



Hypertension

Not so essential after all

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Disclosures

Disclosure of financial relationships: NONE

Off-label usage: NONE



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 Worldwide¹

CVD has been the #1 COD since 1920

- 2200 deaths EVERY DAY from CVD & CVA²
- Equivalent to four 747's 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 decreased 3.7% per year
- Stroke mortality decreased 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 productivity²
- 2014 - stroke and heart failure were the most expensive chronic conditions in the Medicare fee-for-service program¹
- CVD **Expenses are expected to “soar”** in the coming years¹
- 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 Worldwide¹

We WERE getting better, but...

- Burden of CVD is now growing faster than our ability to combat it
- 2015 - death rate from CHD increased by 1% for the first time since 1969
- 41.5% prevalence in 2015 which was not predicted to occur until 2030² (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



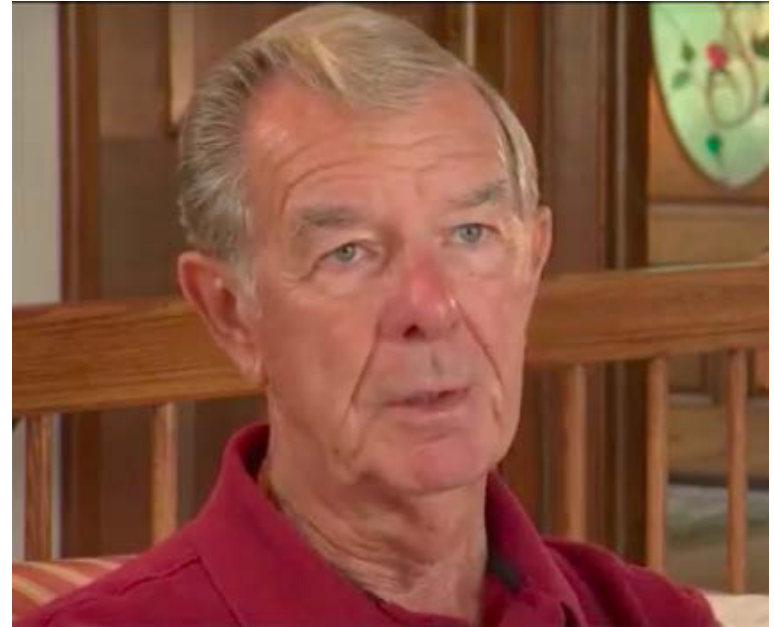
CARDIOVASCULAR DISEASE: A COSTLY BURDEN FOR AMERICA

PROJECTIONS THROUGH 2035

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



Top 5 Risk Factors

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

Hypertension, CVD, and CKD

Hypertension is number one cause of CVD in the US

Hypertension is one of the leading causes of CKD in the US

CVD is the #1 cause of death in the US: 36% of all deaths. CHD, CVA, CHF

Cost of CVD was over \$475 Billion dollars in 2009 and over \$800 billion in 2020.

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

Hypertension is NOT a disease!

Hypertension is not a disease but is a marker for endothelial and vascular dysfunction.

Hypertension is a “correct” but chronic dysregulated response with an exaggerated outcome of the infinite insults to the blood vessel with the subsequent environmental gene expression patterns.

Vascular system is the innocent bystander.

How do we fix this?

Modulate the environmental insults, finite responses, and downstream disturbances of gene expression patterns. This is the key to the prevention and treatment of hypertension and cardiovascular disease.

HTN is a Vasculopathy

It is characterized by:

1. Increased oxidative stress in the vasculature
2. Vascular inflammation
3. Vascular autoimmune dysfunction
4. Abnormal vascular biology with:
 1. Endothelial Glycocalyx dysfunction
 2. Endothelial dysfunction
 3. Vascular smooth muscle dysfunction (VSMD)
5. Structural remodeling
6. Increased arterial stiffness

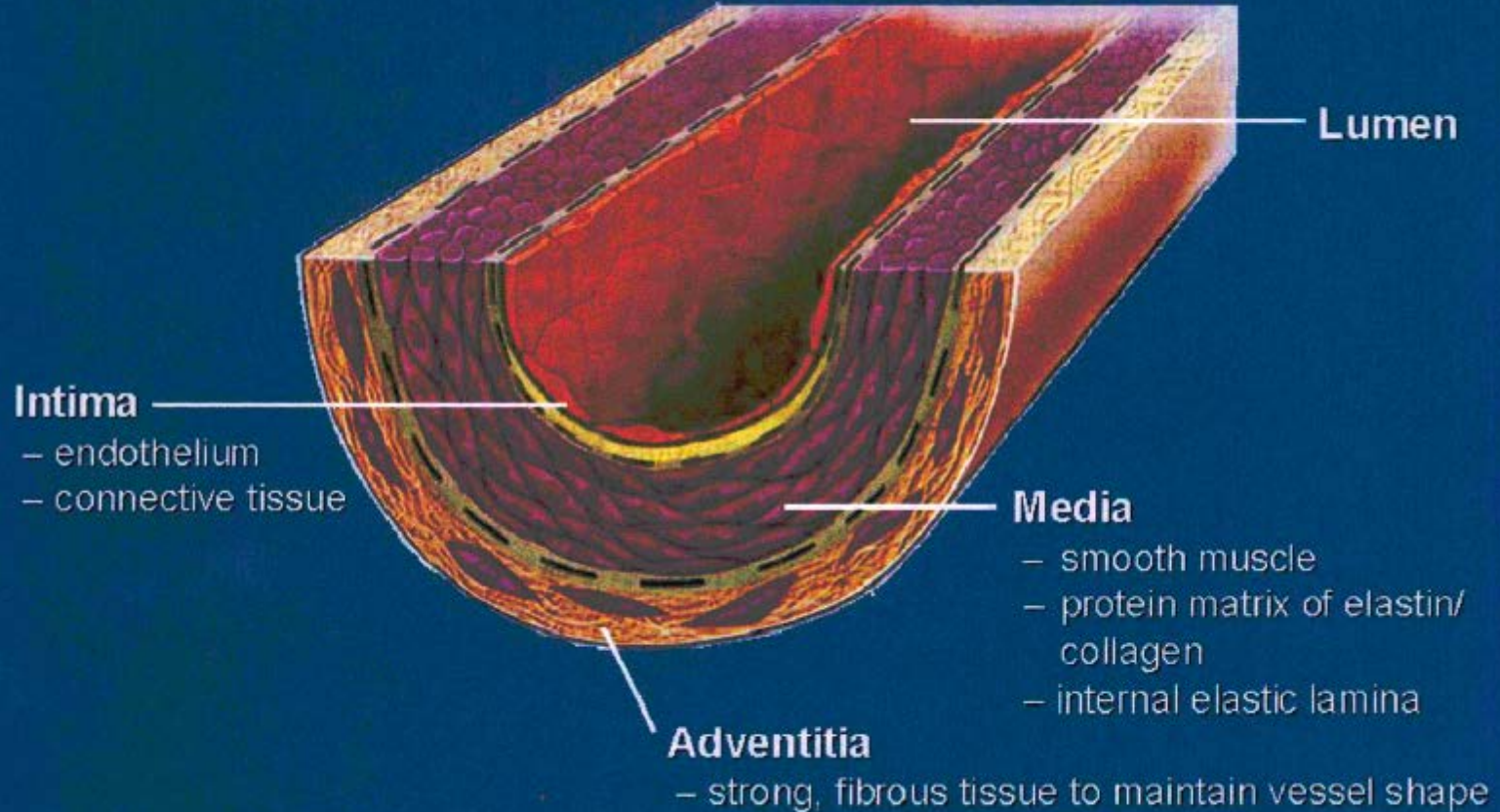
Initially these processes are adaptive to the increased BP, but then become maladaptive leading to a bi-directional contributing factors. Endothelial dysfunction and vascular smooth muscle dysfunction **precede the development of hypertension by decades.**

1. Curr Opin Nephrol and Hypertension 2012;21:119-121

2. J of Hypertension 2012;30:2440

Vascular Biology

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.

