapy central vs peripheral pressure discrepancies

- ↑ Pulse wave velocity (PWV) correlates with ↑ 24 hour heart rate & BP (increased central & peripheral pulse pressure after age 50)

- PWV is independent risk factor for CVD, HTN, CVA, CKD.

Pulse Wave Analysis (CAPWA)

CVProfile™ Report

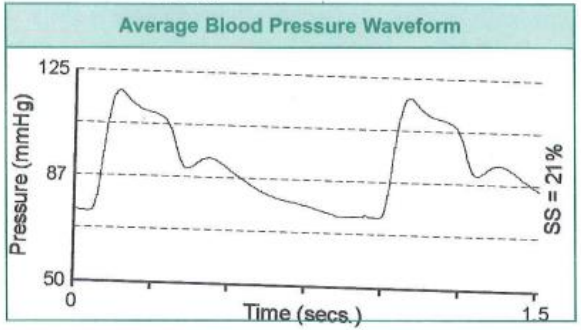
CVProfilor®
Profile for life.

ID#: 0009

Profile by: CHAD EDWARDS
REVOLUTION
9189353636

Name:

SSN:
Date: Dec 19, 2019
Time: 15:16
Age: 47 years
Gender: Male
Height: 5 ft 6 in
Weight: 170 lbs
BSArea: 1.87 meters²
Body Mass Index: 27.5



PARAMETER	VALUE
Systolic Blood Pressure (mmHg)	118
Diastolic Blood Pressure (mmHg)	75
Mean Arterial Blood Pressure (mmHg)	91
Pulse Pressure (mmHg)	43
Pulse Rate (beats/min)	64
C1 – Large Artery Elasticity Index (ml/mmHg x 10) (Capacitive Arterial Compliance)	16.7
C2 – Small Artery Elasticity Index (ml/mmHg x 100) (Oscillatory or Reflective Arterial Compliance)	7.5

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Pulse Wave Analysis (CAPWA)

Arterial Elasticity Guidelines

Instructions: (1) Circle the gender and age range of the individual tested.
(2) Write the C1 and C2 arterial elasticity index values printed on the CVProfile™ Report in the brackets at the top of the guideline table which matches individual's gender.
(3) In the same row as the individual's range, circle the C1 and C2 table values which match those written in the brackets in order to interpret the individual's vascular health.

MALE	C1 – Large Artery [16.7] Elasticity Index Range			C2 – Small Artery [7.5] Elasticity Index Range		
Age Range	Abnormal	Borderline	Normal	Abnormal	Borderline	Normal
15 - 19	< 10	10 – 17	> 17	< 6	6 – 9	> 9
20 - 29	< 9	9 – 16	> 16	< 6	6 – 8	> 8
30 - 39	< 8	8 – 14	> 14	< 6	6 – 8	> 8
40 - 49	< 7	7– 12	> 12	< 5	5 – 7	> 7
50 - 59	< 6	6 – 11	> 11	< 5	5 – 7	> 7
60 - 69	< 5	5 – 10	> 10	< 4	4 – 6	> 6
> 70	< 5	5 – 9	> 9	< 4	4 – 5	> 5

Lab Evaluation of HTN

Standard Measurements

- CBC
- CMP
- Urinalysis
- Microalbumin/Creatinine Ratio
- BNP
- EKG

Additional Tests

- PRA
- Aldosterone
- Genetics
- Nutrients

Plasma Renin Activity (PRA)

<u>High PRA (70%) – ↑'d risk of</u>:

1. MI, ischemic heart disease & mortality (total & CV) beyond the Framingham score.
2. For every 2 unit increase in PRA there is a 25% increase in MI risk
   - "plasma renin activity is directly and independently associated with the occurrence of total CVD, especially MI"[6]
3. Stroke
4. CHF
5. CKD
6. Morbidity & Mortality (total & CVD)

1. J of Hypertension 2011;29:2226
2. NEJM 1993;329:616
3. Am Heart J 2011;162:585-96
4. Am J Hypertension 2011;24:1181
5. Am J Cardiol 2010;106: 764
6. Am J Hypertension 1997;10:1-8
7. Curr Opin Nephrol Hypertens 2012;21:508

Why Use PRA For HTN Tx?

