Module II Cardiology 2018

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New and Revolutionary Concepts in the Pathophysiology, Diagnosis and Treatment of Hypertension: Role of Nutrition, Supplements and Integrative Metabolic Medicine

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MMI CVD MODULE 2 2018

Hypertension

Learning Objectives

1. Review the pathogenesis of hypertension and the role of vascular biology, three finite vascular responses (inflammation, oxidative stress and vascular immune function), plasma renin activity (PRA) and aldosterone to select optimal integrative anti-hypertensive therapy to reduce BP and decrease CVD.
2. Review diagnostic testing for hypertension: 24 hour ambulatory BP (ABM), endothelial function and arterial compliance testing.
3. Identify and personalize the most important nutritional, nutraceutical supplements and life style treatments for hypertension.
4. Specify micronutrient testing in the treatment of hypertension.
5. List the most important cardiovascular drug-nutrient interactions
6. Review briefly the optimal drug therapy for hypertension and combination use with nutraceutical supplements.

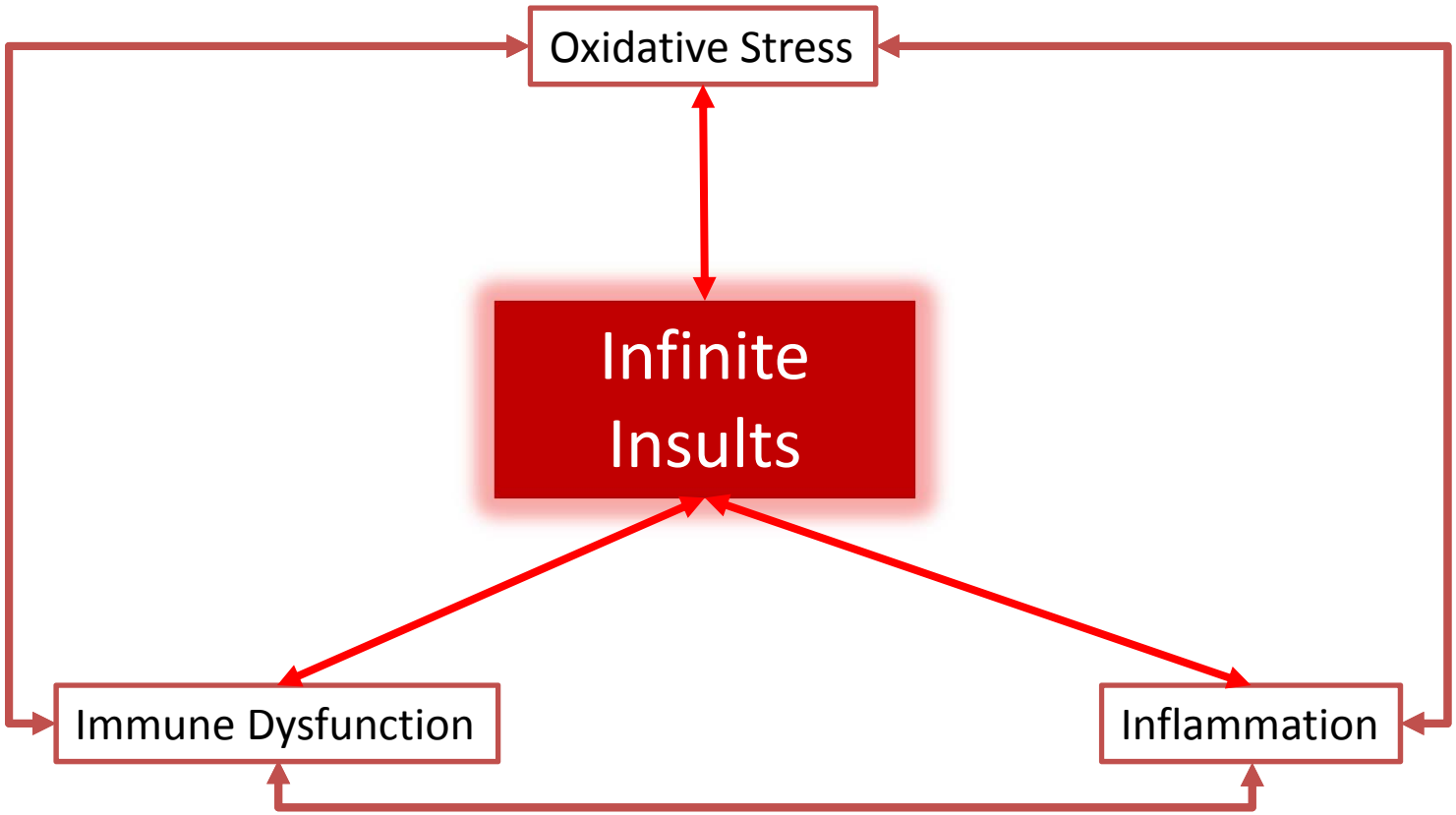
"The blood vessel has a finite number of responses to an infinite number of insults."

The three finite responses are:

- Inflammation
- Oxidative stress
- Vascular immune dysfunction

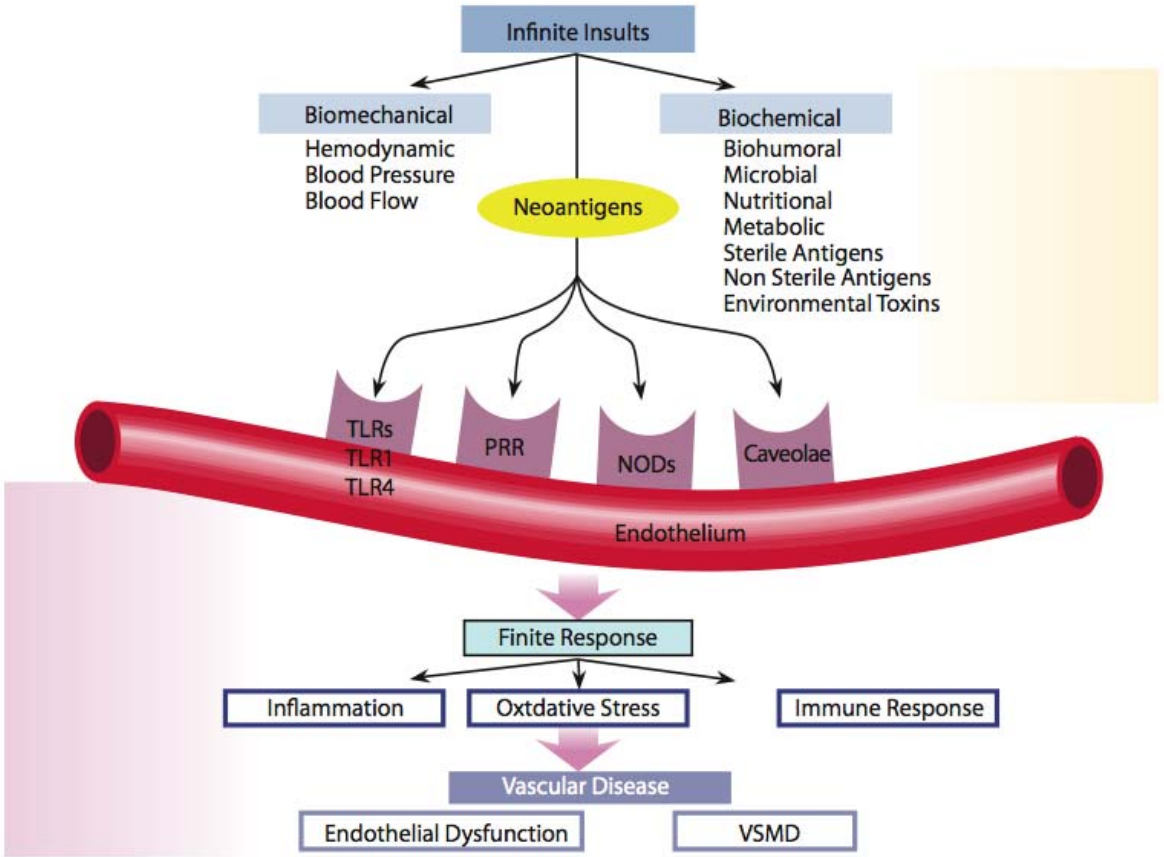
Mark Houston MD, MS, MSc 2000
He, Feng. Int J Mol Sci 2015;16:1-12

Mechanism Of Model

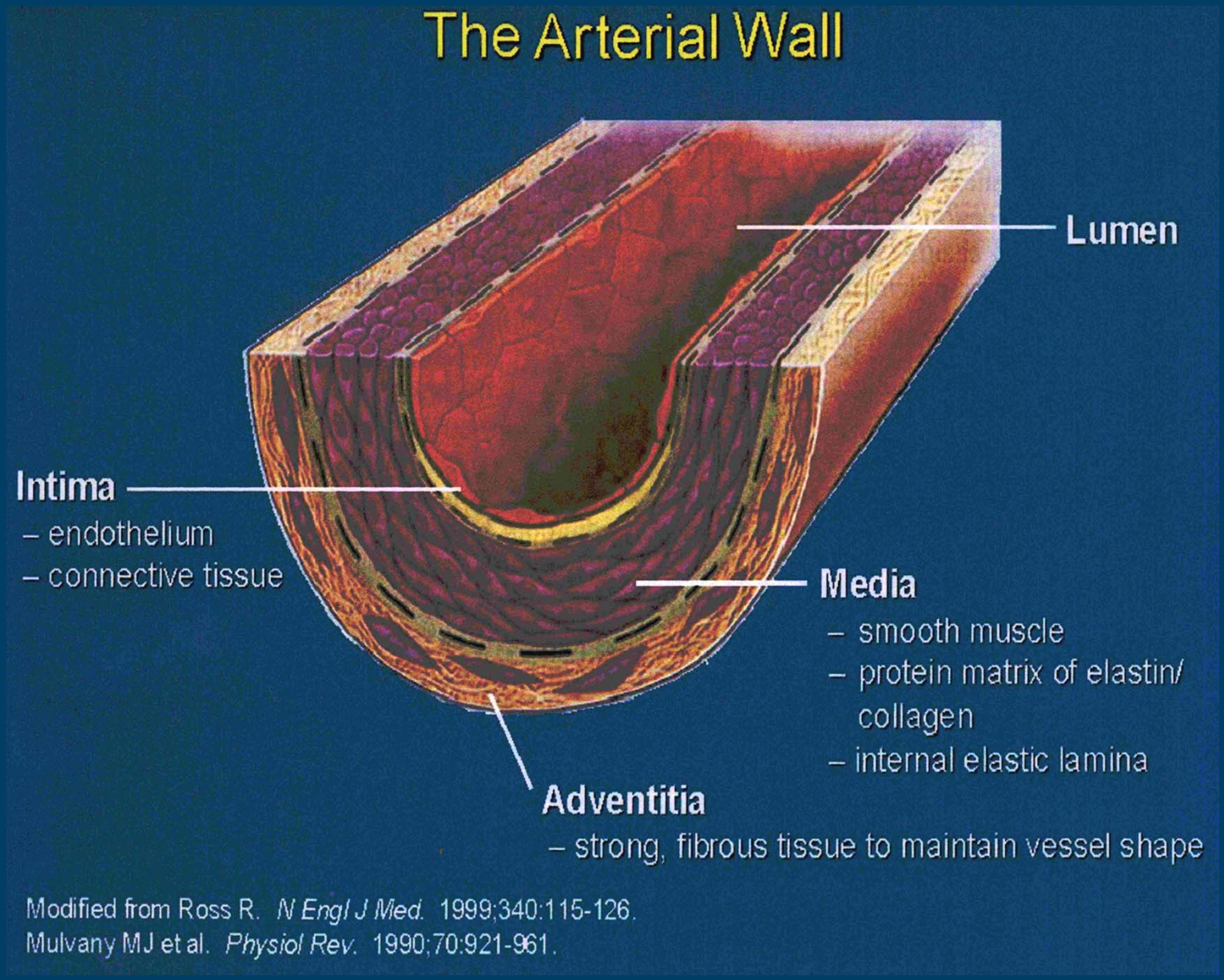


Finite Responses

Infinite Insults



Hypertension INSTITUTE



Houston MC. Vascular Biology in Clinical Practice. Hanley and Belfus 2000
Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Hypertension is not a disease

It is the “correct” but chronic dysregulated vascular response with vasoconstriction and hypertension. The blood vessel is an innocent bystander. Houston

- **Hypertension is not a disease, but is the “correct” chronic dysregulated vascular response with an exaggerated outcome from infinite insults to the blood vessel.**
- **The infinite insults are biomechanical (BP and hemodynamic alterations) and biohumoral, (biochemical, metabolic and nutritional)**
- **This results in the subsequent environmental-gene expression patterns in which the vascular system is the innocent bystander resulting in altered vascular biology, vasoconstriction and hypertension.**
- **Modulation of environmental insults and downstream disturbances of gene expression patterns is the key for the prevention and treatment of hypertension and cardiovascular disease.**

Hypertension is Not a Disease but is a MARKER for Vascular Dysfunction

Hypertension, Vascular Biology and the Blood Vessel
Eftekhari A et al. J of Hypertension 2011;29:896-905

- An elevated blood pressure is one of many responses of the blood vessel to endothelial dysfunction and vascular smooth muscle dysfunction. (impaired microvascular function and structure).

- Endothelial dysfunction and microvascular smooth muscle dysfunction precede the development of hypertension by decades.

Endothelial Dysfunction predicts CVD and Hypertension

J of Hypertension 2014;32:2393

Journal of Hypertension 2016;34:1464-1472

- 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 by FMD 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.

Vascular Disease: A Balance of Nitric Oxide vs Angiotensin II

Vascular Biology in Clinical Practice. Hanley and Belfus 2000 Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Journal of Hypertension 2016;34:1464-1472

- **Angiotensin II:** vasoconstriction, hypertension, inflammation, oxidative stress, vascular immune dysfunction, thrombosis, growth and is pro-atherogenic

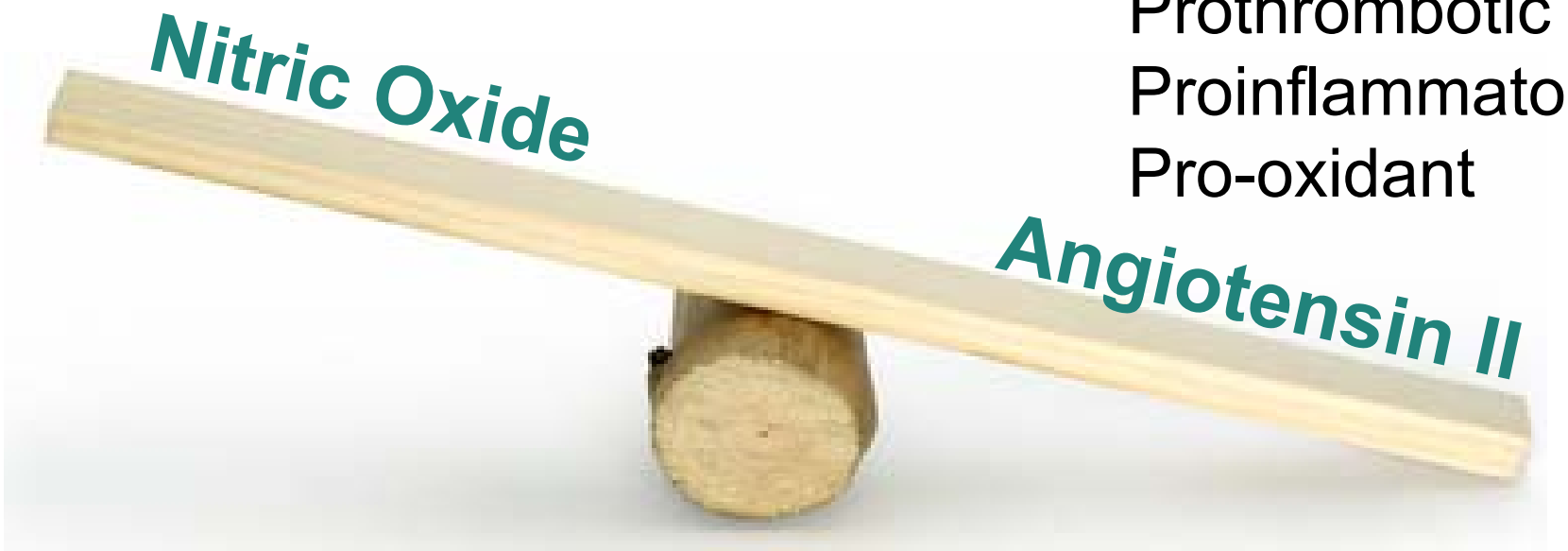
- **Nitric Oxide:** vasodilation, anti-hypertensive, anti-inflammatory, reduces oxidative stress, reduces vascular immune dysfunction, decreases thrombosis and is anti-atherogenic