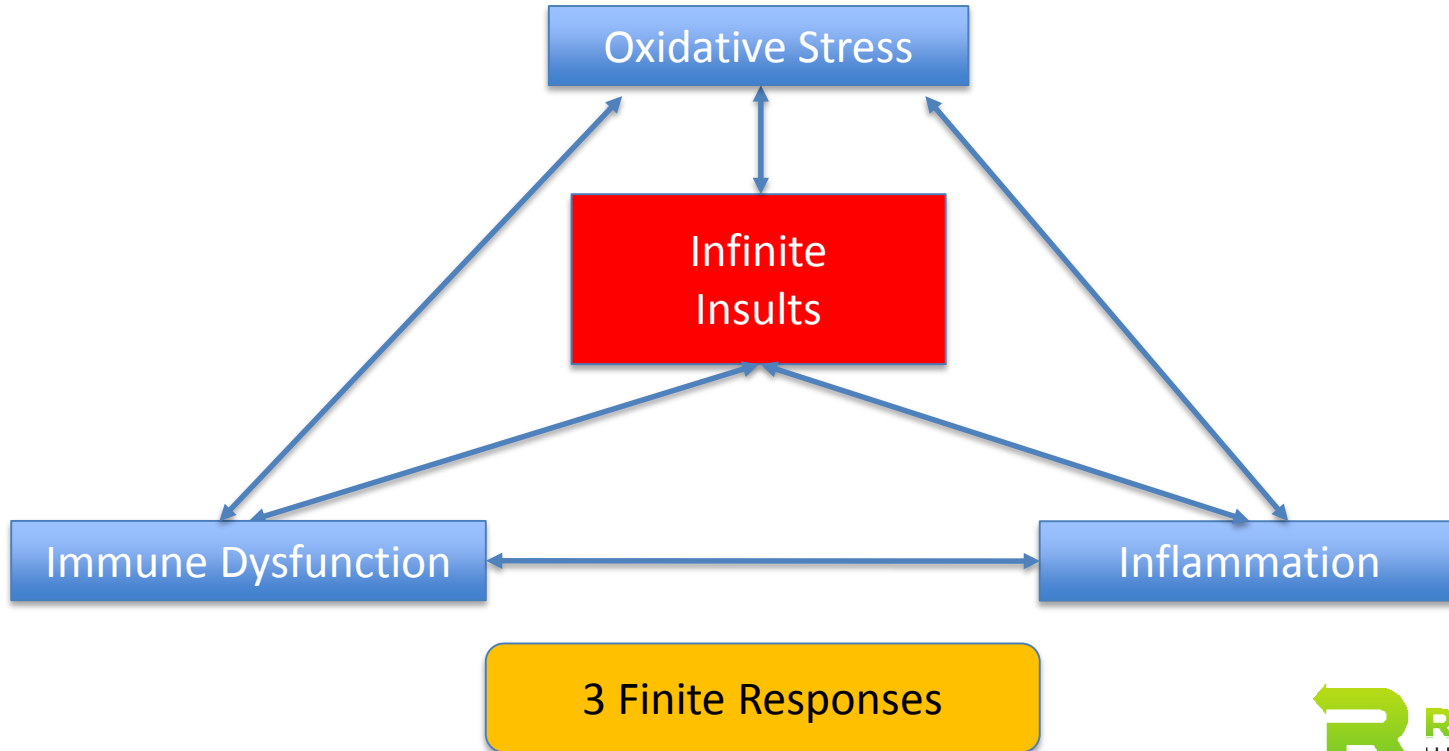
Your vessels are under attack!



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: \uparrow 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

Infinite Insults



Vascular Disease is a Balance

Vascular Injury

Nitric oxide vs
angiotensin II
endothelin and
aldosterone

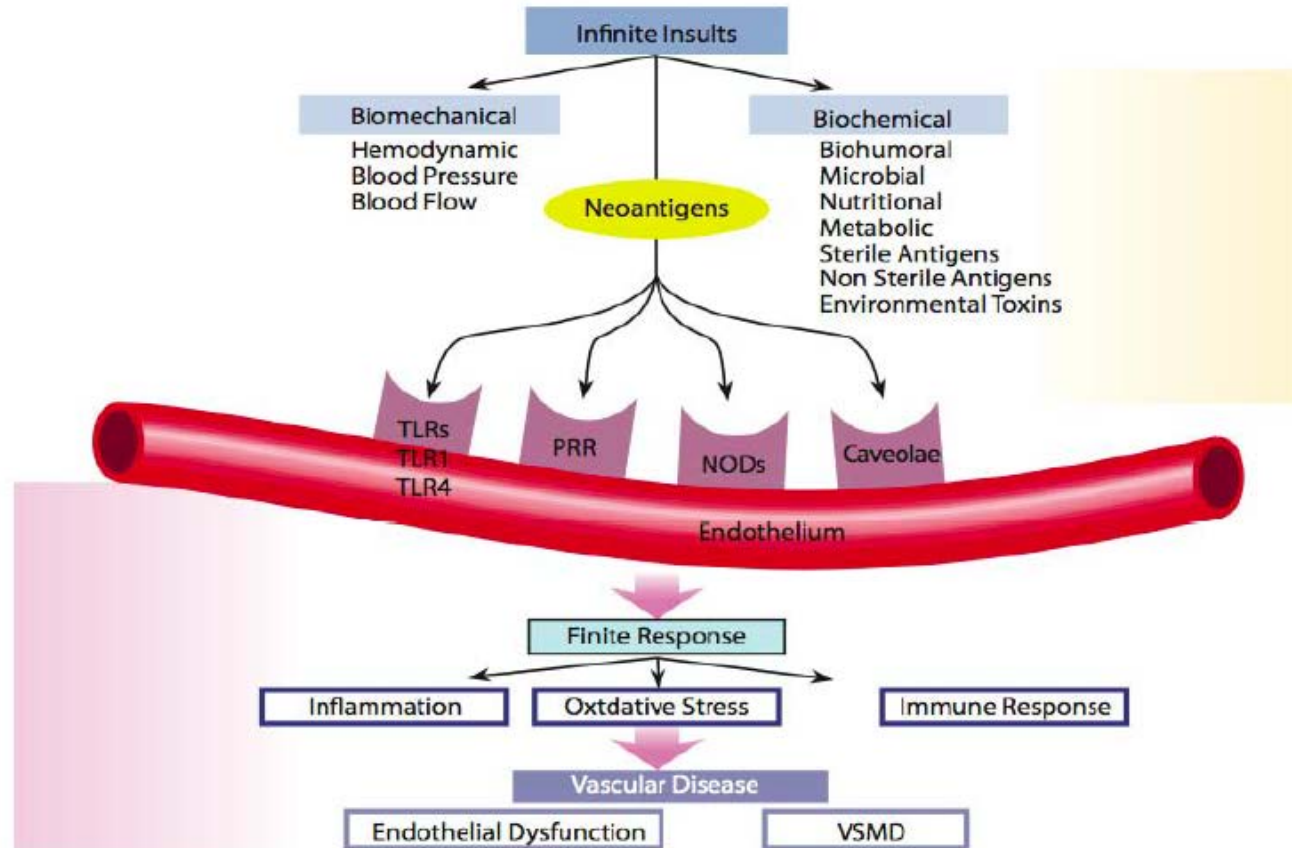
VS

Vascular Repair

Endothelial
Progenitor Cells
(EPC's)



Infinite Insults



Endothelium

The endothelium serves a critical role as a barrier and primary sensor of physiological and chemical changes in the blood stream.

It is the “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, initial and earliest event in vascular disease. Present with only risk factors but no atherosclerosis.

It is the loss of Nitric Oxide

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

Endothelial Dysfunction Predicts CVD

Endothelial dysfunction is a **very accurate predictor of future cardiovascular events** (CVD) and 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.