Antihypertensive efficacy study using PRA

- 170 Caucasian hypertensive patients, no antihypertensive medications, age 18-70 yrs Tx'd x 1 month

- **Better control**: % of patients achieving BP control higher in those treated with appropriate drug.
  38% vs 29%

- **Lower DBP**: DBP was positively correlated to appropriate drug (p= 0.02) as was % reduction (p=0.04). The DBP was 3 mmHg lower

1. Blood Pressure 2010;19:218-224

How to Measure PRA

- RANDOM ambulatory serum levels of plasma renin activity (PRA) and serum aldosterone

- Does not require alterations in patient position, time of day, sodium intake etc.

- Most accurate in drug naïve patients - Altered by most anti-HTN medications

Plasma Renin Activity (PRA)

Laragh Method

- Low Renin Hypertension (LRH): Increased Intravascular Volume (Volume dependent) PRA
  - < 0.65 ng/ml/hr
  - 30% of patients
- High Renin Hypertension (HRH): Decreased Intravascular Volume
  - PRA > 0.65 ng/ml/hr
  - 70% of patients
- Very high Renin: Volume Depleted
  - PRA> 6.5 ng/ml/hr

1. N Engl J Med 1972;286:441-449

Pathophysiology of HIGH-Renin HTN

- Elevated PRA > 0.65 ng/mL/hr
- Normal to low serum aldosterone levels
- ↓ intravascular volume
- ↑ risk of CVD, MI, CVA compared to LRH
- Treatment responsive to ACEI, ARB, RI, BB and CAA
- Also nutraceuticals with similar mechanisms of actions as these drugs

1. N Engl J Med 1972;286:441-449
2. Am J of Hypertension 2013;26:727

Pathophysiology of LOW-Renin HTN

- ↓ PRA
- **Aldosterone Problem!** Inappropriately ↑ Aldosterone level that cannot be suppressed with salt loading.
- ↓ serum ionized Ca^{+}
- ↑ serum PTH: Secondary hyperparathyroidism (SHPT)
- ↑ intracellular Ca^{+} especially mitochondria, cardiac myocytes, & arteries. Increased oxidative stress and cardiac fibrosis
- Increased intravascular volume – "**Wet Hypertension**"
- Association between Ca^{+} and Na^{+} metabolism
- More common in Blacks
- Commonly have ↓ Mg^{+}, ↓ zinc, ↓ ionized Ca^{+} and ↓ Vit D.
- Treatment responsive to Ca^{+}, Zinc, Vitamin D, DHP-CCB, diuretics, and SARAs.

1. Ann Intern Med 1986;105:649-54
2. J of Hypertension 2010;28:s25-32
3. N Engl J Med. 1972; 286:441-449

PRA & Aldosterone

Use IF your PRA = 0.65 (+/-)

Aldosterone Renin ratio (ARR) – (pg/ml) / (ng/ml) per hr

- ARR > 80 = LRH (or primary hyperaldosteronism)
- ARR > 40 is probably LRH with a sensitivity & specificity of 100% and 92% for primary aldosteronism.
- ARR less < 10 = HRH
- ARR between 10 and 40: not sure

Higher ARR is associated with development of CKD[4]

1. Zhonghua Nei Ke Za Zhi 2012;51:294
2. Exp Clin Endocrinol Diabetes 2012;120:388
3. Hypertension Res 2011;34:361
4. J Hypertension 2012;30: 1632
5. Journal of Hypertension 2014;32;115

Medications & PRA

Medications that ↑ PRA

- Diuretics
- ACEi
- ARBs

Medications that ↓ PRA

- Beta-Blockers
- DRIs
- Central Alpha Agonists

Medications that are Neutral for PRA

- CCBs

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Genetic Testing

1. ACE I/D: HTN, LVH, CRF, MAU, nephroangiogenesis, CIMT, MI & CHD.
2. COMT: CHD, MI, HTN, ASA, & Vitamin E responses
3. MTHFR: HTN, CHD, MI, CVA, thrombosis, homocysteine, ED.
4. CYP 1A2: Caffeine, HTN, MI, aortic stiffness, PWV, tachycardia, arrhythmias, vascular inflammation, cateholamines.
5. Corin: HTN, CHF, volume overload, sodium sensitive, CVD, CRF, pre-clampsia, ANP & BNP.
6. CYP 11B2: HTN, aldosterone & response to spironolactone.
7. GSHPx: CHD, MI, HTN, LVH, CHF, Glutathione, ALA 6 alleles, selenium.
8. ADR B2: HTN, PRA, inflammation & DASH diet with ACEI, ARB or DRI.
9. CYP 4A11: HTN, ENaC & sodium, volume overload, CHD and Amiloride.
10. AGTR1 (ATR1AA): HTN, ARBs & potassium.
11. NOS3: Nitric oxide, HTN, MI, CHD, CVA, thrombosis, ED, oxidative stress, inflammation.