The Endothelium Maintains Vascular Health

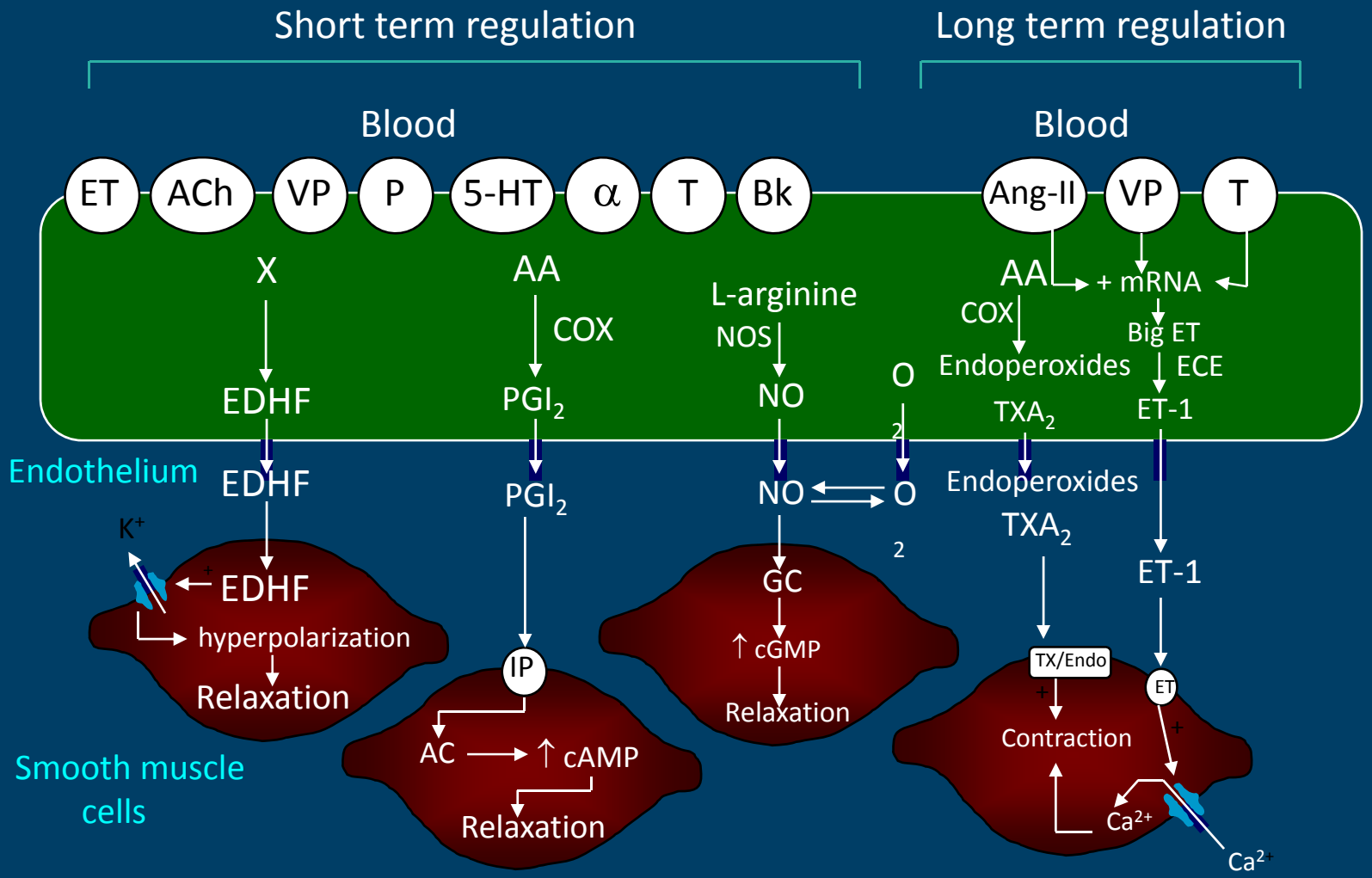
Houston MC. Vascular Biology in Clinical Practice. Hanley and Belfus, Philadelphia. 2000
Houston MC. Handbook of Hypertension. Wiley-Blackwell Oxford UK. 2009

Dilatation
Growth Inhibition
Antithrombotic
Anti-inflammatory
Antioxidant

Constriction
Growth promotion
Prothrombotic
Proinflammatory
Pro-oxidant



Endothelium-Dependent Responses (not present in all blood vessels)



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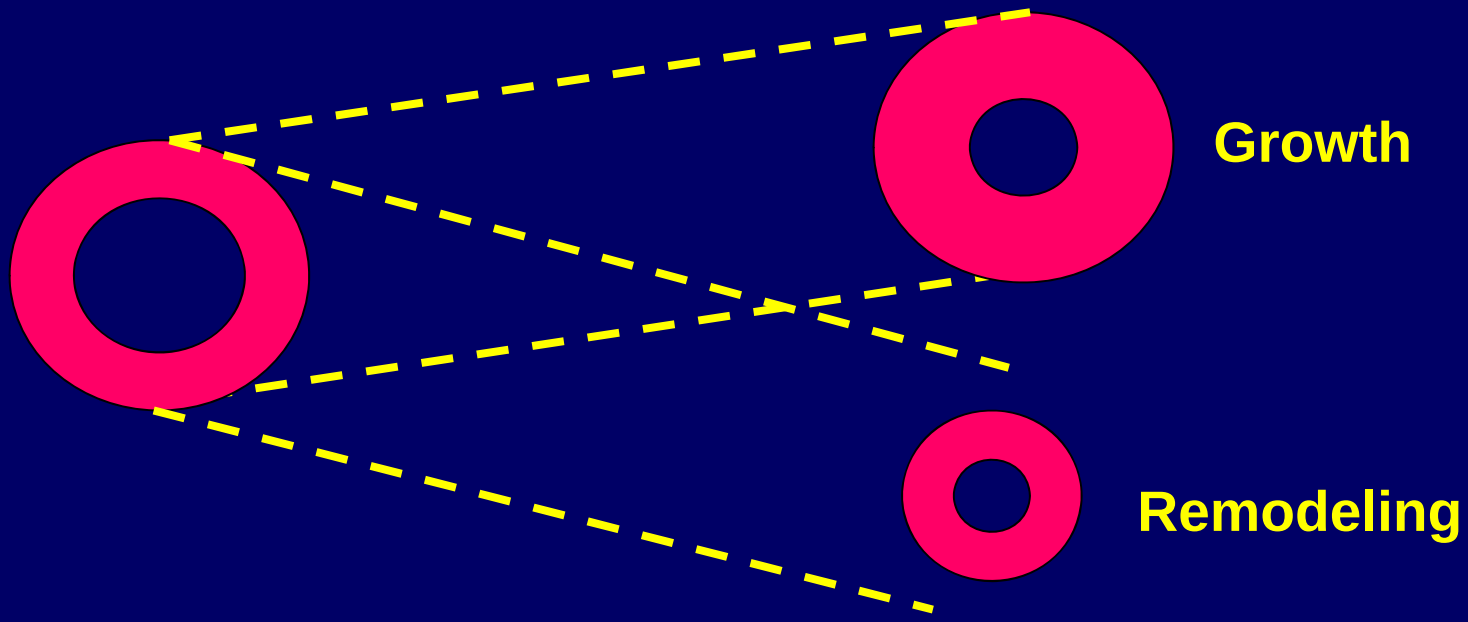
Houston MC. Handbook of Hypertension. Wiley-Blackwell, Oxford UK 2009

Vascular Remodeling

J of Hypertension 2017;35:914



Microvascular Disease and Vascular Remodeling

J of Hypertension 2017;35:914

- Involves small resistance arteries, arterioles, capillaries and post-capillary venules.
- 100-300 um size arterioles involved due to hypertension, DM and obesity.
- In hypertension and DM and obesity there is increase in MLR: media/lumen ratio.

In essential or primary hypertension it is **eutrophic remodeling**: rearrangement of normal material around a narrowed lumen

In DM, MS, obesity and secondary forms of hypertension it is **hypertrophic remodeling**: VSMC hypertrophy or hyperplasia.

Microvascular Disease and Vascular Remodeling

J of Hypertension 2017;35:914

- Vascular remodeling and rarefaction of arterioles occur at the same time and lead to reduced tissue perfusion and oxygenation
- Reduced coronary flow reserve and dilation
- There is an increase in the MLR in arterioles prior to the onset of hypertension. Once hypertension occurs then the MLR and BP parallel one another.
- Due to integrins, ROS, inflammation and vascular immune dysfunction.
- Increased MLR of over 0.098 increased CV events in hypertension, especially if hypertrophic remodeling.
- Correlation with retinal and subcutaneous arteries
- Best treatment: ACEI, ARB, CCB. Not BB or diuretic.
- Also lowers CBP best with ACEI, ARB and CCB

Vascular Remodeling[69]

(Endothelial Dysfunction)

(Vascular Remodeling)

(Media / Lumen Ratio)

(Vascular Wall thickness)

(Arterial Compliance)

(Systemic Vascular Resistance)

(Blood Pressure)

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Small resistance and pre-capillary arteries that are < 100 um 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.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Larger arterioles that are 100 to 300 uM in size have a lower myogenic constrictive response which leads to vascular media wall hypertrophy with reduced lumen size and increased media to lumen ratio (MLR).

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Microvascular adaptive mechanisms protect fragile capillaries from excess pressure but necessarily reduce blood flow with a mismatch in local tissue demands and induce ischemia.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Macrovascular and microvascular adaptive changes are intercorrelated with bidirectional feedback that leads to accelerated vascular disease.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Retinal laser scanning flow doppler flowmetry correlates with central pulse pressure.
- Subcutaneous arteriole MLR correlates with carotid femoral PWV and aortic stiffness.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Adventitial microvascular adaptations also occur that effect arteriolar function
- The vaso-vasorum arteriolar dysfunction that supplies blood to the outer arterial wall may also induce macrovascular dysfunction.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Microvascular changes occur with HLP, DM and CRI.
- The endothelial dysfunction that leads to microvascular disease is secondary to inflammation, oxidative stress and immune vascular dysfunction.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Increase aortic stiffness increases pressure pulsatility
- Functional rarefaction or microcirculation occurs first (increased nonperfused arteries)
- Structural rarefaction of microcirculation follows (anatomical absence).

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

- Macrovascular changes: large arterial stiffness with loss of arterial compliance
- Microvascular changes of abnormal vasomotor tone, functional and structural network rarefaction, decreased vasodilatory reserve and altered wall to lumen ratio.
- Both macrovascular and microvascular changes are independent predictors of CV events in hypertensive patients.

Pathophysiology of Hypertension: Interactions between microvascular and macrovascular alterations through endothelial dysfunction

J of Hypertension 2014; 32:216-224

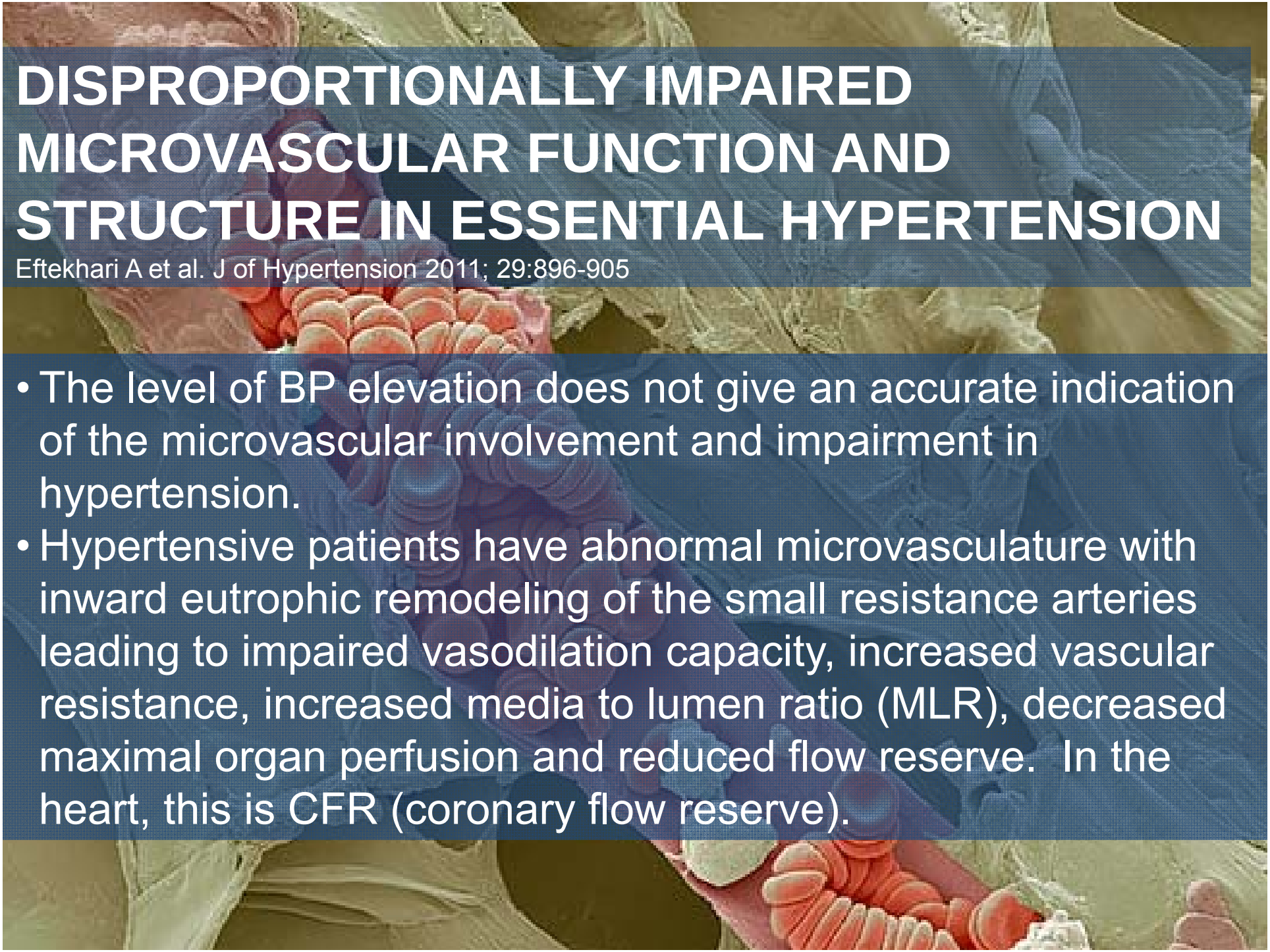
- The adaptive response of the vasculature to wall tensile stress during hypertensive disease depends on the level of myogenic constriction ability, which is inversely related to the diameter of the vessel.
- Resistance precapillary arteries (< 100 um) show the largest myogenic constriction. These determine tissue perfusion and organ function by three mechanisms:
  1. Tissue nutritive role
  2. Capillaries protection against increased BP
  3. Local and systemic peripheral resistance determination.
- Wall tension stress determines vascular adaptive remodeling during hypertension
- Small arteries undergo eutrophic inward remodeling without growth response which reduces mean blood flow and resulting mismatch
- Functional and structural rarefaction occur later.
- Large arteries undergo hypertrophic remodeling with medial hypertrophy and increased MLR.
- Skin capillaries and retina are good surrogate markers for microvascular circulation.

Microvascular impairment precedes the development of hypertension

J of Hypertension 2011;29:896-905

J Hypertension 1995;13:259

- Significant functional then structural microvascular impairment occurs even before the BP begins to rise in normotensive offspring of hypertensive parents
- Endothelial dysfunction, diastolic dysfunction impaired vasodilation, 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..