Endothelial Dysfunction Measurement

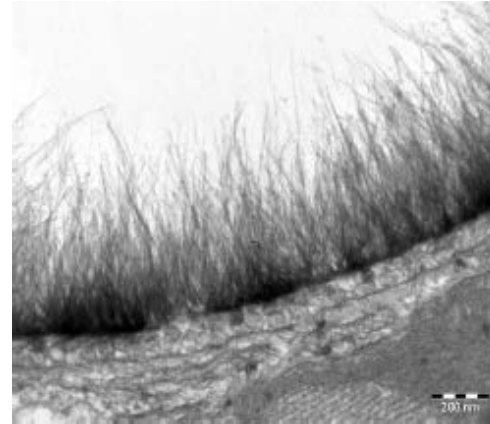
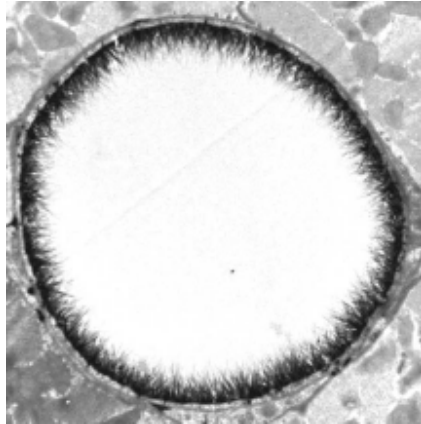
- EndoPAT, Endothelix
- Measures reactive hyperemia and endothelial dysfunction
- FDA approved
- About \$25,000
- 5 minute occlusion of brachial artery with BP cuff
- Digital measurement for ED-FMD as increase in signal amplitude
- Measure pre and post occlusion ratio index
- Index of 1.67 (EndoPAT) has sensitivity of 82% and 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

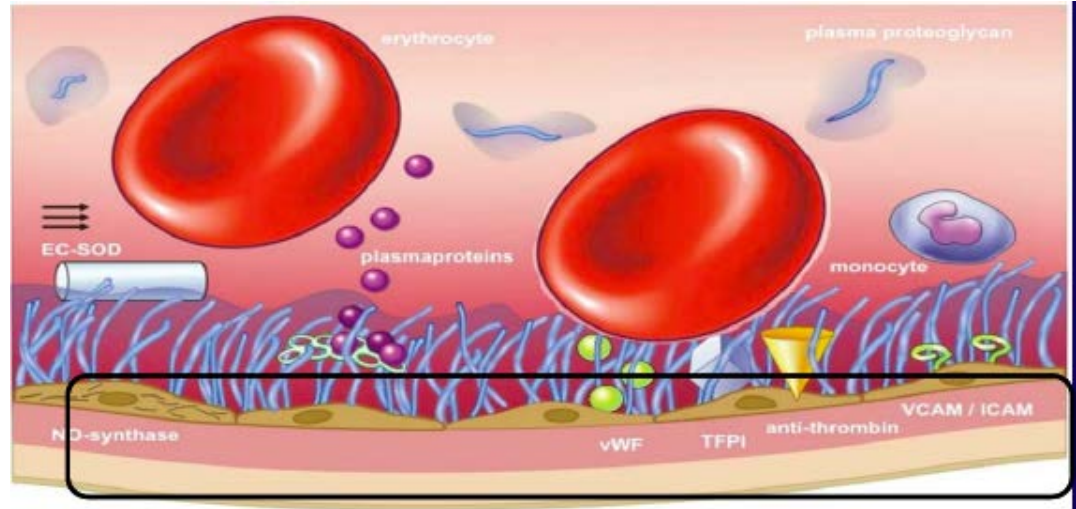
The Endothelium's "First Line of Defense"

The endothelial glycocalyx ("sugar coating") is a microscopically thin gel-like layer that coats the entire luminal side of the vascular endothelium and provides a nonadherent shield.



Functions of a Healthy Glycocalyx

- Triggers shear induced nitric oxide, decreases ED and decreases BP and ASCVD
- Shear stress sensors
- Houses extra-cellular superoxide dismutase (ec-SOD)
- Acts as sieving barrier (LDL, etc.)
- 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

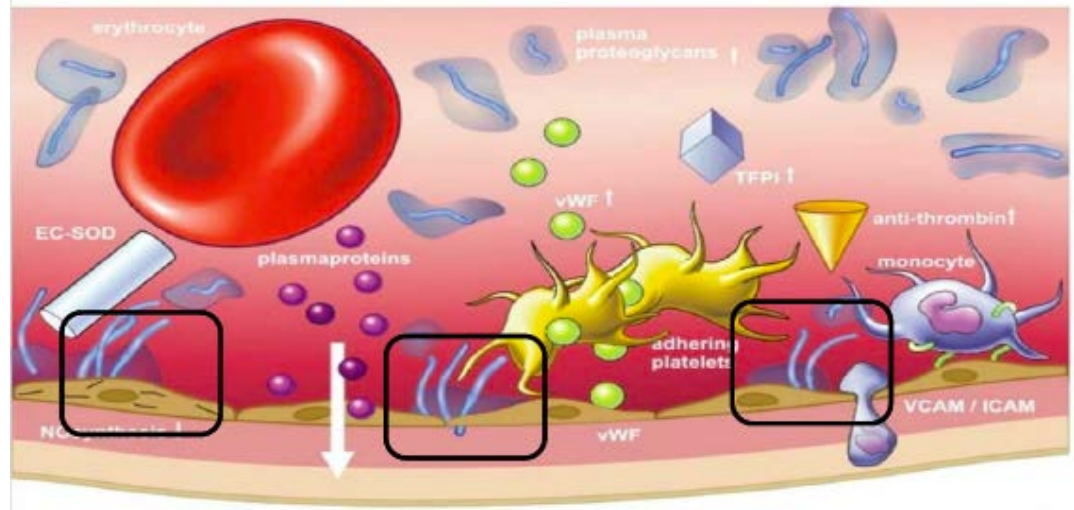


- Mediation of fibroblastic growth factor (FGF), AT-III, heparin cofactor, thrombomodulin, tissue factor inhibitor (TFI)
- Inhibits inflammation, oxidative stress, and vascular immune dysfunction
- Forms an interface between the blood and the endothelium
- Regulator of mechanotransduction