Hypertension Treatment

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Step 1: To Treat or Not To Treat?

Criteria to decide hypertension treatment

- BP Level
- CHD risk factors?
- COSHEC or Rasmussen CVD risk scoring system
- CVD target organ damage (TOD)?
- High risk tests? EndoPAT, CAPWA, central BP, augmentation index, ECHO, CPET, plethysmography, CAC, PULS, etc.
- Symptoms related to BP? (headache, chest pain at rest or with exercise, dyspnea etc.)

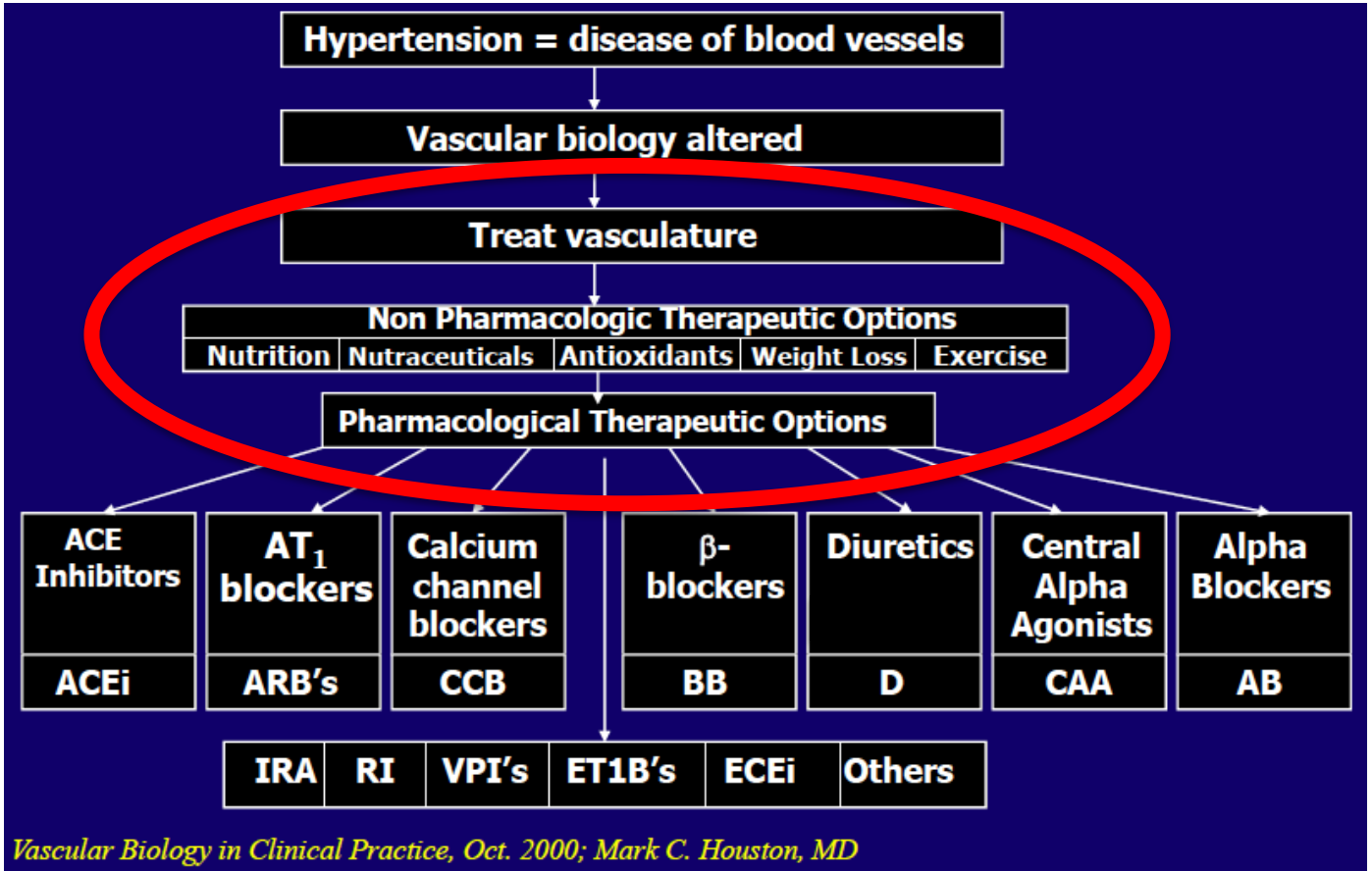
Step 2: Exclude 2º Causes

1. OSA
2. Renal vascular hypertension with renal artery stenosis: atherosclerotic and fibromuscular dysplasia
3. CKD
4. Pheochromocytoma
5. Hyperaldosteronism
6. Cushings
7. Hyperparathyoidism
8. Acromegaly
9. Hyper- and hypo- thyroidism
10. Licorice intoxication
11. Heavy metals and pesticides
12. Nutritional deficiencies
13. Stress, anxiety, depression
14. Coarctation of the aorta
15. Neurological
16. Caffeine in slow metabolizers CYP1A2
17. COMT SNP
18. Oral contraceptives
19. Acetaminophen
20. Alcohol, amphetamines, ecstasy (MDMA and derivatives), and cocaine
21. Angiogenesis inhibitors (including tyrosine kinase inhibitors and monoclonal antibodies)

Step 2: Exclude 2º Causes

22. Antidepressants (including venlafaxine, bupropion, and desipramine)
23. Corticosteroids
24. Cyclosporine
25. Ephedra and many other herbal products
26. Sudafed
27. Erythropoietin
28. Estrogens (including birth control pills) and other hormones
29. Immunosuppressants
30. Many over-the-counter medicines such as cough/cold and asthma medicines
31. Migraine medicines
32. Nasal decongestants
33. Nicotine
34. Nonsteroidal anti-inflammatory drugs (NSAIDs)