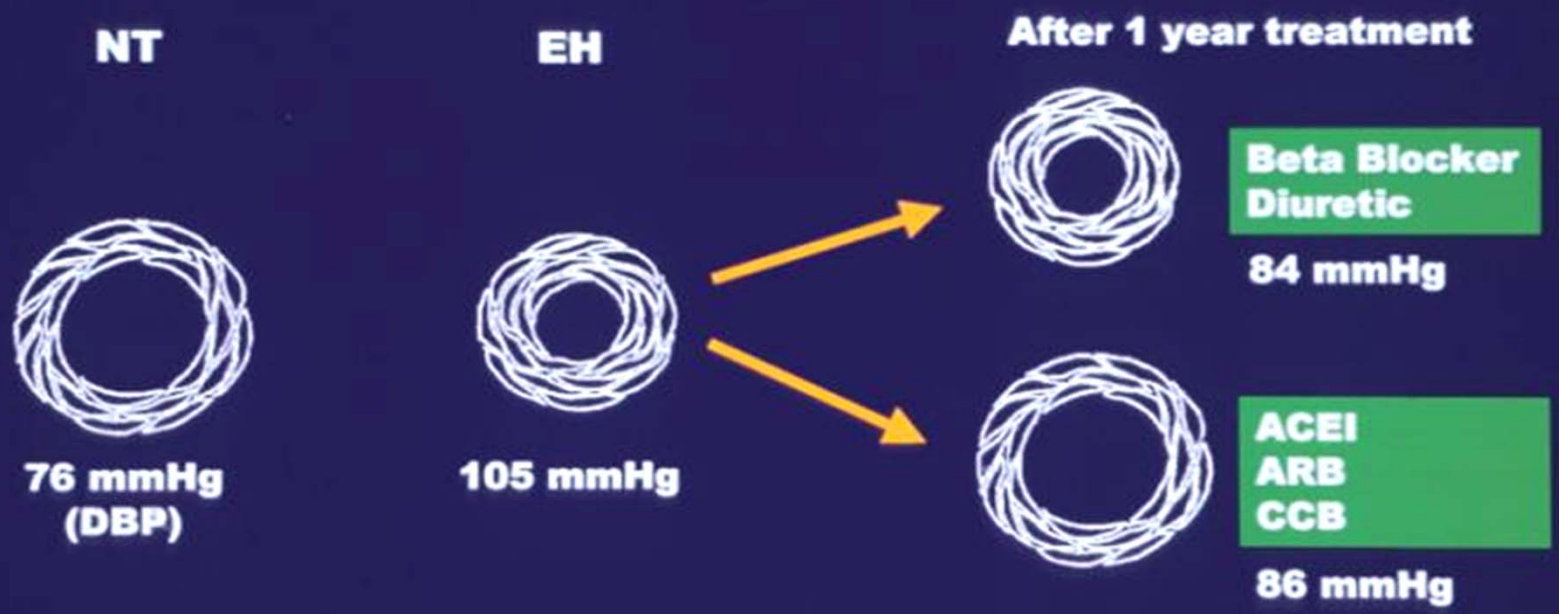


DISPROPORTIONALLY IMPAIRED MICROVASCULAR FUNCTION AND STRUCTURE IN ESSENTIAL HYPERTENSION

Eftekhari A et al. J of Hypertension 2011; 29:896-905

- The level of BP elevation does not give an accurate indication of the microvascular involvement and impairment in hypertension.
- Hypertensive patients have abnormal microvasculature with inward eutrophic remodeling of the small resistance arteries leading to impaired vasodilation capacity, increased vascular resistance, increased media to lumen ratio (MLR), decreased maximal organ perfusion and reduced flow reserve. In the heart, this is CFR (coronary flow reserve).

Anti-Hypertensive Drug Effects on Vascular Remodeling in Humans[108]



Microvascular Impairment Precedes the Development of Hypertension

Eftekhari A. et al. J of Hypertension 2011;29:896-905
Giannattasio C. et al. J Hypertension 1995;13:259

- **Significant endothelial dysfunction and structural microvascular impairment** occurs long before the BP begins to rise in normotensive offspring of hypertensive parents.

- Diastolic dysfunction, increased left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH) may also occur early in these offspring but is usually a later development *related more to cardiac and vascular structural dysfunction, large artery functional and structural impairment and loss of arterial compliance and elasticity.*

Hypertension is a Disease of the Blood Vessel

Houston MC. Vascular Biology in Clinical Practice. Hanley and Belfus. Philadelphia 2000
Houston MC. Handbook of Hypertension. Wiley-Blackwell, Oxford UK 2009

- Which occurs first?
  Hypertension, the diseased blood vessel, or both?

Hypertension ⟷ **BIDIRECTIONAL** ⟷ **Diseased Blood Vessel**

- Hypertension is part of vascular disease and vascular aging. A marker of vascular dysfunction.
- The best approach to manage hypertension is to improve vascular health, optimize vascular biological function and structure, slow vascular aging and subsequent CVD.

Pathophysiology of Hypertension

J of the American Society of Hypertension 2010;4:272
Circulation 2007;115:1020.
Expert Rev in CV Therapy 2010;8:821
J of Hypertension 2016;34:1464
Nephrol Dial Transplant 2006:21:850
He, Feng. Int J Mol Sci 2015;16:165

1. **Oxidative Stress (ROS-radical oxygen species- and reactive nitrogen species –RNS-** are increased in the arteries and kidneys with a concomitant decreased oxidative defense.
2. **Inflammation** is increased in the vasculature and kidneys: increased hsCRP, leukocytosis, increased neutrophils and decreased lymphocytes. Increased renin-angiotensin-aldosterone system (RAAS) activity in the kidney.
3. **Autoimmune dysfunction** of the arteries and kidneys: increased WBC, and involvement of CD4+ (T-helper cells) and CD 8+ (cytotoxic T –cells).
4. **Abnormal vascular biology** with
    1. Endothelial dysfunction (ED)
    2. Vascular smooth muscle (VSM) dysfunction and cardiac dysfunction
5. **Epigenetics, genetics, and environmental-genomic interactions**

Inflammation GGTP and hsCRP High Sensitivity-C-Reactive Protein Downregulates Vascular AT2R Receptor

J of Am Society of Hypertension 2010;4:272; J of Hypertension 2015;33:704

- Increased inflammation and hs-CRP levels increase BP proportional to level of hsCRP and leukocytosis.
- hs-CRP is both a risk marker and risk factor for hypertension and CVD.
- hs-CRP inhibits endothelial nitric oxide synthase (eNOS) and reduces nitric oxide (NO).
- NO regulates AT2R.
- hs-CRP downregulates AT2R which increases BP and CVD risk. AT2R when stimulated lowers BP and CVD. AT2R counterbalances the AT1R which increases BP and CVD. AT1R is inflammatory, increases oxidative stress and vascular immune dysfunction. AT2R is the opposite of AT1R

- GGTP predicts hypertension and DM via promotion of inflammation, oxidative stress, increased fibrinogen, ROA and hsCRP.

GGTP and Hypertension

J of Hypertension 2015;33:704
J of Am Soc Hypertension 2016;9(12): 951
JASH 2016;10:772;J of Hypertension 2017;35:493

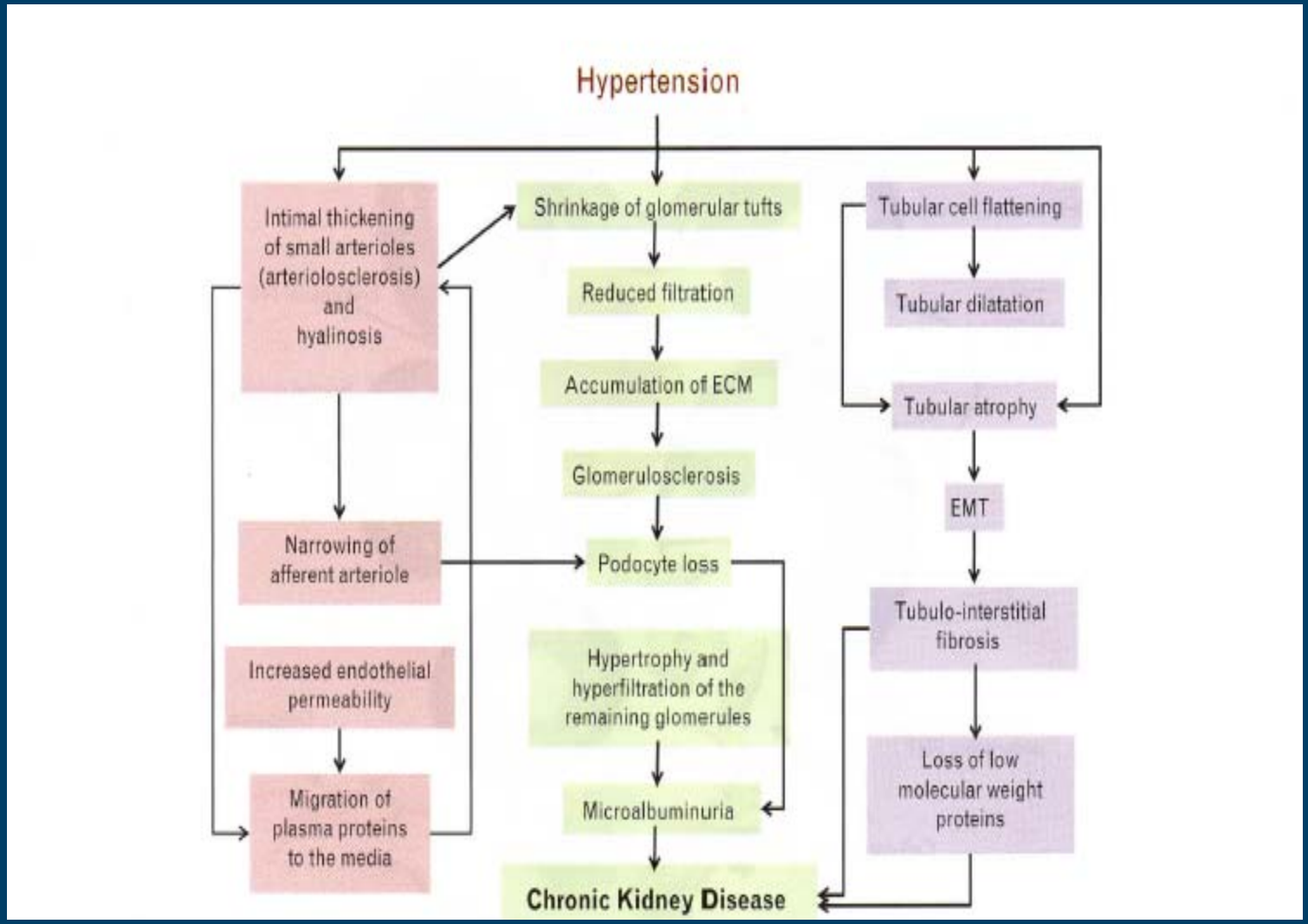
- GGTP increases predictive risk of hypertension, CHD, CVD, all cause mortality and DM
- Increased arterial stiffness and increased PWV
- Increase inflammation
- Increase ROS and oxidative stress
- Reduced GSH and oxidative defense
- Increase heavy metals
- Reduced hepatic detoxification and increased NAFLD
- Increased fibrinogen
- Increase MS, IR and NAFLD
- Increased hsCRP
- Alcohol
- Obesity
- NAFLD also increases risk of hypertension.

Air Pollution Increases BP

J of Am Soc Hypertension 2017:11;709

- Air pollution increases BP and CHD by inducing arterial stiffness, inflammation, oxidative stress , arterial remodeling and imbalance of the autonomic nervous system
- Also effects HR, HRV, vascular tone, blood coagulability and atherosclerosis, MI,CHF arrhythmias and sudden death.
- Changes occur rapidly, within hours.

Changes Associated With Hypertensive Nephropathy



J Hypertens 2017;35:205-212

Mitochondrial oxidative stress contributes to hypertension

Curr Opin Nephrol Hypertens 2016;25:73

- Increased production of superoxide anion by mitochondria increases BP
- Use of SOD or SOD mimetics will reduce BP
- SIRT 3 increases SOD
- SIRT 3 is decreased by age, A-II and inflammation
- SIRT 3 is increased by caloric restriction
- CR increases AMPK, NO, endothelial function, SIRT 1 and SIRT 3. Increases mitochondrial biogenesis and lowers BP
- ACEI and ARB attenuate age-related mitochondrial dysfunction and reduces superoxide anion, reduce ROS, reduce NADPH oxidase and increase NO
- Treatments: mitoTEMPO (SOD 2 mimetic), Ubiquinone, Bendavia(inhibits cytochrome c/caridiolipin peroxidase)

Dynamic thiol/disulphide homeostasis in patients with newly diagnosed primary hypertension.

J Am Soc Hypertens. 2016 Feb;10(2):159-66.

- Primary target of ROS is thiol groups of sulphur containing amino acids lie cysteine, methionine of proteins. The thiol is oxidized to disulphides. Blood thiol/disulphide homeostasis, which consists of native thiol/disulphide exchanges results from oxidative stress, lowers nitric oxide , induces ED and hypertension
- The levels of native thiol, total thiol, and native thiol/total thiol ratio were lower while the disulphide level and disulphide/native thiol and disulphide/total thiol ratios were higher in patients with primary hypertension when compared with those in the control group.
- Positive correlation was detected between 24-hour systolic and diastolic blood pressure levels and disulphide/native thiol ratio.
- increase in disulphide/native thiol ratio and log(24-hour urine microalbumin) and decrease in native thiol/total thiol ratio are independent predictors of 24-hour systolic and diastolic blood pressure.
- Thiol/disulphide homeostasis was shifted toward disulphide formation in patients with primary hypertension.

Mitochondrial oxidative stress contributes to hypertension

Curr Opin Nephrol Hypertens 2016;25:73
Kidney Blood Press Res 2016;41:721

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Autoimmune Dysfunction in Arteries

Hypertension.2008;51:259
Circ Res 2010;107:263
Curr Opin Pharmacol 2010;10:203
Curr Opin Neprhol Hypertens 2011;20:113
Curr Opin Nephrol Hypertens 2010;19:181
J of Am Soc of Hypertension 2014;8:2014
J of Hypertension 2015;33:1046

- Monocytes, macrophages and CD4+ T lymphocytes invade the arterial wall with toll like receptor(TLR) involvement.
- CD4+ cells are attracted and enter as T-helper 0 cells , encounter antigens and APCs, convert into T-helper cells and release pro-inflammatory mediators, TNF alpha, interferon and interleukins.
- CD4+ cells express AT1R and PPAR gamma receptors
- Angiotensin-II activates T cells, macrophages, and dendritic cells
- Inflammation and oxidative stress in CNS increase BP.
- IL-17 produced by T cells plays a pivotal role in the genesis of hypertension caused by angiotensin II.
- Antibodies to the AT1R receptor have agonist actions that increase BP and also cause pre-clampsia.

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

- Presence of T cells is necessary for full development of A-II induced hypertension.
- Roles for both cytotoxic (CD8+) T cells and T helper (Th, CD4+) T cells in hypertension.
- The fours subtypes of T helper (Th, CD4+) T cells are Th1, Th2, Th17 and T regs.
- CD8+ cytotoxic T cells are deleterious in hypertension and express apoptotic effector molecules, perforin and granzyme B and IFN gamma and TNF alpha with a pro-inflammatory state. Accumulation in both kidney and vasculature. Alters renal hemodynamics and sodium and water excretion and induce endothelial and vascular dysfunction.
- Also CD4+ cells such at IL-17 and the ratio of Th17/Treg is related to immune- induced hypertension.

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

- **T Cell activation : Activates the SNS**

1. AV3V (anteroventral third ventricle) of the CVO have hormonal signals that influence CV vascular functions and fluid balance. These central signals and SNS drive are required for A-II induced hypertension and T cell activation of CD69. Increase dietary sodium increases CNS sodium and increases SNS via quabain. PIGF (placental growth factor) is an angiogenic cytokine necessary for A-II induced hypertension as a modulator for the neuroimmune link of SNS to splenic immune system.

- **Active T cell receptors**
- **Activate humoral immunity**
- **Produce Neoantigens**

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

T Cell activation

- Activates the SNS
- Active T cell receptors
- Activates humoral immunity
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Curr Opin Neprhol Hypertens 2015;24:470-474

T Cell activation activates the SNS

AV3V (anteroventral third ventricle) of the CVO have hormonal signals that influence CV vascular functions and fluid balance. These central signals and SNS drive are required for A-II induced hypertension and T cell activation of CD69. Increase dietary sodium increases CNS sodium and increases SNS via quabain. PIGF (placental growth factor) is an angiogenic cytokine necessary for A-II induced hypertension as a modulator for the neuro-immune link of SNS to splenic immune system.

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

T Cell activation actives T cell receptors and co-stimulation.

1. Major histocompatibility (MHC) antigens on APCs present peptides to the T cell receptor. Then a 2nd signal of co-stimulation occurs with CD28 on T cells interacting with B7 ligands CD80 and CD86 on the APCs.

2. Both signals are required for the activation of T cells.

3. Blockade of interaction of T cells and APCs by inhibition of the B7/CD 28-dependent co-stimulation by fusion proteins CTLA4-Ig blocks A-II induce hypertension, blocks salt sensitive hypertension, blocks T cell activation and cytokine production and migration of T cells into the vascular wall.