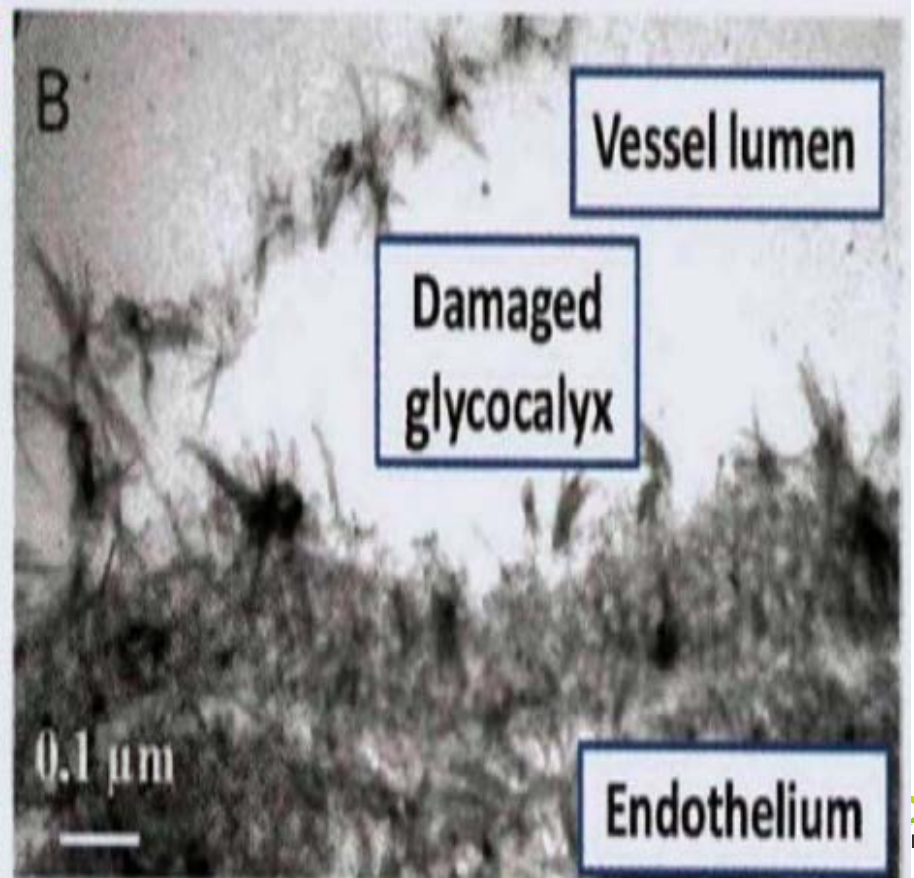
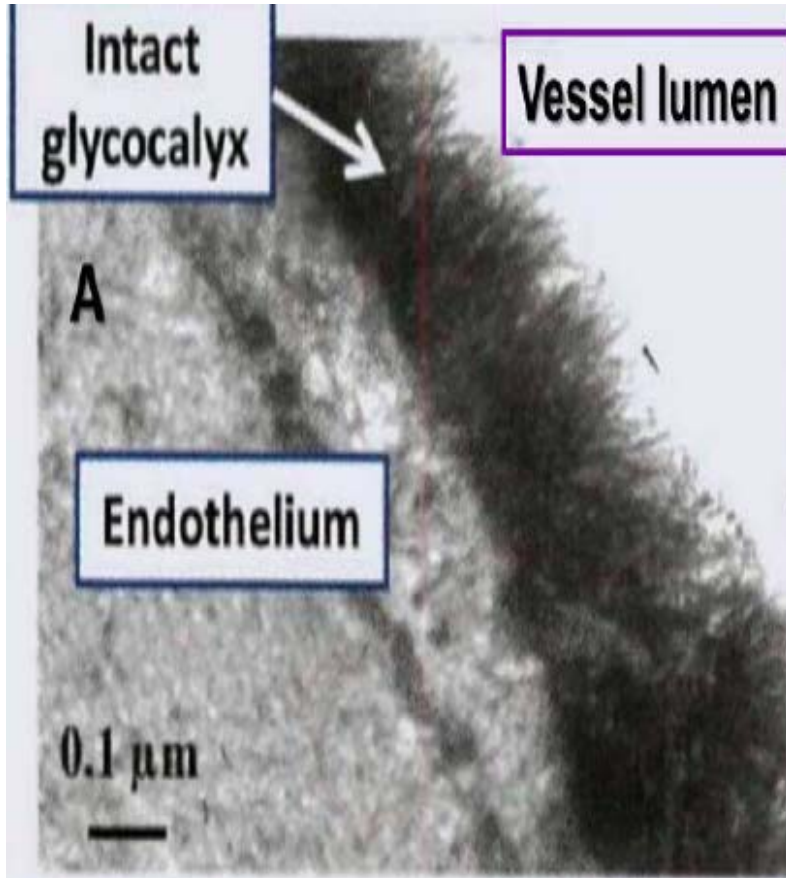
Compromised Endothelial Glycocalyx

Damage to the EGC precedes damage to the endothelium

- Reduced NO production
- Increased oxidative stress
- Increased macromolecule leakage
- DM complications
- Ischemia-reperfusion injury
- Increased platelet adherence
- Increased thrombin generation
- Increased 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

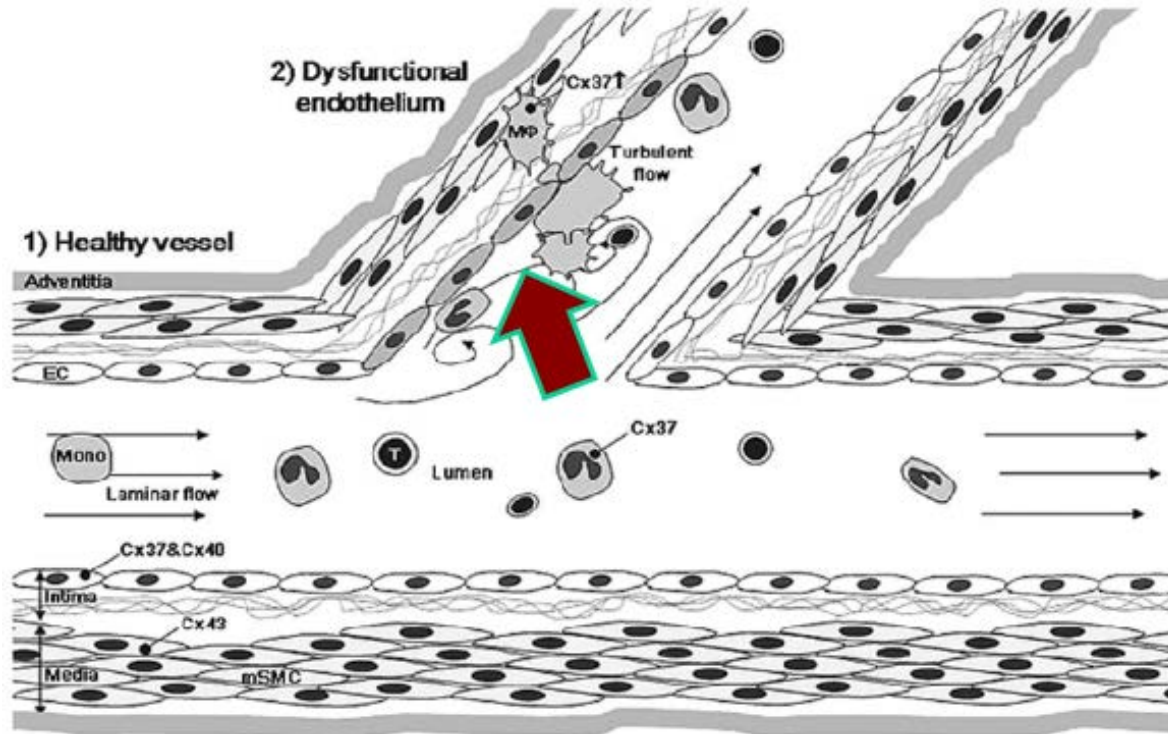
Spatial Variation of EGC Thickness



The glycocalyx dimension is significantly decreased at atheroprone locations such as branches, bifurcation, and curvatures.

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

High Risk of Plaque at Bifurcations



The EGC as Focus for CVD Intervention

Endothelial dysfunction is the starting point of CVD

Endothelial glycocalyx is the primary protector of the endothelium

Endothelial glycocalyx has multiple additional functions essential to cardiovascular health

Maintaining a healthy endothelial glycocalyx may be one of most important intervention targets for prevention of CVD

Strategies to Regenerate the EGC

- Hydrocortisone
- Calcium channel blockers
- Glycemic control: Metformin, Sulodexide
- Sulodexide (Vessel) is a highly purified mixture of glycosaminoglycans composed of low molecular weight heparin (80%) & dermatan sulfate (20%)
- Statins
- Reduction of inflammatory mediators: hydrocortisone, anti-TNF
- Antagonizing enzyme-mediated glyocalyx injury: doxycycline
- Glycocalyx regenerating compounds (GRCs): hyaluronan, antithrombin III, heparin, sulodexide, **special sulfated polysaccharides (SSP)**, and protein C
- Nitric oxide
- NAC (N acetyl cysteine)

Artery Elasticity

- Buffering the forward propagation flow from heart and the pulse wave velocity (PWV)
- Backward resistance from peripheral arteries
- Hemodynamic cushioning and aortic buffering effect.
- Compression - "accordion" effect to maintain diastolic blood pressure.
- Maximize cardiovascular efficiency
- Arterial stiffness is a marker for cardiovascular disease and events

Arterial Compliance - Overview

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

Endothelial dysfunction is the earliest marker of these changes **followed by arterial stiffness** and loss of small and medium and large arterial compliance.

Pharmacological Tx of HTN has reduced CVA to predicted levels
BUT... CHD reduction has been sub-optimal.