35. Testosterone and other anabolic steroids and performance-enhancing drugs
36. Yohimbe
37. NSAIDS and COX 2 inhibitors, indomethacin

New Treatment Approach



Hypertension Management

- **Interrupt the process causing the vasculopathy**
  - Carbon Monoxide patient
- Measure PRA/Aldosterone
- Nutrient Depletion Evaluation
- Subset of HTN: Individualize Rx
- Genetic Phenotype (SNPs)
  - Those that predispose an individual to hypertension in some or all conditions
  - Those that predict response to a drug or nutrient.

1. Blood Pressure 2010;19:218-224

Weight Loss

<u>One of the most effective means to reduce BP</u>

- Weight loss ↓'s cardiovascular events[1]
- 4-5 Kg weight reduction decreases BP (7/5 mmHg)
- Potentiates other nonpharmacologic & pharmacologic treatment
- ↓'s BP independent of IBW
- ↓'s adipokines which will ↓ BP & inflammation

1. Mayo Clin Proc 2014;89:1368
2. J Hypertens 1998; 7: S19-S23
3. JAMA 1993; 279: 839-46
4. JAMA 1993; 270: 713-24
5. Am J Med 2000; 109: 734-5
6. Ann Int Med 2001; 134: 1-11
7. NEJM 1981; 304: 930-3
8. Prog Cardiovas Disease 1999; 41: 451-60
9. NEJM 1978; 298: 1-6
10. Current Atherosclerosis Report 2000; 2: 521-8
11. J Obesity Res 1998; 6 (2): 51S-209S

Exercise

Regular aerobic exercise

- lowers BP significantly
- Decreases risk of CHD
- reduces inflammation, CRP, IL-6, VCAM & fibrinogen.

Fit patients have lower prevalence of hypertension

Combination of Resistance training AND Aerobics (40:20)

- Once trained, BP reduction may be as great as:

  SBP: ↓ 10-15 mmHg

  DBP: ↓ 5-10 mmHg

Meta-analysis of 13 controlled trials: mean BP reduction of 11.3/7.5 mm Hg

- Equivalent effect of 1 BP medication.