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

T Cell activation activates humoral immunity

1. B cells produce antibodies against the alpha 1, beta 1 and ATR1 receptors with agonist effects that increase BP.
2. There is interplay and interaction of T cells with B cells to increase BP.

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

T Cell activation produces neo-antigens.

1. Activation of adaptive immune system implies presence of an antigen and loss of self-tolerance via oxidation, nitrosylation, adducts or post translational modifications of proteins that make hypertension an autoimmune disease.
2. Autoimmune reaction of HSP 70 (heat shock protein) may induce salt sensitive hypertension generating T cell activation and T regs, with modulation of IL- 6, IL-10 and hypertension.
3. A-II increases oxidative stress (ROS) in dendritic cells to produce isoketal adducts via

Hypertension and immunity: Mechanisms of T cell activation and pathways of hypertension

Curr Opin Neprhol Hypertens 2015;24:470-474

Dietary Contributions to T Lymphocyte Activation in Hypertension

1. Sodium-Dependent Effects

Sodium-dependent immune activation related to Th 17 andIL-17 and SGK-1 (glucocorticoid-inducible kinase-1.

Increased dietary sodium intake increased IL-6 and IL-23 (both inflammatory) and decreased IL-10 (anti-inflammatory)

2. Non Sodium-Dependent effects: protein, sucrose and fat.

Stop gluten, refined CHO, trans fat, SFA = lower BP

Aldosterone is a Modulator of Immunity, Hypertension, and CVD

J of Hypertension 2011;29:1684

- Aldosterone is an independent risk factor for CVD due to hypertension and non-hemodynamic effects.
- Mineralocorticoid receptors exist in heart, blood vessels, brain and immune cells.
- Blockade of aldosterone even with persistence of hypertension and in normotensive patients reduces CV risk
- Increased adaptive immunity and autoimmune responses with CD4+T cell activation and Th-17 polarization, increased IL-10, TGF-beta and TNF-alpha, to modulate over 30 inflammatory genes

The Spectrum of Subclinical Primary Aldosteronism and Incident Hypertension

Annals Intern Med; 2017:167:630
J of Hypertension 2017;35:2510

- There is a clinically relevant spectrum and continuum of subclinical primary aldosteronism (PA) in normotensive, prehypertensive and hypertensive patients
- This varies from small clusters of aldosterone producing cells (found in 50% of normal adrenal glands and is age related) to adrenal adenomas and hyperplasia
- More common in blacks and women. Overall incidence is about 5-10 %, but may be 20% in resistant or severe hypertension.
- The degree of PRA suppression predicts the severity of PA. A level of PRA < 0.50 has a high correlation with PA
- Serum Aldosterone is independently associated with microalbuminuia and CKD.

Cardiovascular Neuroimmunology

J of Hypertension 2015;33:525,
Hypertension.2008;51:259;Circ Res 2010;107:263
Curr Opin Nephrol Hypertens 2010;19:181
Curr Opin Pharmacol 2010;10:203
Curr Opin Neprhol Hypertens 2011;20:113

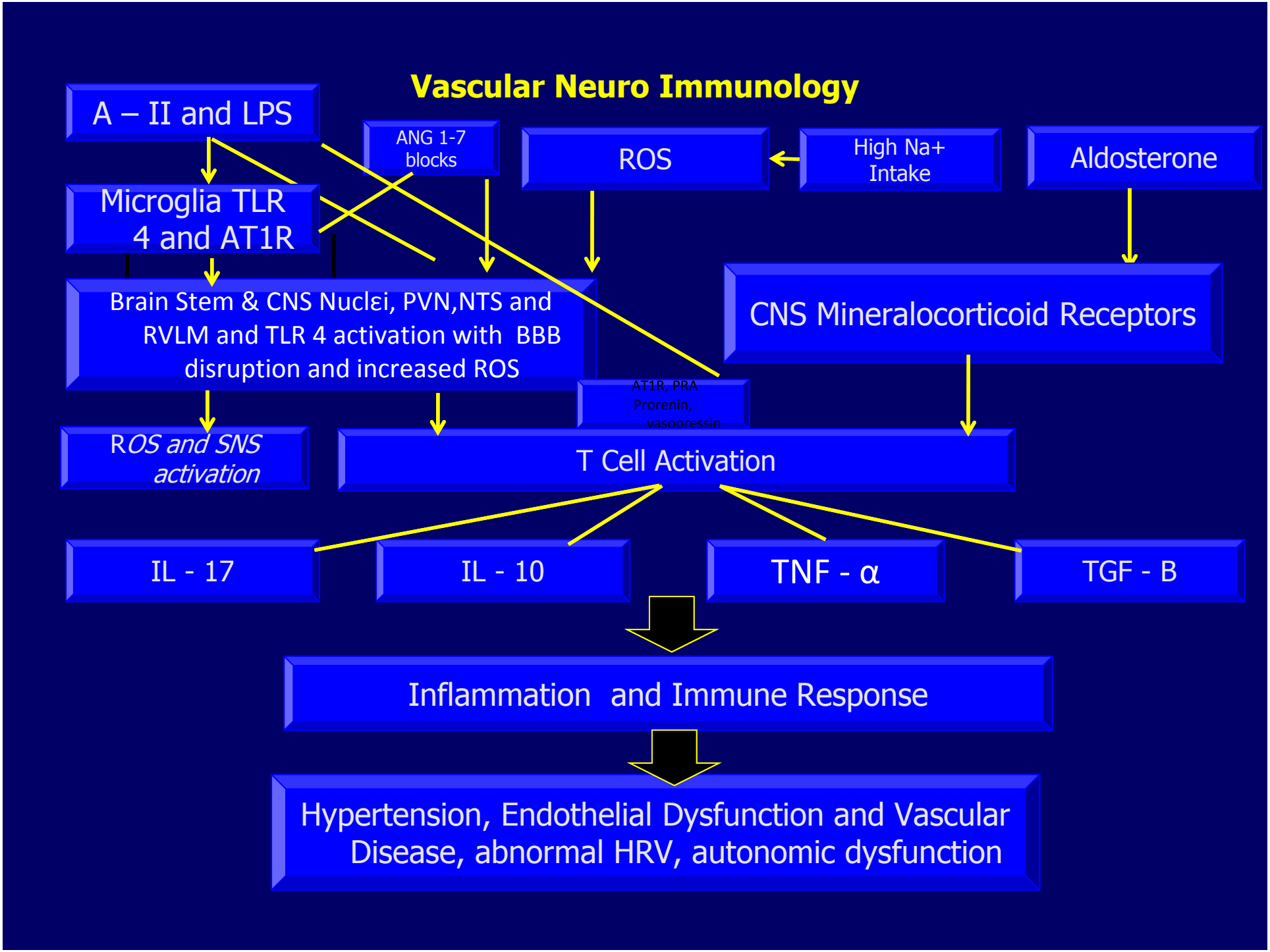
- A-II crosses into subfornical organ and area postrema that reside outside BBB and sense circulating A-II.
- A-II increases BBB permeability
- TLR 4 is expressed on microglia in corpus callosum and are the prime immune and inflammatory cells to mediate neuroinflammation.
- AT1 R and LOX-1 are expressed on neuronal tissue.
- A-II stimulates and upregulates LOX-1 via AT1R in brain, (also in endothelium and VSMC) , NADPH oxidase, NfKb and TLR 4 in brain and increases CNS inflammation, oxidative stress and immune dysfunction and autophagy
- A-II- induced hypertension involves activation of microglia and cytokines in the paraventricular nucleus

Neuroinflammatory mechanisms of hypertension: potential therapeutic implications.

Curr Opin Nephrol Hypertens.2016 Sep;25(5):410-6.

- Inflammation of forebrain and hindbrain nuclei has recently been highlighted as an emerging factor in the pathogenesis of neurogenic hypertension.
- Microglia Toll-like receptor 4 causally links angiotensin II (Ang II)-mediated microglia cell activation and oxidative stress within the hypothalamic paraventricular nucleus (PVN).
- Toll-like receptor 4 can also be activated by lipopolysaccharides.
- PVN infusion of nuclear factor κB inhibitor lowers the blood pressure and ameliorates cardiac hypertrophy.
- Ang-(1-7) exerts direct effects on microglia, causing a reduction in both baseline and prorenin-induced release of proinflammatory cytokines.
- A compromised blood-brain barrier (BBB) constitutes a complementary mechanism that exacerbates AngII-driven neurohumoral activation, contributing to the development of hypertension.

- SUMMARY: PVN and BBB seem to be pivotal targets for therapeutic intervention in hypertension. Recent advances in imaging techniques enable visualization of the inflammatory state in microglia and BBB integrity in humans. Ang II type I receptor blockers and Ang II-converting enzyme inhibitors are the most likely candidates for controlled randomized trials in humans aimed at amelioration of brain inflammation in the forthcoming years


Vascular Neuro Immunology
A – II and LPS
ANG 1-7 blocks
ROS
High Na+ Intake
Aldosterone
Microglia TLR 4 and AT1R
Brain Stem & CNS Nuclεi, PVN,NTS and RVLM and TLR 4 activation with BBB disruption and increased ROS
CNS Mineralocorticoid Receptors
AT1R, PRA Prorenin, vasopressin
ROS and SNS activation
T Cell Activation
IL - 17
IL - 10
TNF - α
TGF - B
Inflammation and Immune Response
Hypertension, Endothelial Dysfunction and Vascular Disease, abnormal HRV, autonomic dysfunction

Gut Microbiotia and Hypertension

Curr Opin Neprol Hyperten 2015;24:403

- Gut microbiota, genetics, epigenetics and salt sensitivity regulate blood pressure.
- Primary microorganisms include Firmicutes, Bacteroides, Actinobacteria and Proteobacteria.
- Multiple mechanisms may increase or decrease risk for CVD and hypertension

Gut Microbiotia and Hypertension Mechanisms

Curr Opin Neprol Hyperten 2015;24:403

- Microbiome produced toxic products: TMAO, p-cresol and indoxyl sulfate.
- SCFA alter BP via renal sensory nerves and active several receptors such as GPCRs (GPR 41, GPR 43) and Olfr 78
- Olfr 78 increases renin release from afferent renal arteriole is vasoconstrictive and increases BP.
- GPR43 is vasodilatory and lowers BP. Lowers insulin signaling in adipocytes and reduces adipose tissue.
- GPR 41 increases energy expenditure by stimulating SNS and increases BP.

Gut Microbiotia and Hypertension Mechanisms

Curr Opin Neprol Hyperten 2015;24:403

- Chronic inflammation blocks AT2 R which increases BP related to changes in microbiome ratios
- Increase Firmicutes / Bacteroides ratio is increased which modulates A-II induced hypertension
- Lactobacilli produce biologically active peptides that inhibit ACEI (fermented milk , sour milk and blueberries).
- Phenyl-acetyl glutamine, a gut metabolite, is negatively associated with PWV and SBP.
- Probiotics with over 10^{11} CFU of multiple strains for 8 weeks decreased SBP and DBP.

Gut Microbiotia and Hypertension Mechanisms

Curr Opin Neprol Hyperten 2015;24:403

- Monoamine-containing enterochromaffin cells in the mucosa and submucosa of different portions of the stomach and small intestine that produce serotonin, dopamine and norepinephrine.
- These alter the brain-gut microbiome axis and the gastro-renal reflex.
- Absence of some gut microbiota increase anxiety, decrease dopamine in frontal cortex, hippocampus and striatum.
- NE increases virulence factors in Gram negative bacteria.
- Alterations in renal dopamine with salt intake and microbiome
- Changes in microRNA, DNA methylation, and acetylation.

TMAO and CVD

Nature Medicine 2013 April 7 Epub
Cell Metabolism 2013;17:49
Cell 2015;16 3: 1585-95
J Nutritional Biochemistry 2016;33:145

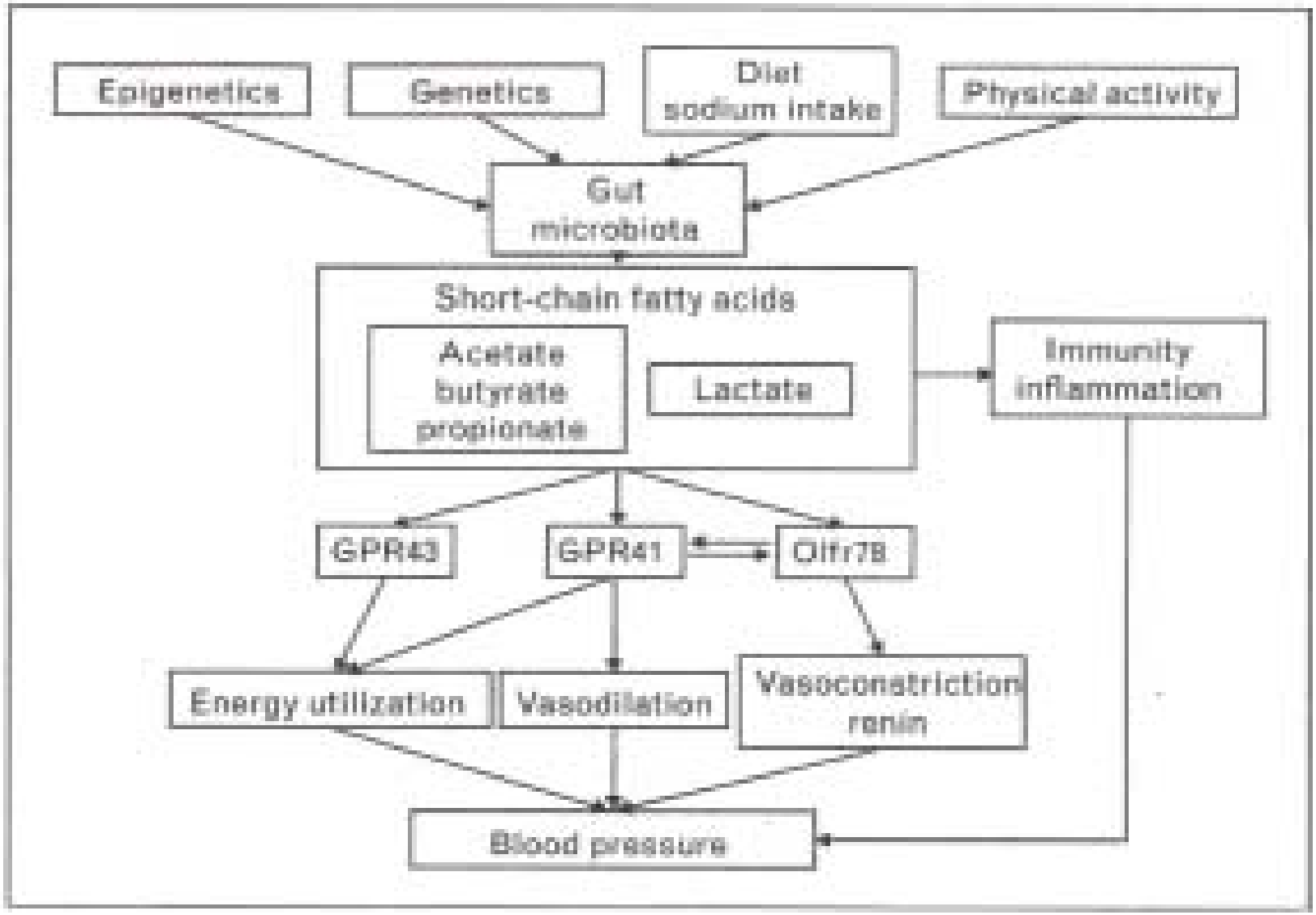
- **Elevated TMAO levels related to the microbiome and hepatic FMO3 conversion, increase the risk of CHD, hypertension, dyslipidemia and CRI.**
- **FMO3 is increased by estrogens and bile acids**
- **FMO3 is increased by dioxin- like pollutants and PCBs which increase TMAO and CVD. PCBs also modulate gut microbiome.**
- **FMO3 is decreased by arginine, nitric oxide and androgens.**
- **TMAO explains 11 % of the variation in CHD**

The role of short-chain fatty acid on blood pressure regulation.