This “**CHD GAP**” may be 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 - Anatomy

Artery Structure Determines Vascular Stiffness/Compliance

- 1) Intima: Glycocalyx
Endothelium
Sub-endothelium
- 2) Media: Elastic SM fibers
Protein matrix: elastin + collagen
Internal elastic membrane
- 3) Adventitia: Fibrous tissue (strong vessel shape large arteries)

Arterial Compliance – Artery Types

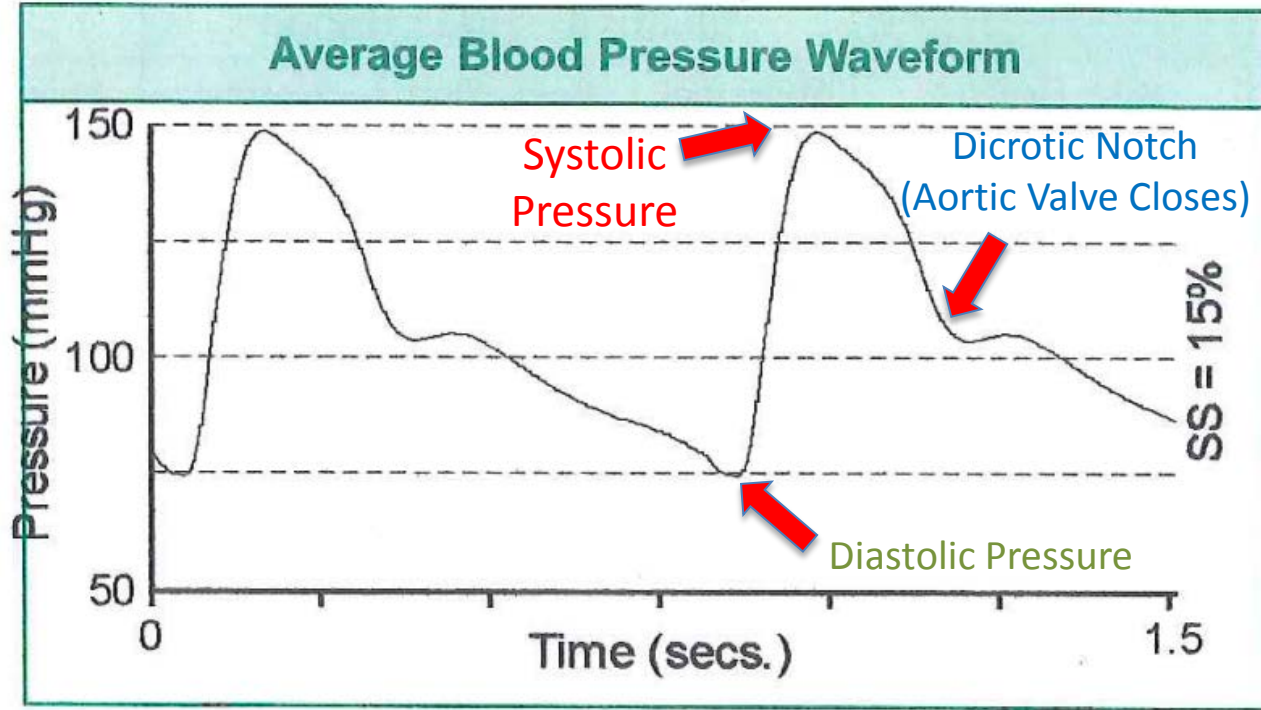
- Conduit (Capacitive): C1 (store blood in systole) (buffer) (thin endothelium with thick elastin and collagen), less VSM
- Branch (Oscillatory): C2 (pressure oscillations/reflected waves) (intermediate structure)
- Arterioles (Resistance): C2 (control blood flow), VSM + endothelium primarily with minimal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

The role of the endothelium is greatest in thin wall vessels – (oscillatory and resistance). ED earlier and greatest in C-2 vessels.

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
- Converts pulsatile flow in aorta to continuous flow in capillaries (Windkessel effect)
- Loss of buffering with ↓ arterial compliance (AC) causes reduced continuous flow but increased pulsatile flow to precapillary and capillary vasculature inducing small vessel damage, end organ dysfunction and damage (↑ pulse wave velocity - PWV)
- Out of phase propagation of flow and pressure waves.
 - Pressure wave faster and distorted
 - Reflected wave
 - Augmentation index (systole)
 - Augmented central systolic blood pressure

Blood Pressure Waveform



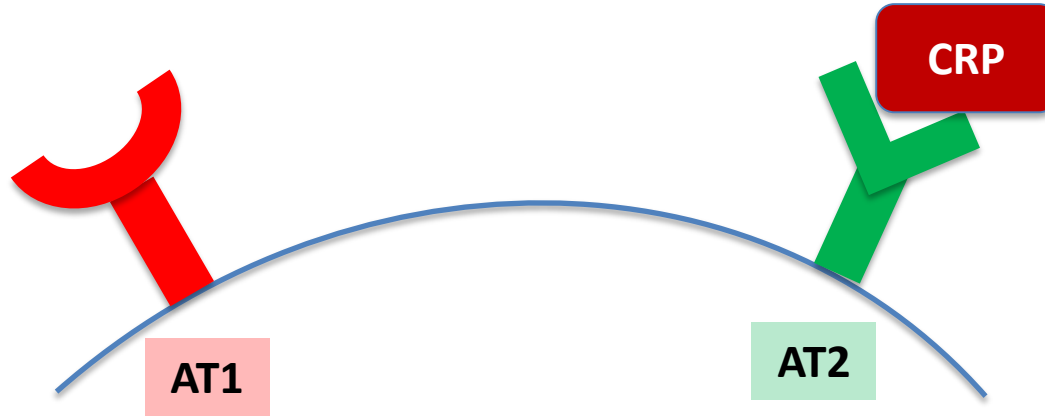
Vascular Remodeling

Small resistance and pre-capillary arteries that are $< 100 \mu\text{m}$ in size, maintain wall tensile stress by eutrophic remodeling inward without a growth processes

Due to the greatest myogenic response and constriction that decreases the lumen size.

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

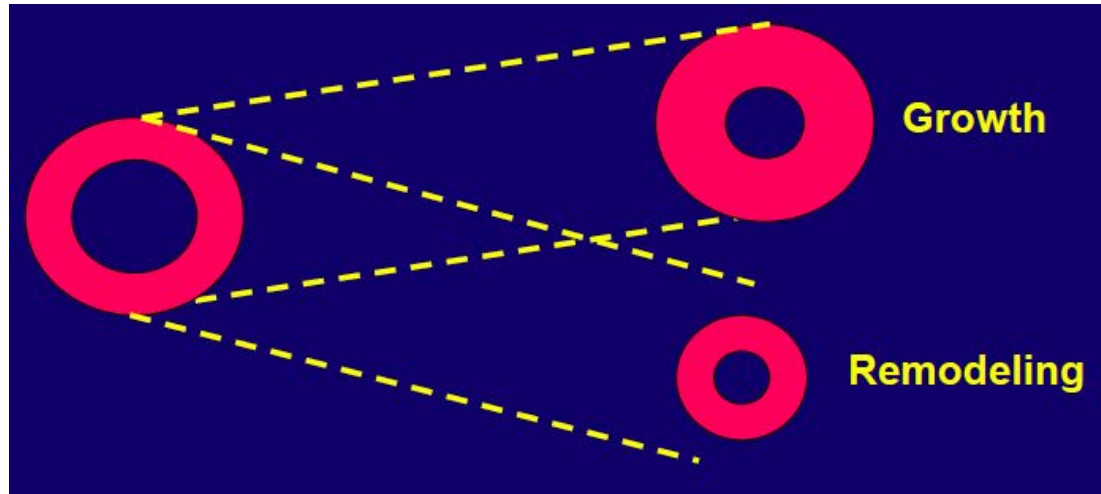
- Nitric Oxide



- Vasoconstriction
- Na⁺ & H₂O Retention
- Growth Stimulation
- Disease Progression
- Increased oxidation

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

Vascular Remodeling



Hypertrophic Remodeling:

Increased Media Lumen Ratio (MLR). Typical with HLD, DM, CKD, & other 2° 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 in the form of inward eutrophic remodeling of the small resistance arteries leading to impaired vasodilatory capacity, ↑ vascular resistance, ↑ MLR, ↓'d maximal organ perfusion and ↓ flow reserve. In the heart this is CFR (coronary flow reserve).