1. CANNT 2005;15:60Dtsch
2. Med Wochenschr 2011;136:2367
3. J Hum Hypertens 2010;24:796
4. Am Heart J 2012;163:666
5. Circulation 1986; 73:30-9
6. Circulation 1990; 81:1560-7
7. J of Hypertens 2019;37:820

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DASH-I

459 adults, BP <160/80-95, 3 week run-in, 8 week study

3 Groups: Na^+ controlled to 3g/d in all 3 groups

- Control – standard American diet
- Fruit & Veggie diet -
  - Reduced BP 2.8/1.1 (P=0.07)
- Combination diet – fruits, veggies, low-fat dairy (reduced SFA, total fat)
  - Reduced BP 5.5/3.0 (P<0.001)
  - Similar results as taking 1 medication for HTN

1. N Engl J Med 1997;336:1117-1124

DASH-II

412 adults (not everyone was hypertensive - 120-159/80-95)

- Na^+ varied Low, Intermediate, or High for 30 consecutive days
  - High – 150 mmol (3.45 grams Na^+)
  - Intermediate – 100 mmol (2.3 grams of Na^+)
  - Low – 50 mmol (1.15 gram of Na^+)
- 2 Groups
  - Control – standard American diet
  - DASH (combination) diet
    - Lower BP at every Na^+ level
    - ↓ **DBP 11.5 mmHg** in the low Na^+ hypertension group