Curr Opin Nephrol Hypertens.2016 Sep;25(5):379-83

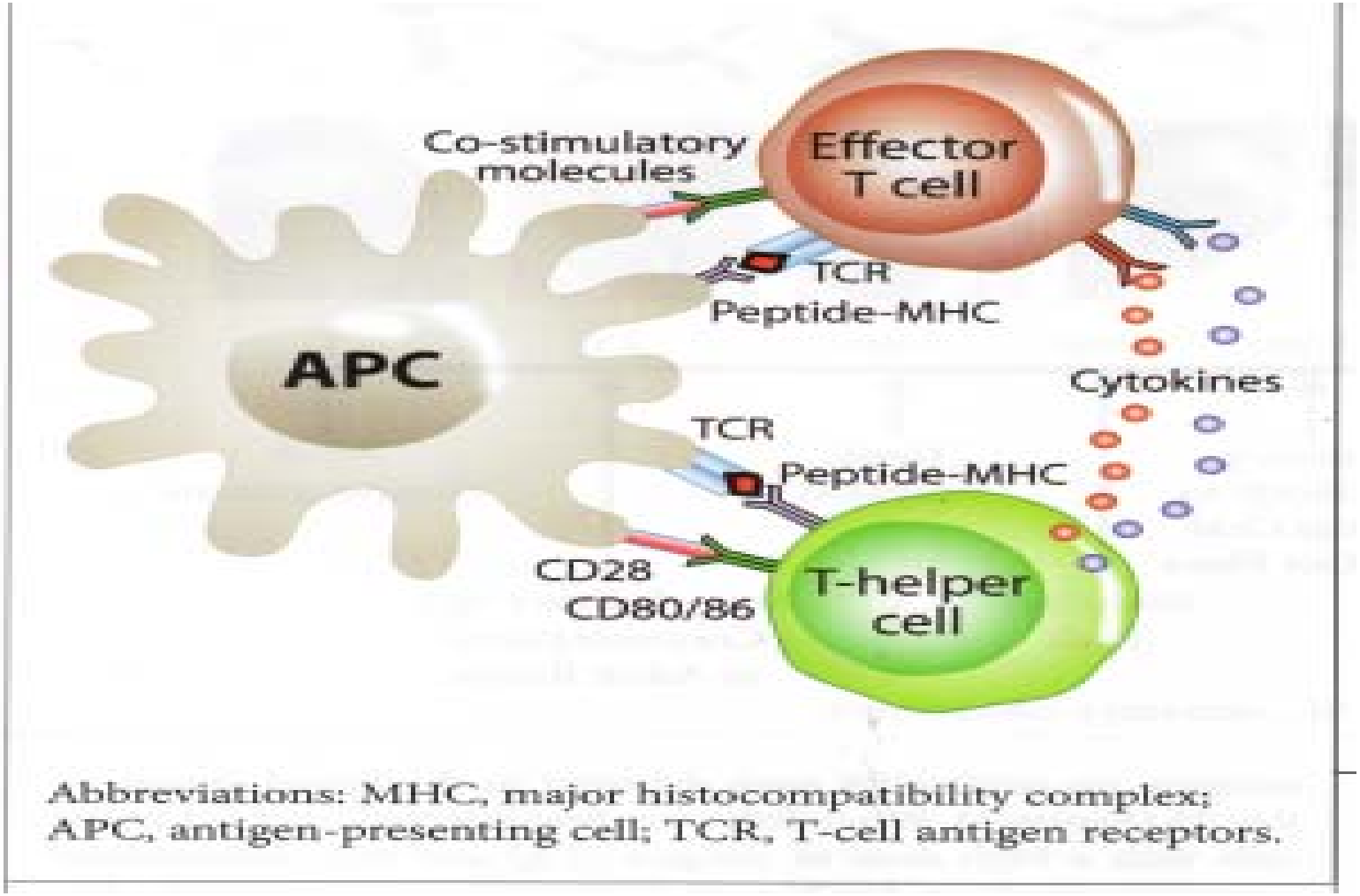
- The gut microbiota and its metabolites have been implicated in the regulation of host physiological functions such as inflammatory and metabolic responses.
- SCFA are produced by gut microbe from dietary fibers and polysaccharides.
- The short-chain fatty acid (SCFA) receptor is expressed in the kidney and blood vessels as well, and has been reported to function as a regulator of blood pressure (BP).
- Olfactory receptor 78 (Olfr78) is a member of the G-protein-coupled receptor family, and it plays a key role as a chemosensor in various tissues. Both Olfr78 and G protein-coupled receptor 41 and 43 (GPR41 and 43) are expressed in smooth muscle cells of blood vessels and the kidney and they recognize SCFAs.
- Oral administration of SCFAs was found to increase BP in vivo via renin release mediated by cAMP production, an effect that was altered in Olfr78 and GPR41-deficient mice.
- ACEI peptides are made by the microbiome fermentation that lower BP
- Increased Firmicutes/Bacteroides ratio lowers BP
- Increased gut inflammation and increased TMAO and PC increase BP
- Probiotics lower BP
- The regulation of BP via SCFA receptors has provided new insights into the interactions between the gut microbiota and BP control systems.
- These interactions provide a novel pathway involved in BP regulation and therapeutic strategies for the treatment of cardiovascular diseases.

Gut Microbiota in Hypertension



Curr Opin Nephrol Hypertens 2015, 24:403-409

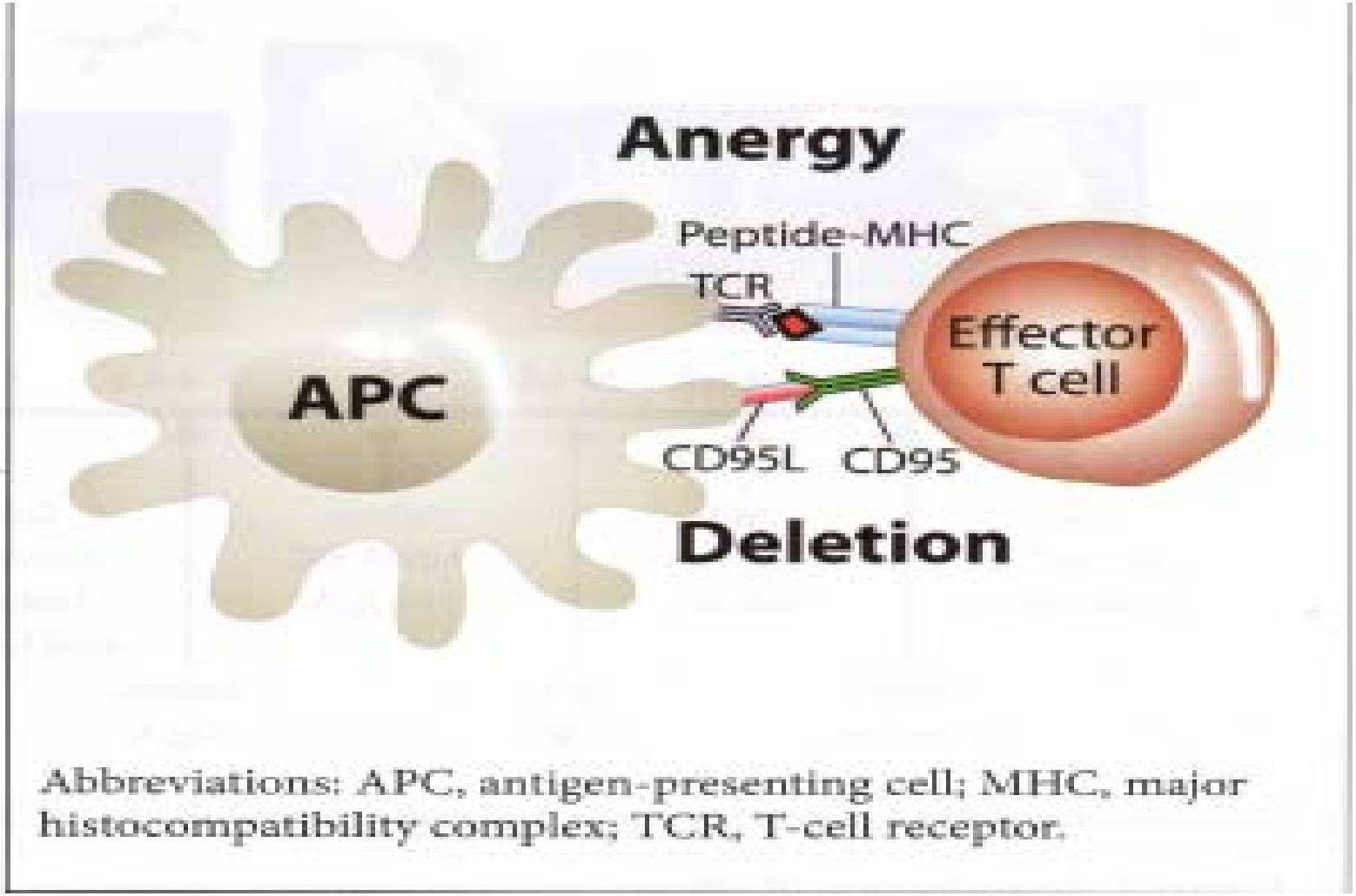
Generation of an Immune Response



Abbreviations: MHC, major histocompatibility complex; APC, antigen-presenting cell; TCR, T-cell antigen receptors.

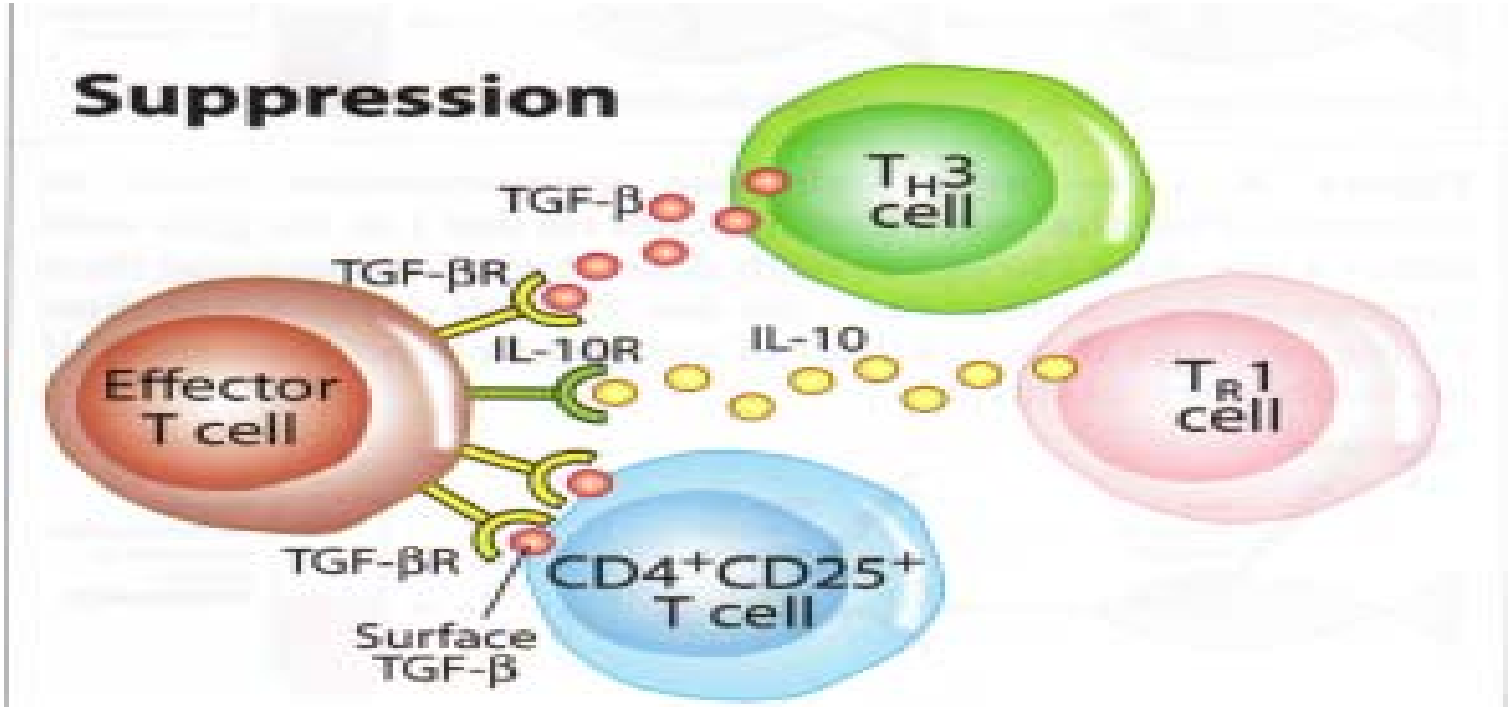
Alternative Therapies, Vol 21, Suppl 1; 26

High-Dose Mechanism



Abbreviations: APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

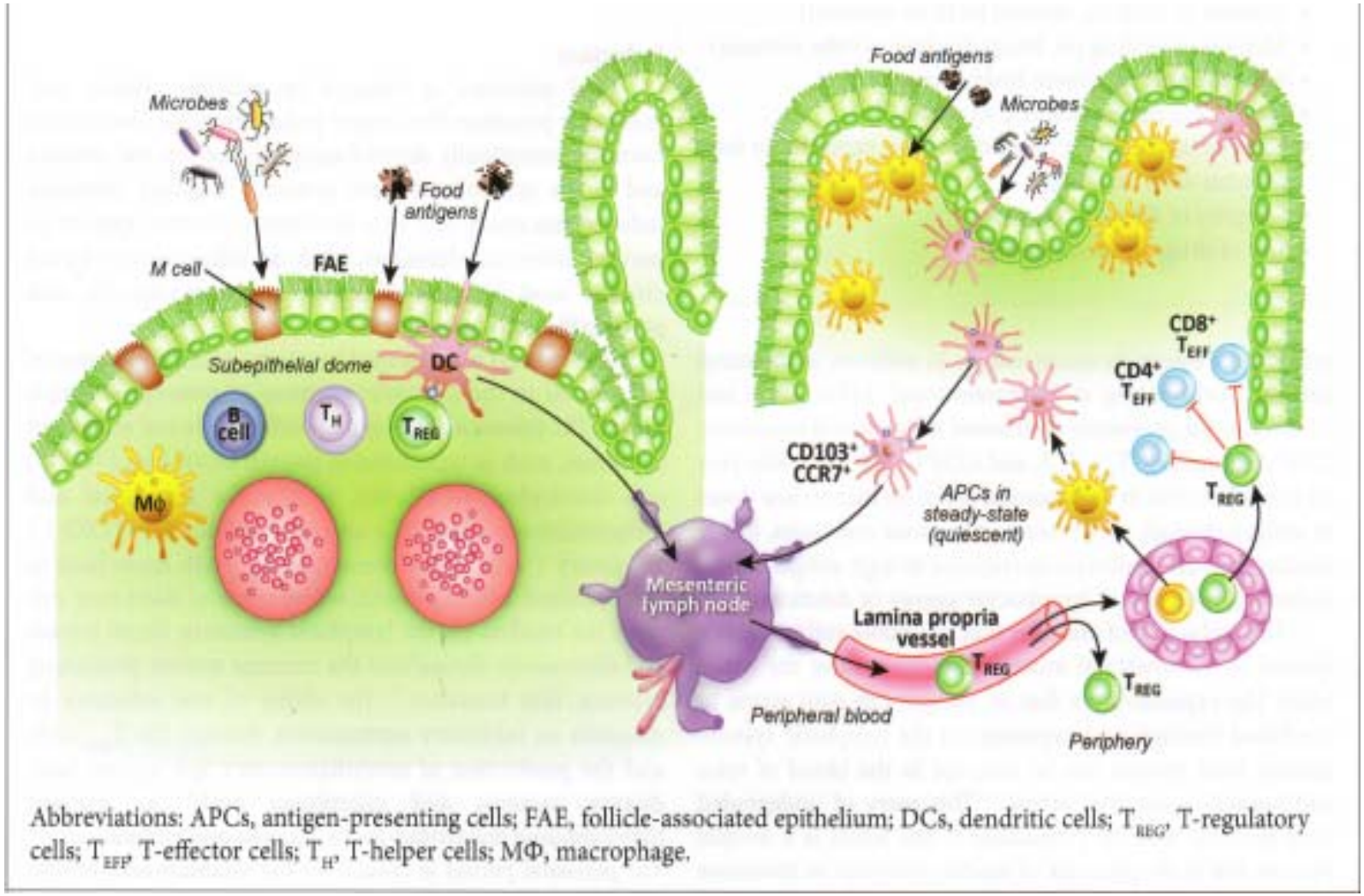
Low-Dose Mechanism



Abbreviations: T_{REG}, regulatory T cells; IL-10, interleukin 10; TGF-β, transforming growth factor beta; T_H3, T-helper 3 cell; TGF-βR, TGF-β receptor; IL-10R, IL 10 receptor; T_R1, type 1 regulatory cell.

Alternative Therapies, Vol 21, Suppl 1; 26

The Immunoregulatory Network



Abbreviations: APCs, antigen-presenting cells; FAE, follicle-associated epithelium; DCs, dendritic cells; T_{REG}, T-regulatory cells; T_{EFF}, T-effector cells; T_H, T-helper cells; MΦ, macrophage.