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

Microvascular Impairment Precedes the Development of HTN

- **Significant functional then structural microvascular impairment occurs even before the blood pressure begins to rise** in normotensive offspring of hypertensive parents
- Endothelial dysfunction, diastolic dysfunction impaired vasodilation, increased forearm vascular resistance, increased septal and posterior wall thickness, LVMI and LVH may also occur early in these offspring but is a later development related more to large arterial impairment.

1. J of Hypertension 2011;29:896-905
2. J Hypertension 1995;13:259

Blood Pressure Evaluation

Blood Pressure Evaluation

Standard Blood Pressure measurements are not adequate, are often misleading, & may not accurately reflect CV risk.

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)

BP Cuff

- Arm circumference measured $\frac{1}{2}$ way between olecranon and 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)

A patient is lying in a hospital bed, partially covered by a white sheet. The patient's back and right arm are visible, showing several tattoos, including a large scorpion on the upper back and a detailed sleeve tattoo on the right arm. Several circular medical sensors are attached to the patient's back. A red arrow points to a green strap on the patient's right arm, which is identified as a blood pressure cuff in the accompanying text. The patient is wearing a patterned hospital gown. The background shows a typical hospital room with a white cabinet and medical equipment.

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 = $\geq 140/\geq 90$

White Coat Hypertension

Untreated subjects with elevated office BP $\geq 140/90$ 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 \geq 130/80 mmHg AND
- Awake ABPM \geq 135/85 AND
- Sleep \geq 120/70 mmHg OR
- Home BP \geq 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 & occurs in about 70% of hypertensive patients

Associated with more TOD independent of dipping/non-dipping status.

Total mortality increases 29% & all CV events increase by 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

Standard BP Evaluation is NOT Sufficient

- Standard BP measurements are not adequate and often misleading and may not accurately reflect CV risk.
- Need indirect arterial measurements & CV function and structure testing with noninvasive technology.
- Measure endothelial dysfunction, Augmentation Index (AI) and heart rate variability (HRV).
- 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 , central BP & PWV.
- Central arterial pressure, pulse pressure, augmentation index, MAP & central to peripheral pressure amplification.
- Plethysmography for type of CV curve parameters, SNS, PNS, mental and physical stress.
- Home BP
- Improved techniques for in office BP measurements.

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:

- 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

24-Hour ABPM HTN Definitions

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

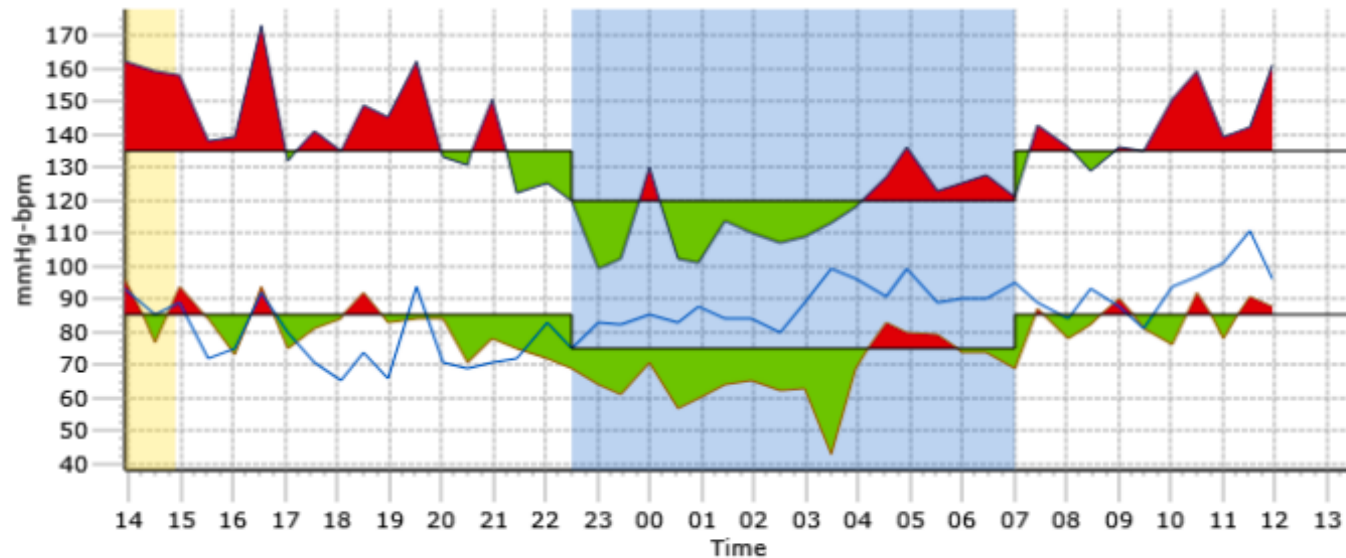
- Dipper: 10-20% is normal
- Non-Dipper: $<10\%$
- Excessive Dipper: $>20\%$

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).

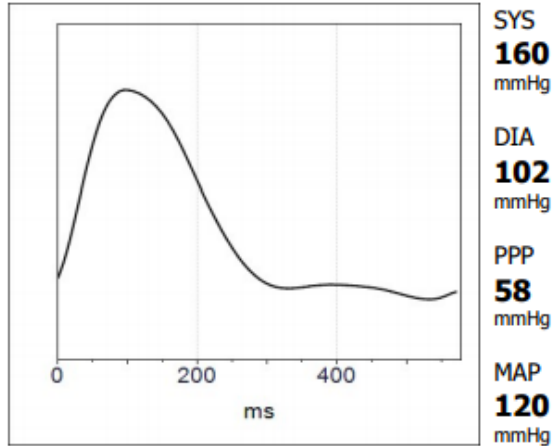


Central Blood Pressure (SphygmoCor)

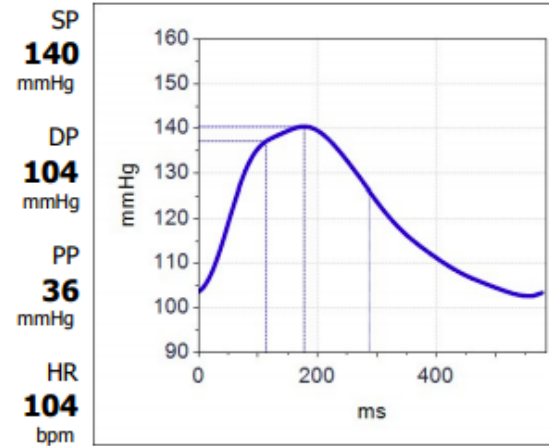
- Ascending aortic BP
- More predictive of CVD mortality, all cause mortality, diastolic dysfunction, and LVH than brachial BP
- Better than brachial BP measurement
 - CBP indicates pressure exerted on heart & brain
 - CAFÉ study indicated that CVD outcome related better to CBP than brachial pressure.
 - CBP ↓'d with CCBs, ACEi, ARBs, and alpha-blockers
 - CBP ↑'d by non-vasodilating BBs and diuretics

Central Blood Pressure (SphygmoCor)

Average Peripheral Pulse



Average Aortic Pressure Pulse



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**

Pulse Wave Analysis (CAPWA)

Computerized Arterial Pulse Waveform Analysis (CAPWA)

- Synthesize central pressure waveform from the brachial or radial waveform
- Central hemodynamics improves diagnosis, 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 & blood pressure (increased central & peripheral pulse pressure after age 50)
- PWV is independent risk factor for cardiovascular disease and hypertension, CVA, CHD, MI, CKD.