1. N Engl J Med 2001;344:3-10

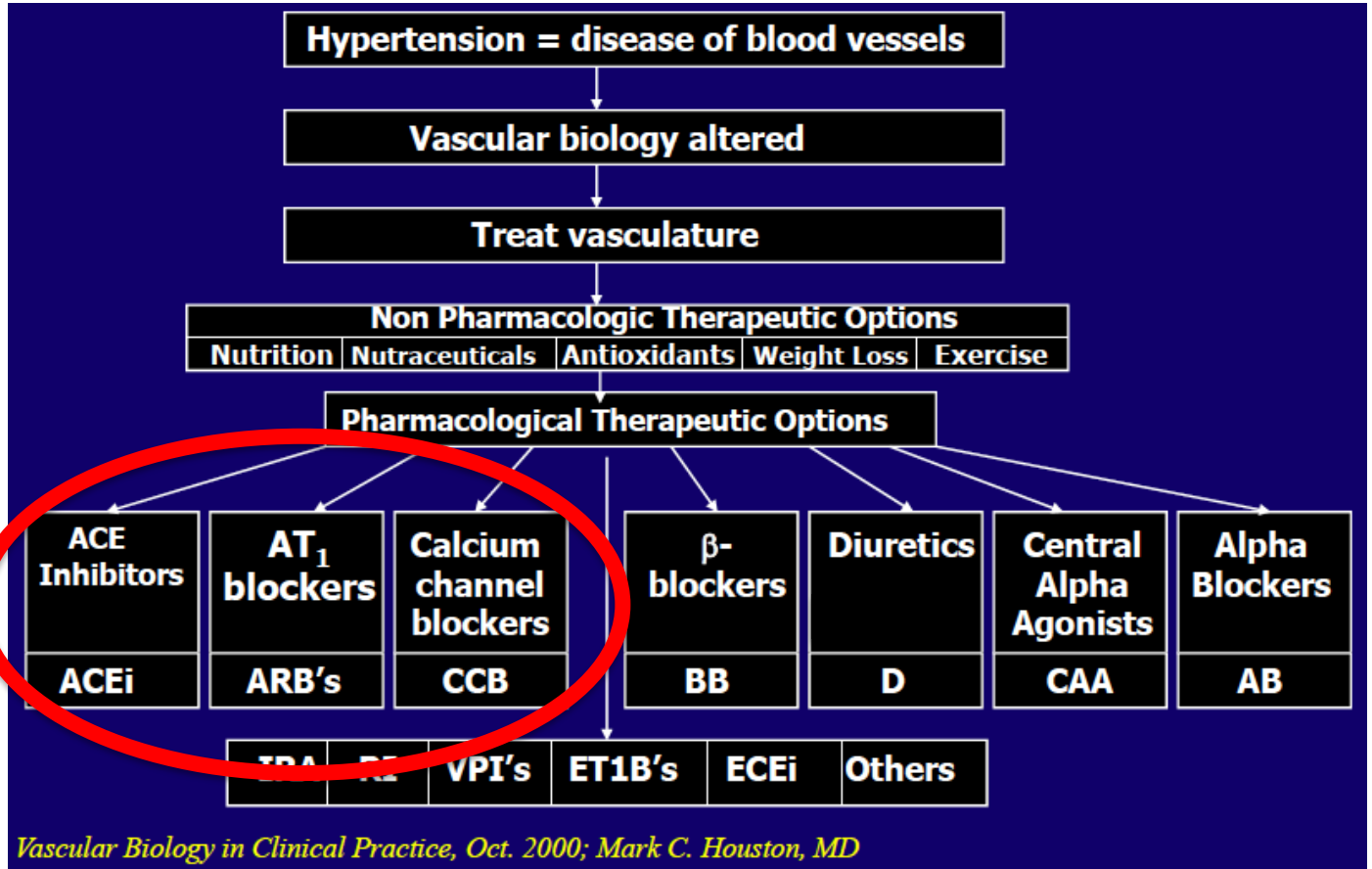
REVOLUTION HEALTH & WELLNESS

Health Coach

- I can’t manage without them!
- Help “translate” therapeutic plan
- Increased compliance with interventions
- Enhanced ability to identify underlying contributing factors
- More cost effective (for patient)
- Saves YOU time

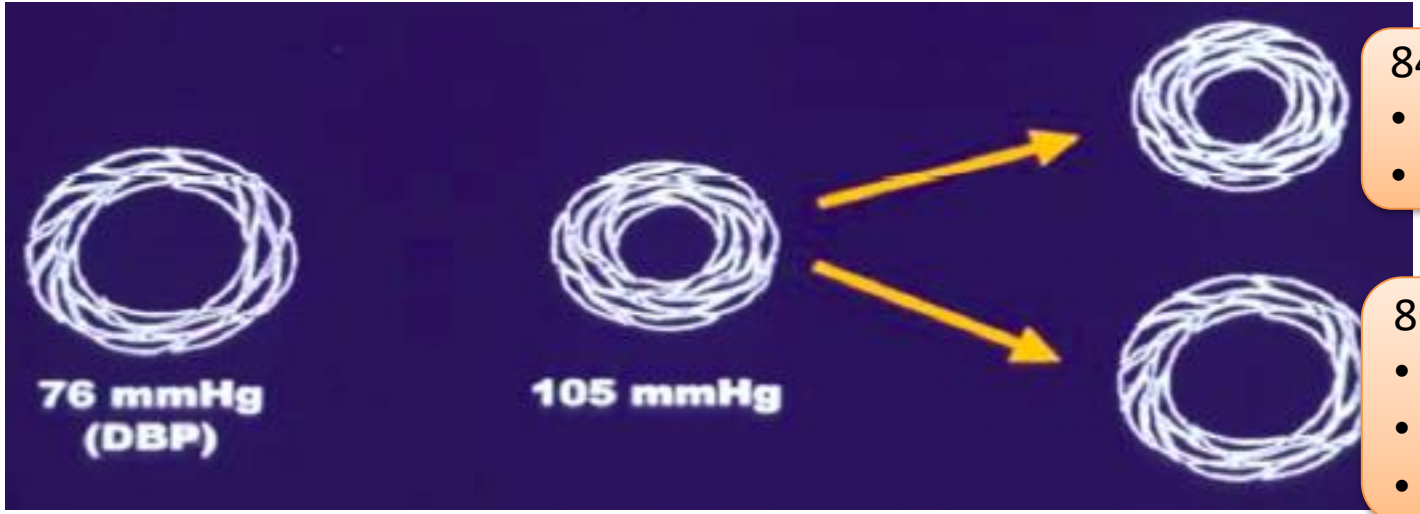
Patient Education and Counseling 2014;97:147-157

New Treatment Approach



Vascular Remodeling

After 1 year of Tx



84 mmHg
- BBs
- Diuretics

86 mmHg
- ACEi
- ARBs
- CCBs

Both groups had SAME BP!