Alternative Therapies, Vol 21, Suppl 1; 28

Polymorphisms of Anti-oxidant Enzymes, Blood Pressure and Risk of Hypertension

Journal of Hypertension 2011;29:492

- Chronic oxidative stress and low oxidative defense create an imbalance to increase the risk for hypertension.
- Increase in pro-oxidant enzymes like NADPH oxidase and xanthine-oxidase.
- Reduction in cytoplasmic anti-oxidant systems.
- Polymorphisms for
  - CYBA for NADPH oxidase
  - Xanthine-oxidase gene
  - SOD 3 : c.172G>A
  - Catalase: c.-20C>T
  - GPx1: c.*891C>T
  - TXN (thioredoxin): c.-793T >C (NFkB, AP-1, Ref-1, SP -1) and DNA binding to transcription factors.

Genetics of Hypertension - Polygenetics

Korkor et al. International J. of Medical Sciences 2011 pending publication
J of the American Society of Hypertension 2009;3:231

- Micro-array analysis of differential gene expression in peripheral blood cell found 31 up-regulated and 18 down regulated genes.
- MHC class II receptor activity and immune response
- Increased inflammation genes and HSCRP
- Environment-genetic interactions
- System biology effects

Conclusion: Hypertension is an inflammatory, oxidative stress and autoimmune disease.

Blood Pressure Regulation and Measurement of Vascular Health and Disease during the aging process: The end of the "hypertension era"?

- Standard BP measurements are not adequate and often misleading and may not accurately reflect CV risk
- Need direct arterial measurements
- Endopat for endothelial dysfunction
- PWV and arterial compliance measurments to assess arterial stiffness: less than12 m/sec is normal PWV.
- Central and peripheral arterial waveforms including pulse wave analysis, wave reflections, augmentation index
- Central arterial pressure, pulse pressure and central to peripheral pressure amplification.
- 24 hour ABM with brachial and central BP
- Home BP

Hypertension: BP Measurements
Office vs home vs 24 hour ABM

J of Hypertension 2012;30: 1894
J of Hypertension 2012;30:1906
J of Hypertension 2012;30:1937

In order of most accurate

1. 24 hour ABM with brachial and central BP
2. Out of office automated BP measurements
3. Mercury sphygmomanometer by MD (MOBP)
4. In office automated BP measurements
   (AOBP multiple measures)
5. Aneroid sphygmomanometer by MD (MOBP)

24 Hour Ambulatory Blood Pressure Monitoring (24 hour ABPM)

J of Clinical Hypertension 2011;13(12):871
J of the Am Society of Hypertension;2014;8:939

- Recommended for routine screening of hypertension in the UK
- Superior to office and home BP monitoring to predict future CV events and target organ damage.
- Determines dipping status, nocturnal BP, white coat and masked hypertension, circadian rhythm with early AM BP surges, adequacy of BP control, load, mean, high, low and variability.
- Cost effective and reduces the number of patients needing drug therapy for hypertension by 25%.

Hypertension

Houston MC. Handbook of Hypertension. Wiley-Blackwell, Oxford UK 2009

- **Normal BP is 120/80 mmHg but risk for CVD starts at 110/70 mm Hg.**
- Increase 20/10 mm Hg doubles risk.
- BP is a continuum of risk.
- Before age 50-55 the DBP predicts risk best.
- After age 50-55 the SBP predicts risk best.
- Pulse pressure may be better predictor than SBP or DBP.
- 24 hour ABM most accurate and better predictor of CV events.
- Central arterial pressure is better than brachial office BP or ABM.
- Mercury cuffs best. Electronic arm cuffs not wrist or finger cuffs.
- Mean BP, AM surges, variability and nocturnal BP alter CV risk.
- BP load: % readings > 140/90 mm Hg should be less than 15%

Intensive BP lowering reduces CV morbidity and mortality

SPRINT (Systolic Blood Pressure Intervention Trial)

NIH September 2015

- Lowering SBP< 120 mm Hg vs 140 mm Hg in patients over age 50 significantly reduces rates of cardiovascular disease such as CHD, MI, CHF and CVA by 33 % and CV mortality by 25 %.

- 9300 patients in 100 centers in US since 2009.
- Aggressive anti-hypertensive drug therapy with 2 to 3 medications

Hypertension - New Concepts

Expert Rev Cardiovasc Ther. 2010;8:260.).

Houston MC. Handbook of Hypertension. Wiley-Blackwell, Oxford UK 2009
J of Hypertension 2011;29:2316
J of Hypertension 2011;29:2433

- Dippers (10-20% difference) vs non-dippers (0-10% difference) between the night and day BP)
- Reverse dipping (0% to +20%) increases ICH
- Excessive dipping > (20%) increases ischemic CVA
- Baroreceptor dysfunction and sensitivity
- Morning BP surges increase CVA ,SCI, MI , arrhythmias, sudden death and LVH. Increased platelet aggregation, plasma nor-epinephrine, PRA/RAAS, vWf , PAI-1, thrombosis. Decrease fibrinolytic activity
- Role of oxidative stress, inflammation, angiotensin-II, norepinephrine, MMPs) metalloproteinases causing intracranial hemorrhage (ICH)
- Pulse wave contour, augmentation index, and PWV: three types of vascular dysfunction with same SBP but with different CV risk.
- White coat hypertension increases CV risk.
- Masked hypertension (also have higher glucose and MAU): 10% incidence, M>F (J Clin Hypertension 2010;12:578.).

White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis.

J Hypertens.2015 Jan;33(1):24-32

- A total of 7382 untreated adult patients (2493 normotensive, 1705 WCH, and 3184 hypertensive individuals) included in 25 studies were considered. Left ventricular mass index was higher in WCH than in normotensive patients [standardized difference in mean (SDM) 0.50, $P<0.01$]; mitral E/A ratio was lower (SDM -0.27, $P<0.01$) and left atrium larger (SDM 0.29, $P<0.05$) in WCH than in the normotensive counterparts. Hypertensive patients showed a greater left ventricular mass index (SDM 0.42, $P<0.01$), reduced E/A (SDM -0.15, $P<0.01$), and larger left atrium diameter (SDM 0.27, $P<0.01$) than WCH patients.
- **CONCLUSIONS:** alterations in cardiac structure and function in WCH patients, as defined by ambulatory blood pressure monitoring, are intermediate between sustained hypertensive patients and normotensive controls. The study supports the view that WCH should not be further considered a fully benign entity

White-coat hypertension is a risk factor for cardiovascular diseases and total mortality

J Hypertens.2017 Apr;35(4):677-688.

- Evaluated the association of WCH and the risk of cardiovascular diseases (CVDs) and mortality, stratified by baseline antihypertensive treatment status. The relative risks of events compared with normotension were calculated.

- A total of 23 cohorts (20445 individuals), 11 cohorts (8656 individuals), and 12 cohorts (21336 individuals) were included for analysis of cardiovascular risk associated with WCH in patients without baseline antihypertensive treatment (untreated), or under antihypertensive treatment (treated) or mixed population (including both untreated and treated patients), respectively.

- In untreated cohorts, WCH was associated with a 38 and 20% increased risk of CVD and total mortality compared with normotension, respectively.

- In the mixed population, WCH was associated with a 19 and 50% increased risk of CVD and total mortality.

- In the treated patients, neither the risk of CVD, nor total mortality was increased in WCH. Meta-regression analyses indicated that neither differences of clinic blood pressure, nor out-of-office blood pressure variables were correlated with risk of CVD in WCH.

- **CONCLUSION: WCH is associated with long-term risk of CVD and total mortality in patients without antihypertensive treatment.**

Hypertension BP- New Concepts
Sleep BP and Nocturnal Dipping

Expert Rev Cardiovasc Ther 2010;8:803 and 8: 781.
Blood Pressure 2010;19:267

- Non-dipping does not allow for renal sodium excretion.
- Non-dipping is highly correlated with CHD, CVD, CVA, LVH, CHF, CRF, increased carotid IMT, multifocal leukoencephalopathy (MFLE), and silent cerebral infarctions (SCI).
- Non-dipping most common in
  - Sodium sensitive patients and African-Americans
  - Renal insufficiency
  - Secondary forms of hypertension
  - Diabetes mellitus
  - Loss of cerebral volume / cognitive impairment
  - LVH (left ventricular hypertrophy)
  - Refractory hypertension
  - OSA (obstructive sleep apnea)
  - Autonomic nervous system dysfunction

HYPERTENSION: Blood Pressure New Concepts :Sleep BP

Expert Rev Cardiovasc Ther 2010;8:803
Arch Int Med 2011;171:1090
J of the Am Society of Hypertension;2014;8:939
J of Hypertension 2015;3:2257

- Awake BP controlled by SNS
- Asleep BP controlled by RAAS and SNS
- Lower BP at sleep is more powerful predictor of outcome that awake BP
- Normal sleep BP is 108/63 and wake BP is 135/78 mm Hg in normotensives (27/15 mm)
- The absolute nocturnal BP rather than dipping status is superior early marker of CV risk.
- Most drugs may partially convert non-dippers to dippers if given at night.
- RAAS drugs work best at night.
- Lack of BP dipping related to renal sodium reabsorption. These respond to diuretics
- Drugs with dual action on SNS and RAAS control awake and sleep BP

Nocturnal Blood Pressure and Nocturnal Hypertension

Blood Pressure 2012;20:335;JCH 2012;14:787
Blood Pressure 2011;20:335;Hypertension 2011;57:3
J of Hypertension 2014;32:2005 and 1999
J of the Am Society of Hypertension;2014;8:939; J of Hypertension 2015;33:1939
J of Hypertension 2017;35:50;J of Hypertension 2017;35:442
J of Hypertension 2017;3:558

- Nocturnal Hypertension is defined as night time BP over 120/70 mm Hg.
- Nocturnal hypertension is more common than non dipping and occurs in about 70% of hypertensive patients
- Associated with more TOD independent of dipping or non-dipping status. Total mortality increases 29%, and all CV events by 38%
- Impaired sleep quality and autonomic functioning
- Nocturnal BP rather than circadian BP, Mean BP or daytime BP is more important in predicting CV morbidity and mortality, CVA and CKD related to BP.

Nocturnal Blood Pressure

Chronobiol Int 2010;27:1629;J Am Coll Cardiol 2011;58:1165

- 2156 hypertensives in MAPEC study 24 hour ABM
- Bedtime administration of all BP medications
- The bedtime administration of BP meds had a lower mean sleep-time BP, higher sleep-time relative BP decline, reduced prevalence of non-dipping (34 vs 62% , p <0.001) and higher prevalence of controlled ambulatory BP (62 vs 53%, p<0.001)
- 5.6 year follow-up : lower risk of total CVD events of 0.39 (61% decrease):CVD death, MI, CVA (p<0.001)
- 17 % reduction in CV risk for each 5 mm Hg decrease in sleep SBP (p< 0.001).
- ACEI, ARB, CCB, Nebivolol best for nocturnal BP treatment

Comparative Effects of an Angiotensin II Receptor Blocker (ARB)/Diuretic vs. ARB/Calcium-Channel Blocker Combination on Uncontrolled Nocturnal Hypertension Evaluated by Information and Communication Technology-Based Nocturnal Home Blood Pressure Monitoring - The NOCTURNE Study.

Circ J.2017 Mar 17. doi: 10.1253/circj.CJ-17-0109. [Epub ahe ad of print]

- Nocturnal blood pressure (BP) is an independent risk factor of cardiovascular events. The NOCTURNE study, a multicenter, RCT using communication technology (ICT) nocturnal home BP monitoring (HBPM) device used to compare the nocturnal HBP-lowering effects of differential ARB-based combination therapies in 411 Japanese patients with nocturnal hypertension (HT)

- Patients with nocturnal BP ≥120/70 mmHg at baseline even under ARB therapy (100 mg irbesartan daily) The ARB/CCB combination therapy (irbesartan 100 mg+amlodipine 5 mg) achieved a significantly greater reduction in nocturnal home systolic BP (primary endpoint) than the ARB/diuretic combination (daily irbesartan 100 mg+trichlormethiazide 1 mg) (-14.4 vs. -10.5 mmHg, $P<0.0001$), independently of urinary sodium excretion and/or nocturnal BP dipping status.

- This is the first RCT demonstrating the feasibility of clinical assessment of nocturnal BP by ICT-nocturnal HBPM.

- The ARB/CCB combination was shown to be superior to ARB/diuretic in patients with uncontrolled nocturnal HT independently of sodium intake, despite the similar impact of the 2 combinations in patients with higher salt sensitivity

Reductions in morning BP surges (MBPS)
JASH 2012;6:66

- Role of nocturnal dosing of BP medications
- Best agents to reduce MBPS
  - ACEI
  - ARB
  - CCB
  - Nebivolol
- Agents that do not control nocturnal hypertension
  - Older non-vasodilator beta blockers
  - Thiazide and thiazide –like diuretics

Circadian BP rhythm and A-II

Therapeutic Advances in Cardiovascular Disease 2012;6:15-29

- Angiotensin II alters the circadian BP rhythm which changes it to a non dipping status and higher nocturnal BP.
- This increases CV risk
- Blockade of the RAAS improves the circadian BP rhythm, improves dipping and lowers nocturnal BP.
- Reductions in both CNS and renal A-II account for this change with decreases in the renal content of A-II that modulate renal afferent traffic activity to the brainstem and hypothalamic circuits which regulate the activity of the circadian blood pressure rhythm.

Circadian Regulation of Renal Function and Hypertension

Curr Opin Nephrol Hypertens;2013;22:439-444

- Renal regulation of sodium and water absorption and aldosterone secretion regulate BP and dipping status.
- Renal mRNA transcripts regulated by circadian clock genes and CNS central pacemaker via SCN (supra-chiasmatic nucleus).
- Implications for nocturnal medication administration for better BP control, improved dipping status and reduction in CV events by 61%
- Improved 24 hour ABM lower by 1.71/1.38 mm Hg with nocturnal medication dosing.

Circadian regulation of renal function and potential role in hypertension.

Current Opinion in Nepthrol and Hypertension. 2013 Jul;22(4):439-44.

- Dysregulation of circadian rhythms can interfere with kidney function.
- Molecular mechanisms are responsible for generating and maintaining circadian rhythms- the circadian clock, drives circadian oscillation in expression levels of a large number of renal mRNA transcripts.
- Several proteins critically involved in renal homeostatic functions have been shown to exhibit significant circadian oscillation in their expression levels or in their posttranslational modifications.
- Disruption of circadian clock activity results in dramatic changes in the circadian pattern of urinary sodium and potassium excretion and causes significant changes in arterial blood pressure.
- Dysregulation of circadian rhythms causes hypertension, progression of chronic kidney disease and cardiovascular disease in humans.
- **SUMMARY:** Major role of circadian rhythms in renal function and in control of blood pressure and thus timing of drug administration. Chronotherapy studies have shown that the efficacy of antihypertensive medication is greatly dependent on the circadian time of drug administration.

Masked tachycardia. A predictor of adverse outcome in hypertension

J Hypertens. 2017 Mar;35(3):487-492

- The relative role of office heart rate (HR) and ambulatory HR for predicting major adverse cardiovascular events (MACEs) and mortality is not well known.
- We performed 24-h ambulatory blood pressure and HR monitoring in 7602 hypertensive patients (4165 men) aged 52±16 years enrolled in six prospective studies in Italy, Japan, and Australia. Participants were divided into four groups: normal office and normal night-time HRs (N=5238), white-coat tachycardia (N=998), masked tachycardia (N=796), and sustained tachycardia (N=570). Median follow-up was 5.0 years.

RESULTS

- White-coat tachycardia was not a significant predictor of excess MACEs or all-cause death.
- In contrast, both masked tachycardia [hazard ratio, 95% confidence interval (CI); 1.40, 1.11-1.77] and sustained tachycardia (1.86, 1.44-2.40) were associated with risk of excess MACE.
- In addition, masked tachycardia (hazard ratio, 95% CI; 1.62, 1.14-2.29) but not sustained tachycardia (1.35, 0.83-2.19) was a significant predictor of excess mortality.
- Masked tachycardia remained an independent predictor of excess MACE (hazard ratio, 95% CI; 1.34, 1.06-1.71) and all-cause mortality (1.68, 1.18-2.41).

CONCLUSION: The current study confirms that measurement of HR adds to the risk stratification for MACE and mortality and shows that an elevated night-time HR confers an increased mortality risk to hypertensive patients who have normal office HR.