Pulse Wave Analysis (CAPWA)

CVProfile™ Report



ID#: 0009

Profile by: CHAD EDWARDS
REVOLUTION
9189353636

Name:

SSN:

Date: Dec 19, 2019

Time: 15:16

Age: 47 years

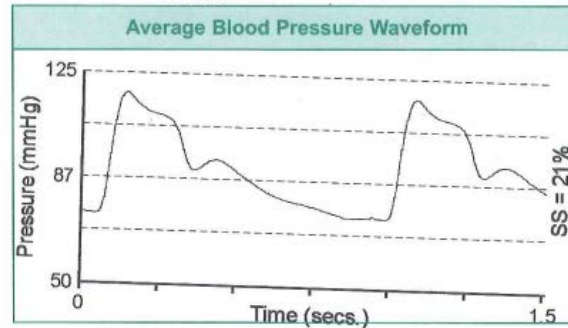
Gender: Male

Height: 5 ft 6 in

Weight: 170 lbs

BSA Area: 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

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		
	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

Plasma Renin Activity (PRA)

High PRA (70% of patients) is associated with increased risk of:

1. MI, ischemic heart disease & all cause CV and total mortality 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. Congestive heart failure
5. Chronic kidney disease
6. Total CVD & mortality and all-cause mortality

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 treated for one month
- Percentage of patients achieving BP control higher in those treated with appropriate drug. 38% vs 29% ($p=0.24$)
- DBP was positively correlated to appropriate drug ($p= 0.02$) as was % reduction ($p=0.04$). The DBP was 3 mmHg lower

Plasma Renin Activity (PRA)

- Random ambulatory serum levels of plasma renin activity (PRA) and serum aldosterone
- Most accurate in drug naïve patients
- Does not require alterations in patient position, time of day, sodium intake etc.
- Levels will be altered by concomitant antihypertensive medications which requires more sophisticated interpretation.

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
 - $\text{PRA} > 0.65$ ng/ml/hr
 - 70% of patients
- Very high Renin: Volume Depleted
 - $\text{PRA} > 6.5$ ng/ml/hr

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
- Inappropriately ↑ serum Aldosterone level that cannot be suppressed with salt loading. Functional derangement in Aldosterone secretion.
- ↓ 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, 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

- 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 (ARR 66 vs 56)(JOH 2012)

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

Treatment of HTN based on PRA

Low Renin Hypertension (LRH): Volume Drugs and Nutraceuticals

- Calcium Channel Blockers (CCB)
- Diuretics
- Serum Aldosterone receptor antagonists like Spironolactone and Eplerenone (SARA),
- alpha blockers

High Renin Hypertension (HRH): RAS or Renin Drugs and Nutraceuticals:

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

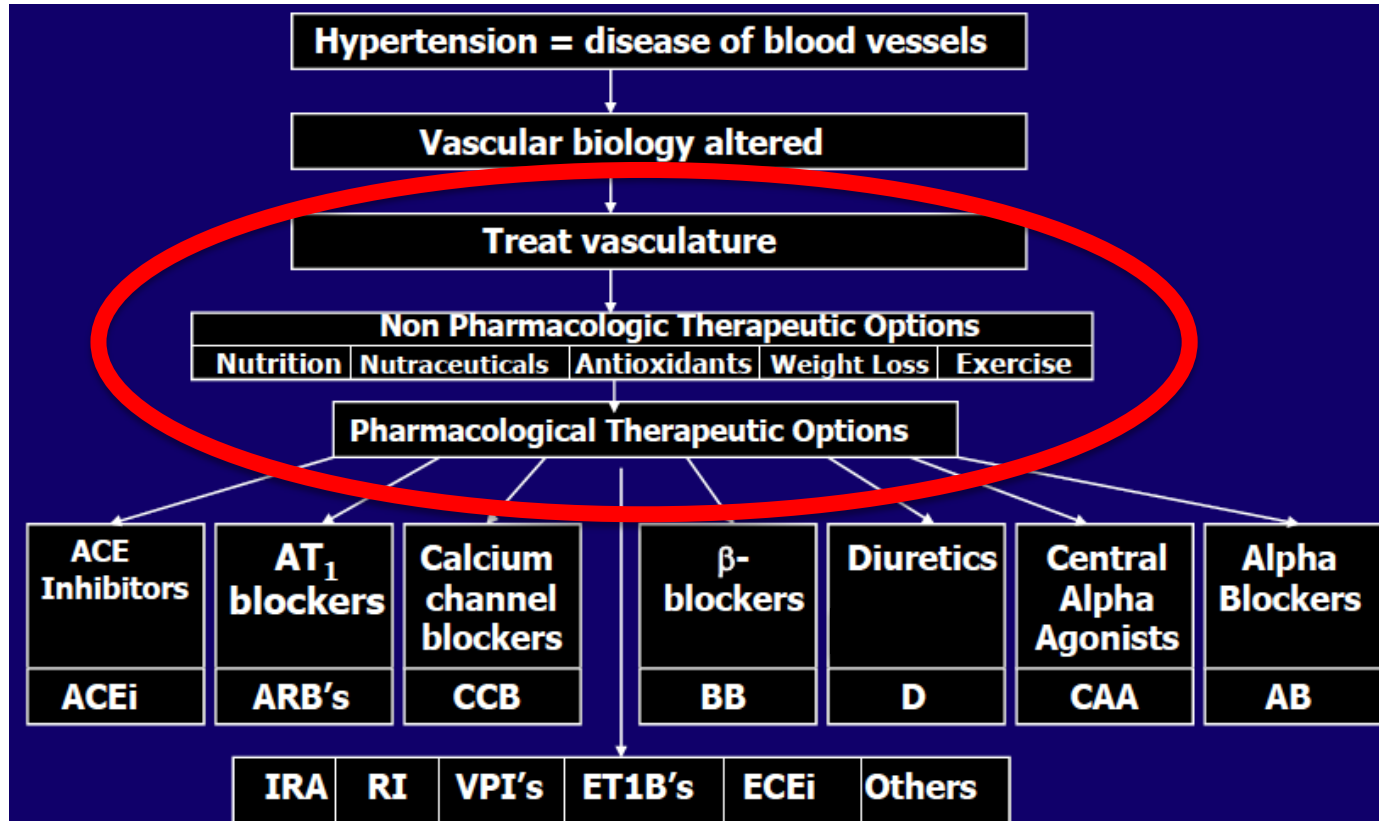
1. Drugs 1988;35:495-503
2. J Clin Hypertension 2002;4:266
3. Am J Hypertension 2010;23:1014
4. Indian J Physiol Pharmacol 1998;42:205

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, catecholamines.
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

New Treatment Approach



Step 1: To Treat or Not To Treat?

Criteria to decide hypertension treatment

- Level of blood pressure
- Presence of other CHD risk factors
- Calculation of CHD risk with COSHEC or Rasmussen CVD risk scoring system that indicates high risk.
- Presence of CVD target organ damage (TOD)
- Presence of other preclinical tests for vascular damage such as EndoPAT, CAPWA, central BP, augmentation index, ECHO, CPET, plethysmography, CAC, PULS etc.
- Presence of clinical symptoms related to BP such as headache, chest pain at rest or with exercise, dyspnea etc.

Step 2: Exclude 2° Causes

1. OSA
2. Renal vascular hypertension with renal artery stenosis:
atherosclerotic and fibromuscular dysplasia
3. CKD
4. Pheochromocytoma
5. Hyperaldosteronism
6. Cushings
7. Hyperparathyroidism
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 2° 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

Hypertension Management

- Interrupt the process causing the vasculopathy
- Measure PRA/Aldosterone
- Nutrient Depletion Evaluation
- Demographics
- 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.

Weight Loss

One of the most effective means to reduce BP - observational and clinical trials show positive direct relationship

- Weight loss ↓'s cardiovascular events¹
- 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 and reduces CHD risk, reduces inflammation, CRP, IL-6, VCAM & fibrinogen.