1. Schiffrin et al. Hypertension 1994
2. Am J Hypertens 1995
3. J Hypertens 1996
4. Circulation 2000
5. J. Hypertension 2002
6. Am. J. Hypertens 2002
7. J Hypertension 1996;14:1237
8. Thybo et al. Hypertension 1995
9. J Hypertens 2009;27:1107
10. Am J Hypertens 2006;19:477
11. Am J Hypertens 2010;23:1136

Treatment of HTN based on PRA

Low Renin Hypertension (LRH): Volume Drugs & Nutraceuticals

- Calcium Channel Blockers (CCB)
- Diuretics
- Serum Aldosterone Receptor Antagonists (SARA) like Spironolactone & Epleronone
- alpha blockers

High Renin Hypertension (HRH): RAS or Renin Drugs & Nutracueticals:

- Angiotensin Converting Enzyme Inhibitors (ACEi)
- Angiotensin Receptor Blockers (ARB)
- Direct Renin Inhibitors (DRI)
- Beta Blockers (BB)
- Central Alpha Agonists (CAA)

1. Drugs 1988;35:495-503
2. J Clin Hypertension 2002;4:266
3. Am J Hypertension 2010;23:1014
4. Indian J Physiol Pharmacol 1998;42:205

CCBs, ACEi, & ARBs

- **CCB, ACEi, & ARB'S are preferred initial & maintenance therapy** (mono or combination therapy)
- DHP CCBs are preferred over non-DHP-CCB.
  - **Amlodipine** is the preferred DHP CCB

- ACEi & ARB are not recommended in combination at this time[1] (except for reduction in proteinuria and renal protection)

- ACEi & ARB are equivalent in reducing CV events, interchangeable[1]

- Higher doses of ACEi or ARB are recommended to control BP & reduce TOD (effects independent of BP reduction)

- ACEi better than ARB for CCB-induced edema.

1. N Engl J Med 2008; 358:1547-1559

Beta Blockers

- 1st & 2nd gen BBs are NOT recommended as 1st or 2nd line therapy
  - (propranolol, metoprolol, atenolol, etc)
  - Still recommended: CHF, post MI & CABG, cardiac arrhythmias.
- Carvedilol & Nebivolol (preferred BBs for HTN)
  - ↓ central arterial pressure (CBP), ↓ augmentation index (AI), & augmentation pressure (AP).
  - Favorable effects: glucose, IR, & lipids
  - Improve ED, ↓ SVR, & improve CO
  - Nebivolol ↑'s NO
  - Carvedilol is an antioxidant.
- Older BBs ↑ (or do not change) CBP, AI, AP, arterial stiffness, PWV, or wave reflections

1. J of Clinical Hypertension 2011;13(12): 917
2. Lancet 2005;366:895 (CAFÉ trial)
3. Circ Cardiovasc Genet 2014;7:199
4. Am Heart J 2014;167:421

Effects of Anti-HTN Treatment

20 hypertensive patients were treated for 6 months with:

1. Lercandipine (CCB) & enalapril
2. Lercandipine & HCTZ

Retinal artery wall-to-lumen ratio were measured using scanning laser doppler flowmetry, capillary density by capillaroscopy, PWV and CBP by Sphygmocor

Lercandipine & enalapril (combined) and lercandipine (alone) improved all parameters measured, but the combination was the best

Lercandipine & HCTZ did NOT improve any of the parameters

1. J of Hypertension 2014;32:565-74

Never Use HCTZ![3]

- First line therapy according to JNC VII & VIII
- Based on studies such as ALLHAT – didn't use HCTZ (chlorthalidone)[1]
  - Chlorthalidone & Indapamide more effective & safer
- "HCTZ is an inappropriate first-line drug for the treatment of hypertension"[2]
- **"there has been no evidence that HCTZ reduces MI, stroke, or death."[2]**
- HCTZ Removes the "Good Effects" of some medications (remodeling)
- Decreases K^+ & Mg^{++}
- ↑'s risk of DM (25%), ↑'s Uric Acid, ↑'s risk of CKD & renal cell cancer
- Spironolactone, Indapamide, Eplerenone, & Chlorthalidone are all superior to HCTZ

- **Conclusion**: no significant benefit, numerous negative effects & risks, other drugs work better

1. JAMA. 2002;288:2981-97
2. J Am Coll Cardiol. 2011;57:590-600
3. https://www.RevolutionHealth.org/never-take-hydrochlorothiazide-hctz

Summary

- HTN is a vasculopathy with “3 Finite Responses”
- Evaluate with
  - proper BP measurement
  - 24-hour ABPM
  - CBP
  - CAPWA
  - Labs
  - Genetics
- Initiate DASH-II/TMD diet, low Na^{+}, high K^{+} & Mg^{++}
- Exercise program (resistance training & interval aerobics)
- Nutritional Supplements (topic for another day)
- Appropriate medications based on evaluation

Questions??

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