Central Blood Pressure (CBP)

Expert Rev Cardiovasc Ther 2010;8:763
Circulation 2006;113:1213 (CAFÉ Trial)
J of Hypertension 2010;28:237
Journal of Hypertension 2011;29:454

- CBP is the ascending aortic BP, exerted on heart and brain.
- More predictive of CVD, CVD mortality, all cause mortality, and LVH than brachial BP.
- CAFÉ study indicated that CVD outcome related to CBP better than brachial pressure and CVD. The CBP is different depending on the anti-hypertensive drug class. Older BB and diuretics like HCTZ lower brachial BP but SBP is 4.3 mm Hg higher and central aortic pulse pressure was 3.0 mm Hg higher, due to pulse wave augmentation. Range in studies is 3.3 to 4.3 mm Hg.
- **CBP reduced by CCB, ACEI, and ARB.**
- **CBP is increased or unchanged by older BB and some diuretics like HCTZ.**

Central BP Measurements

J of Clinical Hypertension 2012;14:575
J of Hypertension 2012; 30:1743

- High correlation of central BP with invasive elective cardiac angiogram and several noninvasive devices on the market within one mm Hg BP.
- SphygmoCOR (Atcor Medical Sydney, NSW Australia)
- BPro device (A-Pulse, Healthstats, Singapore) 24 hour CBP
- Pulse Cor R6.5
- Mobile 0 graph: 24hr brachial and central BP with PWV and AI.

Central aortic pressure not brachial BP enhances the ability to identify CV target organ damage in normotensive patients

J of Hypertension 2013;31:1124

- 1169 patients with normal or prehypertension
- BP 120-139/80-89 mm Hg
- Applanation tonometry with SphygmoCor
- Identifies target organ damage better than brachial BP including and is associated with:
- Increased PWV
- Increased LVMI
- Decreased eGFR.

Blood Pressure Regulation During the Aging Process

The End of the "Hypertension Era"?

- Standard BP measurements are not adequate and often misleading and may not accurately reflect CV risk.
- Need direct arterial measurements with noninvasive technology
- ENDOPAT to measure endothelial dysfunction, augmentation (AI)and heart rate variability (HRV)
- PWV and CAPWA to assess small artery compliance, small vessel vascular remodeling and large arterial compliance. PWV less than 12 m/s is normal
- Central and peripheral arterial waveforms including pulse wave analysis, wave reflections and augmentation index.
- Central arterial pressure, pulse pressure, and central to peripheral pressure amplification
- 24 hour ABM for both brachial and central BP.
- Home BP
- Improved techniques for in office BP measurements.

Plasma Renin Activity (PRA)

J of Hypertension 2011;29:2226
NEJM 1993;329:616
Am Heart J 2011;162:585-96

- High PRA is associated with greater risk of:
  - Myocardial infarction and ischemic heart disease
  - Stroke
  - Congestive heart failure
  - Chronic kidney disease
  - Total cardiovascular disease and mortality
  - Total mortality

Selection of Anti-hypertensive Treatment Based on BP Stratification Using Renin Profiling with PRA and Aldosterone levels

N Engl J Med 1972;286:441-449
Am Heart J 2011;162:585

- 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

PRA and Aldosterone

J of Hypertension 2011;29:2226
NEJM 1993;329:616
Am Heart J 2011;162:585-96

ARR: Aldosterone renin ratio

- ARR over 80 is LRH
- ARR over 40 is probably LRH

- ARR less than 10 is HRH
- ARR between 10 and 40 : not sure

Measurement of PRA and Serum Aldosterone

- 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 of PRA and aldosterone will be altered by concomitant anti-hypertensive medications, which requires more sophisticated interpretation.

Selection of Anti-hypertensive Tx Based on BP Stratification Using Renin Profiling PRA – Laragh Method

N Engl J Med 1972;286:441-449 Am Heart J 2011;162:585

Treatment Selection

- **Low Renin Hypertension (LRH):** Volume drugs and Nutraceuticals: Calcium channel blockers (CCB), diuretics, serum aldosterone receptor antagonists like spironolactone and eplerenone (SARA), alpha blockers, amiloride and triamterine.
- **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)

PRA (plasma renin activity) the Renin to Aldosterone ratio (RAR) correlates with night time BP, 24 hour ABM and pulse pressure in patients treated with ACEI and ARB.

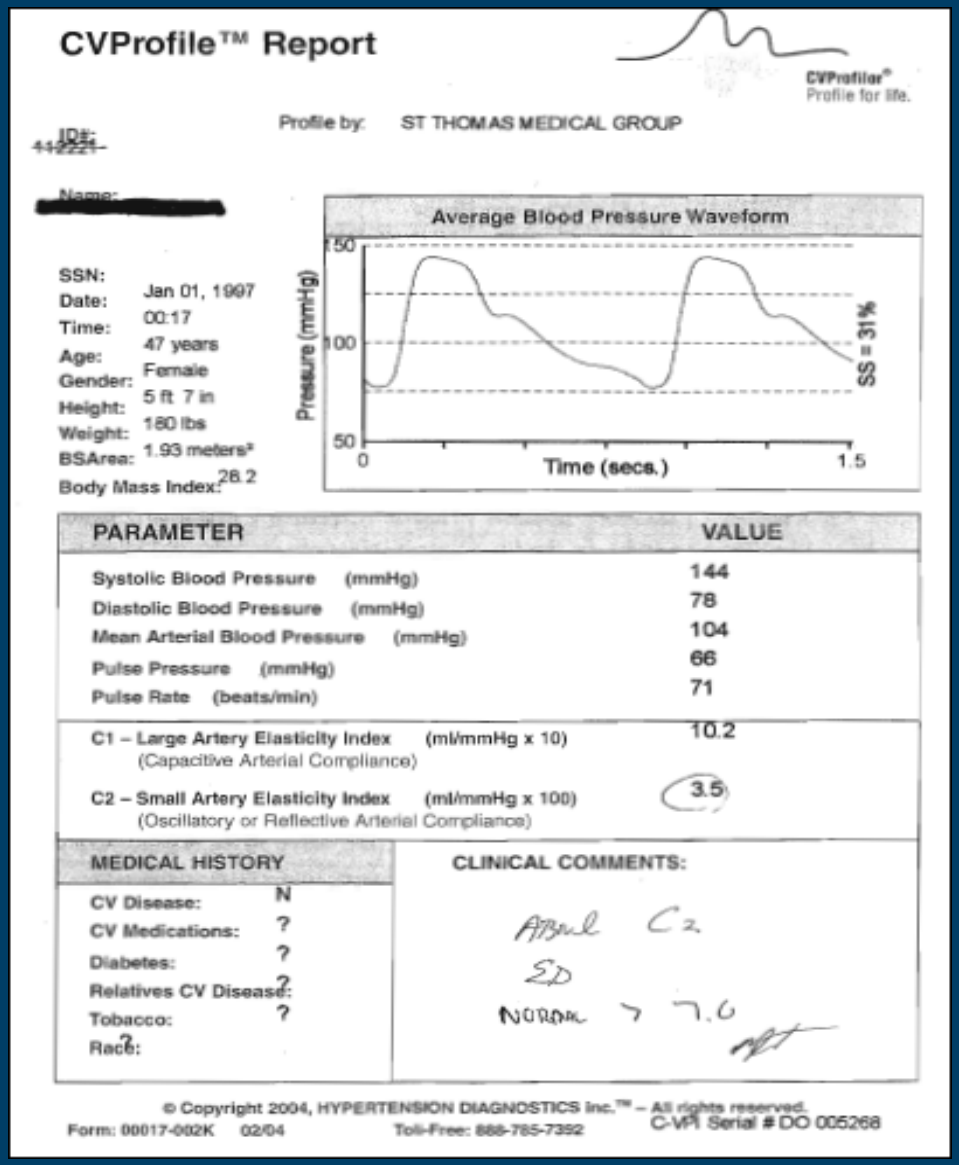
J of Hypertension 2017;35:2315

- Higher the RAR values indicate effective renin-angiotensin- aldosterone system (RAAS) inhibition with lower night time BP and lower pulse pressures in patients that are treated with an ACEI or ARB.
- The reduction in nocturnal BP, 24 hour ABM and PP were best in the highest tertile of RAR compared to the lowest tertile with nocturnal SBP 13 mm Hg lower.

Nutrient Testing and Hypertension

- Determine nutrient deficiencies that contribute to the hypertension and vascular disease.
- Intracellular micronutrient testing (MNT) is recommended
- Replace nutrient deficiencies and re-evaluate at 3 months.
- Initiate therapeutic nutritional program.
- Initiate therapeutic nutritional supplement program with vitamins, antioxidants, minerals and nutraceutical supplements. May take 3 to 6 months to achieve maximal effect compared to drug therapy, but long-term BP reductions may be very similar.

Computerized Arterial Pulse Wave Analysis CV Profile Report



CVProfile™ Report

CVProfiler®
Profile for life.

Profile by: ST THOMAS MEDICAL GROUP

ID#: [redacted]

Name: [redacted]

SSN:
Date: Jan 01, 1997
Time: 00:17
Age: 47 years
Gender: Female
Height: 5 ft 7 in
Weight: 160 lbs
BSArea: 1.93 meters²
Body Mass Index: 28.2

Average Blood Pressure Waveform

Pressure (mmHg) 150 100 50
0 Time (secs.) 1.5
SS = 31%

PARAMETER		VALUE
Systolic Blood Pressure	(mmHg)	144
Diastolic Blood Pressure	(mmHg)	78
Mean Arterial Blood Pressure	(mmHg)	104
Pulse Pressure	(mmHg)	66
Pulse Rate	(beats/min)	71
C1 – Large Artery Elasticity Index (Capacitive Arterial Compliance)	(ml/mmHg x 10)	10.2
C2 – Small Artery Elasticity Index (Oscillatory or Reflective Arterial Compliance)	(ml/mmHg x 100)	3.5

MEDICAL HISTORY	
CV Disease:	N
CV Medications:	?
Diabetes:	?
Relatives CV Disease:	?
Tobacco:	?
Race:	?

CLINICAL COMMENTS:

Abnl C2
SD
Normal > 7.6

Form: 00017-002K 02/04 Toll-Free: 888-785-7392 C-VP1 Serial # DO 005268

Arterial Elasticity

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 [ ] Elasticity Index Range			C2 – Small Artery [ ] 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

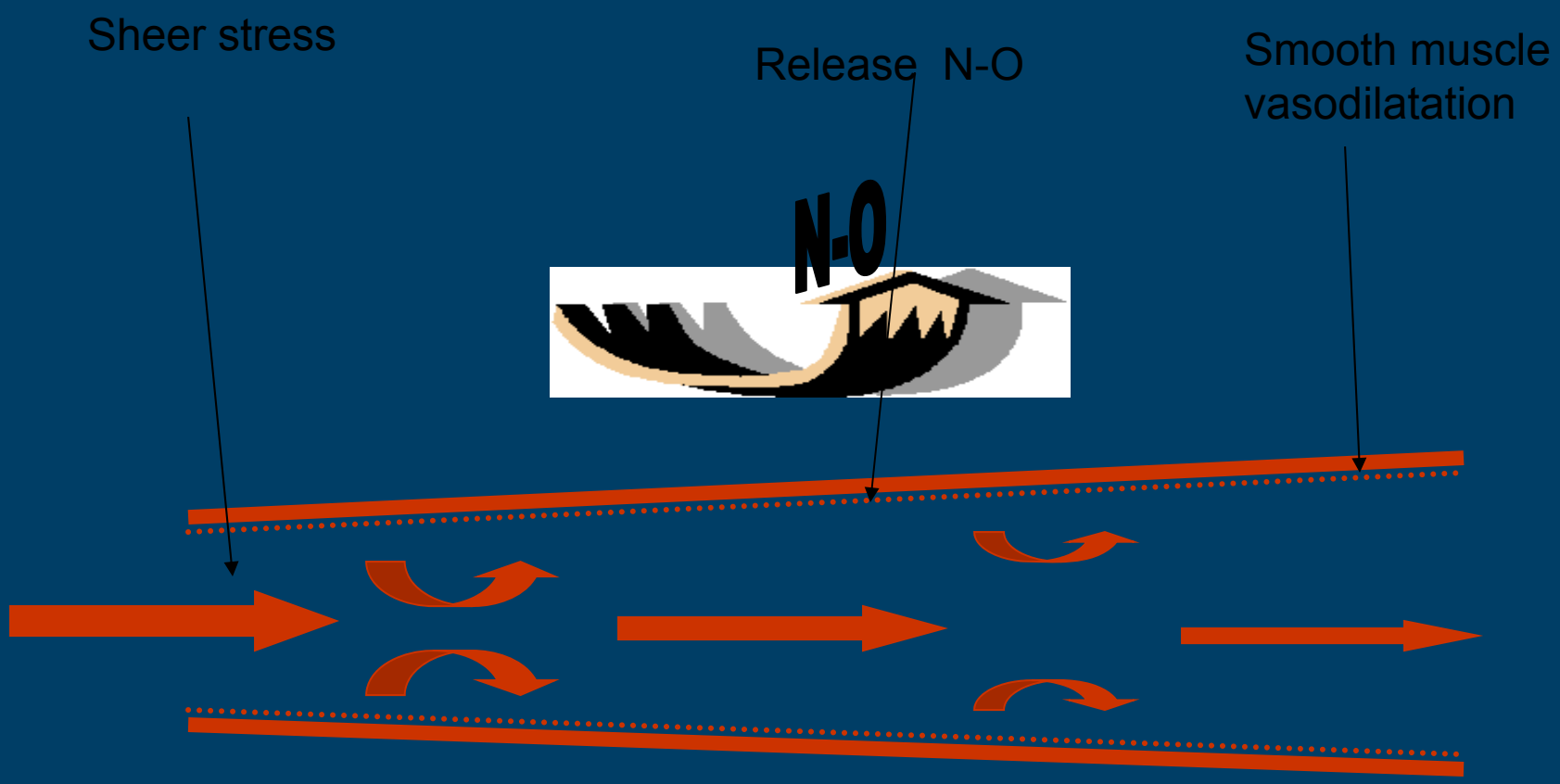
FEMALE	C1 – Large Artery [ ] Elasticity Index Range			C2 – Small Artery [ ] Elasticity Index Range		
Age Range	Abnormal	Borderline	Normal	Abnormal	Borderline	Normal
15 - 19	< 9	9 – 15	> 15	< 6	6 – 8	> 8
20 - 29	< 8	8 – 14	> 14	< 5	5 – 7	> 7
30 - 39	< 7	7 – 12	> 12	< 4	4 – 6	> 6
40 - 49	< 6	6 – 10	> 10	< 4	4 – 6	> 6
50 - 59	< 5	5 – 10	> 10	< 3	3 – 5	> 5
60 - 69	< 4	4 – 9	> 9	< 3	3 – 5	> 5
> 70	< 4	4 – 8	> 8	< 2	2 – 4	> 4

Endothelial Function: ENDO-PAT: ED, Hypertension and CVD

JACC 2010;55:1688
JACC 2004;44:2137
Circulation 2008;117:2467

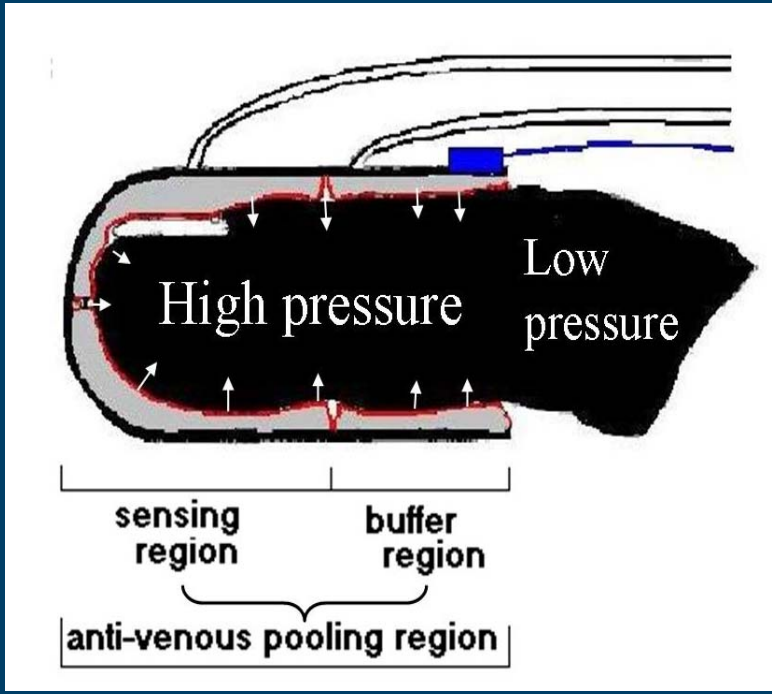
- Measures reactive hyperemia and ED. FDA approved. About $25,000
- 5 minute occlusion of brachial artery with BP cuff
- Digital measurement for ED-FMD as increase in signal amplitude
- Measure pre and post occlusion ratio index
- Index of 1.67 has sensitivity of 82% and specificity of 77% to diagnose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