- Fit patients have lower prevalence of hypertension
- Need combination of aerobic and resistance training
- 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 one 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

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

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

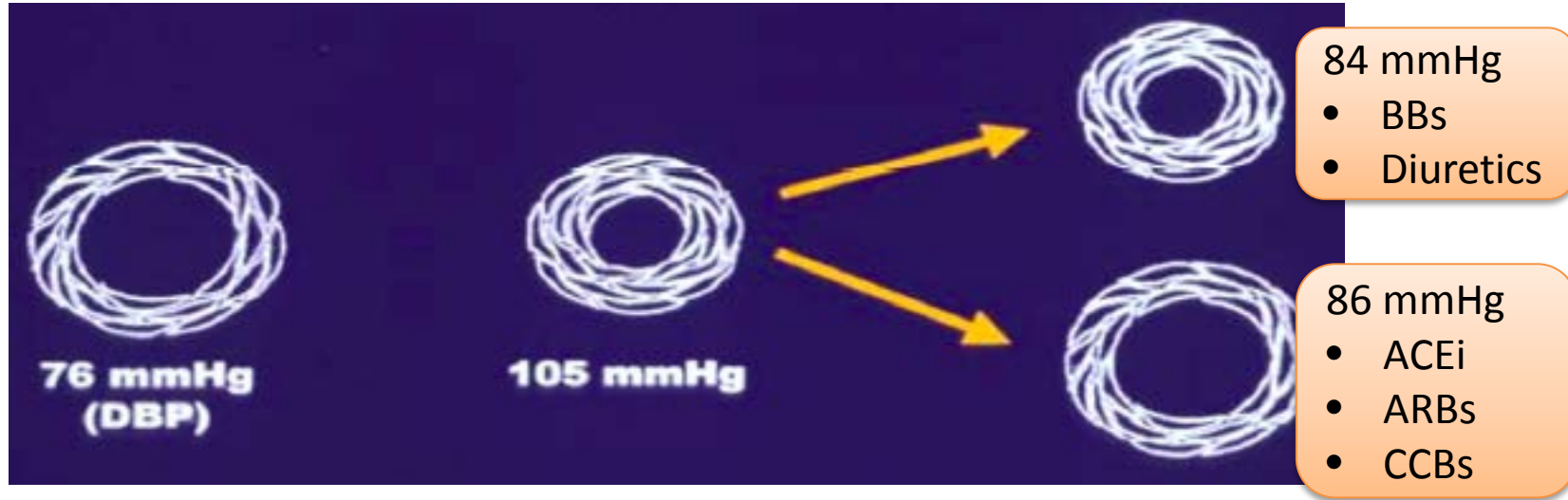
DASH (combination) diet

Lower BP at every Na⁺ level

↓ **DBP 11.5 mmHg** in the low Na⁺ hypertension group

Vascular Remodeling

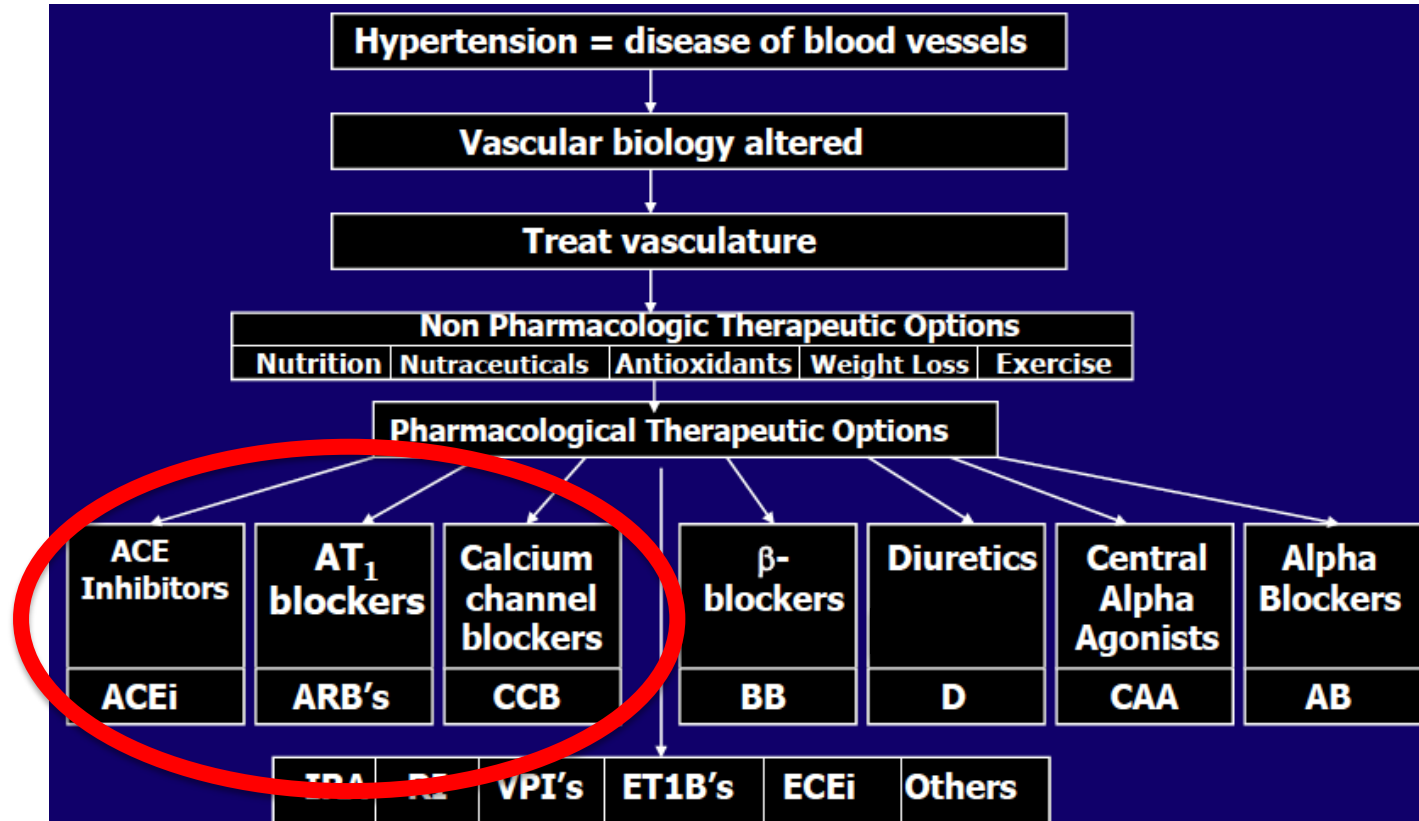
After 1 year of Tx



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

New Treatment Approach



Beta Blockers

- 1st & 2nd gen non-vasodilating BBs (propranolol, metoprolol, atenolol, etc) are NOT recommended for Tx of uncomplicated HTN as 1st or 2nd line therapy
- Older BBs are still recommend for CHF, post MI and CABG, cardiac arrhythmias.
- Vasodilating BBs such as **Carvedilol and Nebivolol are preferred BBs for HTN** as back up therapy after ACEI, ARB and DHP-CCB
- Carvedilol and Nebivolol ↓ central arterial pressure (CBP), ↓ augmentation index (AI), & augmentation pressure (AP). They also have favorable metabolic effects on glucose, IR & lipids. Improve ED, ↓ SVR, and improve CO. Nebivolol ↑'s NO. Carvedilol is an antioxidant.
- Older BB increase 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

CCBs, ACEi, & ARBs

- **CCB, ACEi, & ARB'S are preferred initial & maintenance therapy** in most hypertensive patients as monotherapy or in selected combinations– amlodipine with ACEi or ARB
- DHP CCBs are preferred over non-DHP-CCB. **Amlodipine** is the preferred DHP CCB
- ACEi & ARB are not recommended in combination at this time¹ except for reduction in proteinuria and renal protection
- ACEi & ARB are equivalent in reducing CV events and are interchangeable¹
- 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

Effects of Anti-HTN Treatment

20 hypertensive patients were treated for 6 months with:

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

Non invasive measurements of wall-to-lumen ratio were made of the retinal arteries using scanning laser doppler flowmetry, capillary density by capillaroscopy, PWV and Central BP by Sphygmocor

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

Lercandipine and HCTZ did NOT improve any of the parameters

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 associated with the “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??