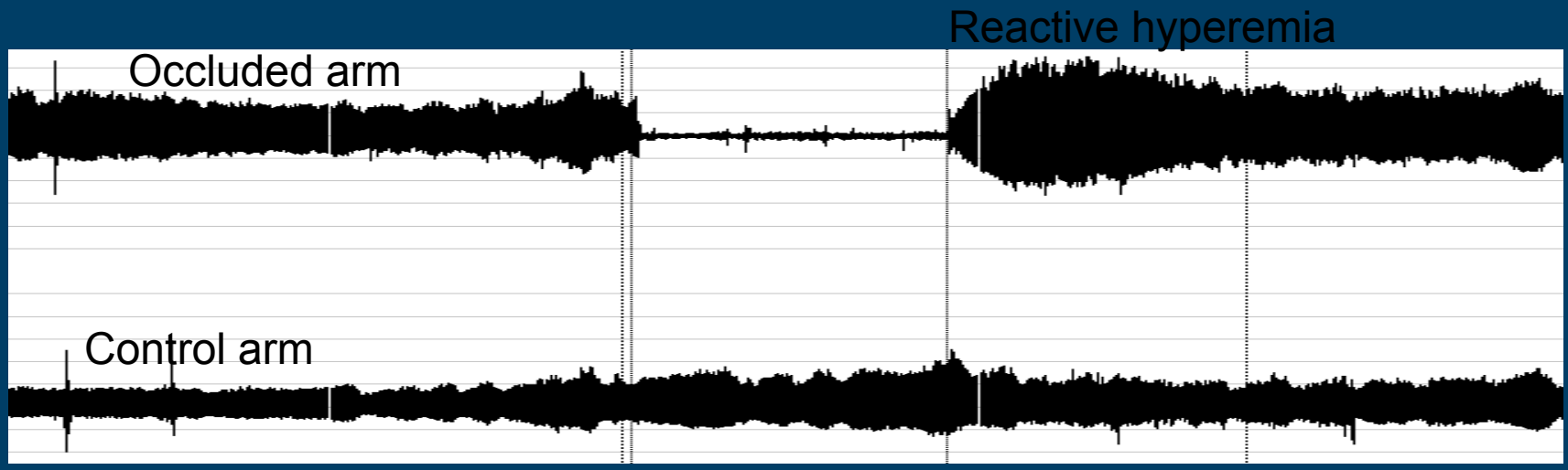
Physiology of Endothelium-Mediated Vasodilation



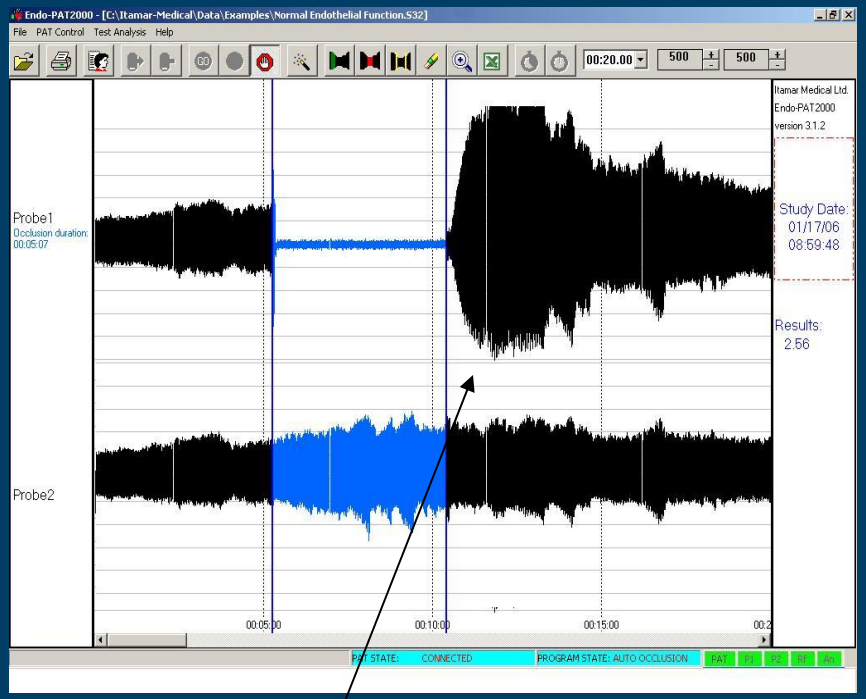
PAT Bio-sensor - unique design
Applies uniform pressure to entire finger surface

- Prevents venous blood pooling
  - Eliminates veno-arteriolar constrictor reflex
- Clamps probe to finger
  - Reduces noise
- Buffers measuring site
  - Buffers noisy venous waves
- Unloads arterial wall tension
  - Increases dynamic volume range

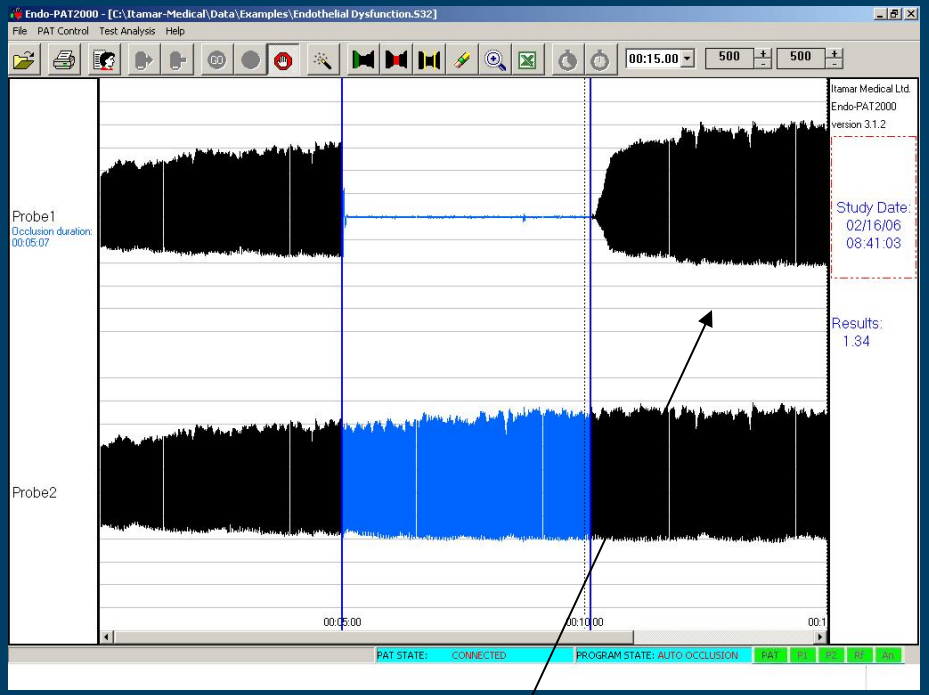



Reactive hyperemia
Occluded arm
Control arm

ENDOPAT Good and poor results



Normal EF



Poor EDF

St. Thomas Medical Group
4230 Harding Road
Nashville, TN 37205

Endo-PAT2000

Test Date: 06/03/13 07:41:07

Patient Information

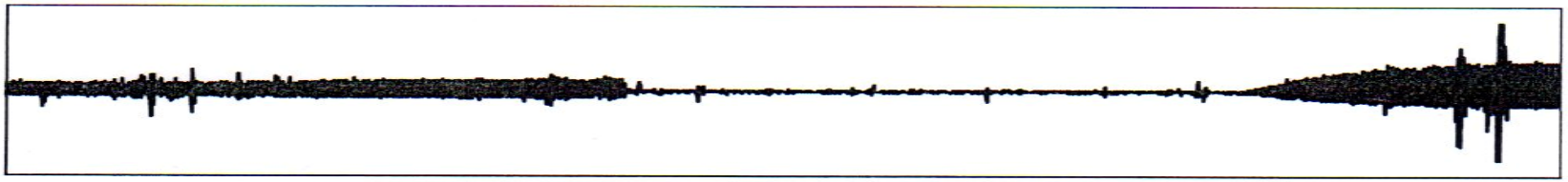
ID:	[redacted] mch 2	Name:	[redacted]	Systolic BP	130 mm Hg
Age:	75	Gender:	Female	Diastolic BP:	76 mm Hg
Height:	5' 3"	Weight:	140 lb	BMI:	24.8
User Field 1:		User Field 2:			
Comments:					

Study Information

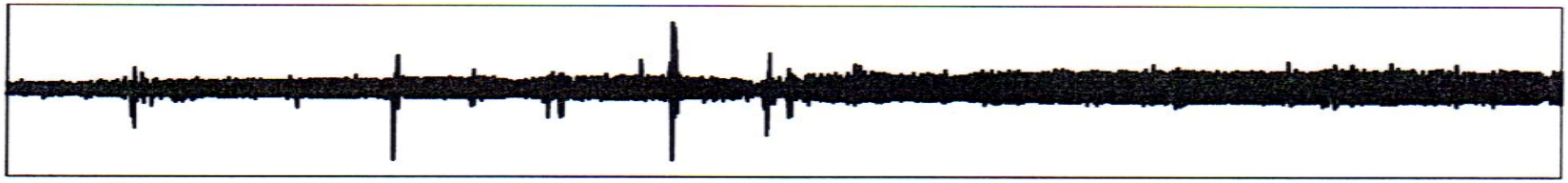
Test Duration:	00:14:20	PATographer:	NK		
Recording Ver:	3.4.4	Analysis Ver:	3.4.4	Occ. Borders:	Automated

PAT Signals

Occluded Arm



Control Arm



Baseline(05:43) Occlusion(05:35) Dilatation(03:02)

Study Results

RHI: 1.58 Endothelial Dysfunction

Heart Rate: 50 bpm

Recommendations

Physician's Name: _____ Signature: _____

St. Thomas Medical Group
4230 Harding Road
Nashville, TN 37205

Endo-PAT2000

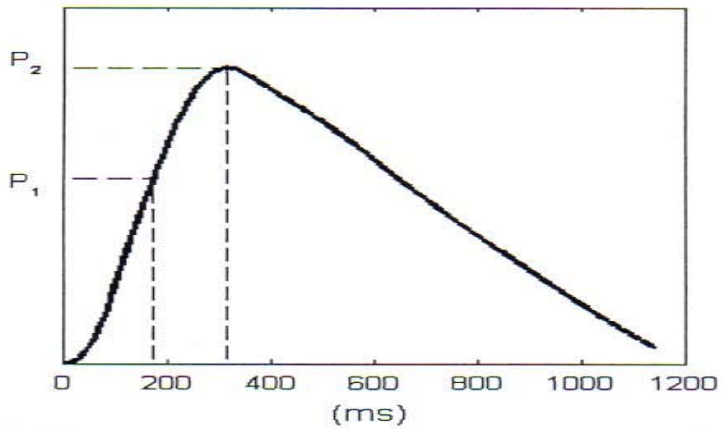
Test Date: 06/03/13 07:41:07

Augmentation Index (AI) - a measure of Arterial Stiffeness

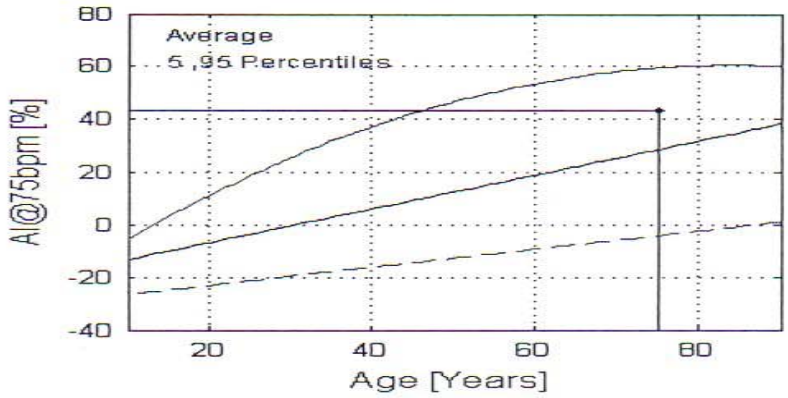
AI: 59%
AI@75bpm: 44%
AI = (P2-P1)/P1 x 100 [%]

Averaged - 123 pulses

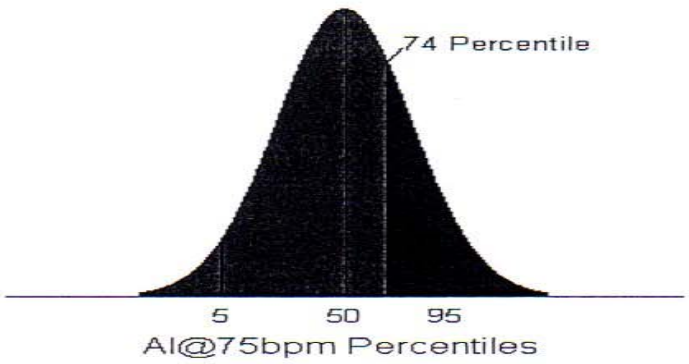
Average PAT Waveform (from baseline segment)



AI@75bpm in female population as function of age



Patient Relative to Age and Gender matched distribution



St. Thomas Medical Group
4230 Harding Road
Nashville, TN 37205

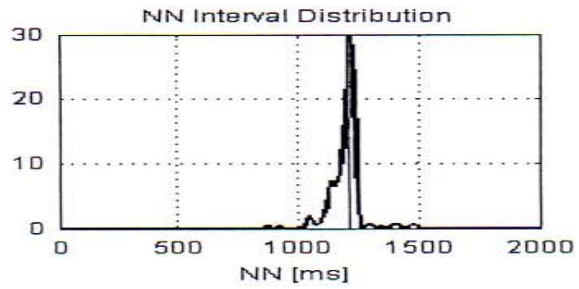
Endo-PAT2000

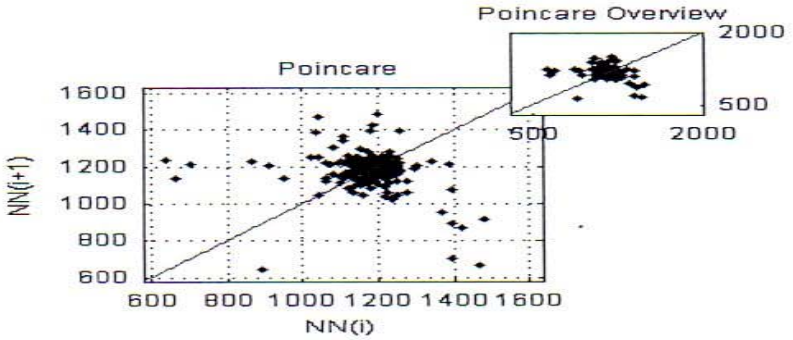
Test Date: 06/03/13 07:41:07

Heart Rate Variability (HRV)

Time Domain

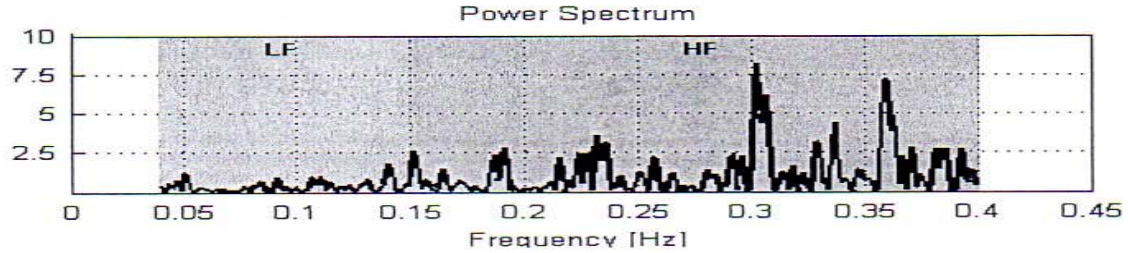
Mean NN:	1196	ms
SDNN:	63.59	ms
RMSSD:	95.00	ms
NN50:	35	
pNN50:	14.58	%
Triangular Index:	8.13	





Frequency Domain

LF (0.04-0.15 Hz):	36.83	ms^2
HF (0.15-0.4 Hz):	279.11	ms^2
LF/HF:	0.13	



ENDOPAT

J Am Coll Cardiol 2004;44:2137– 41

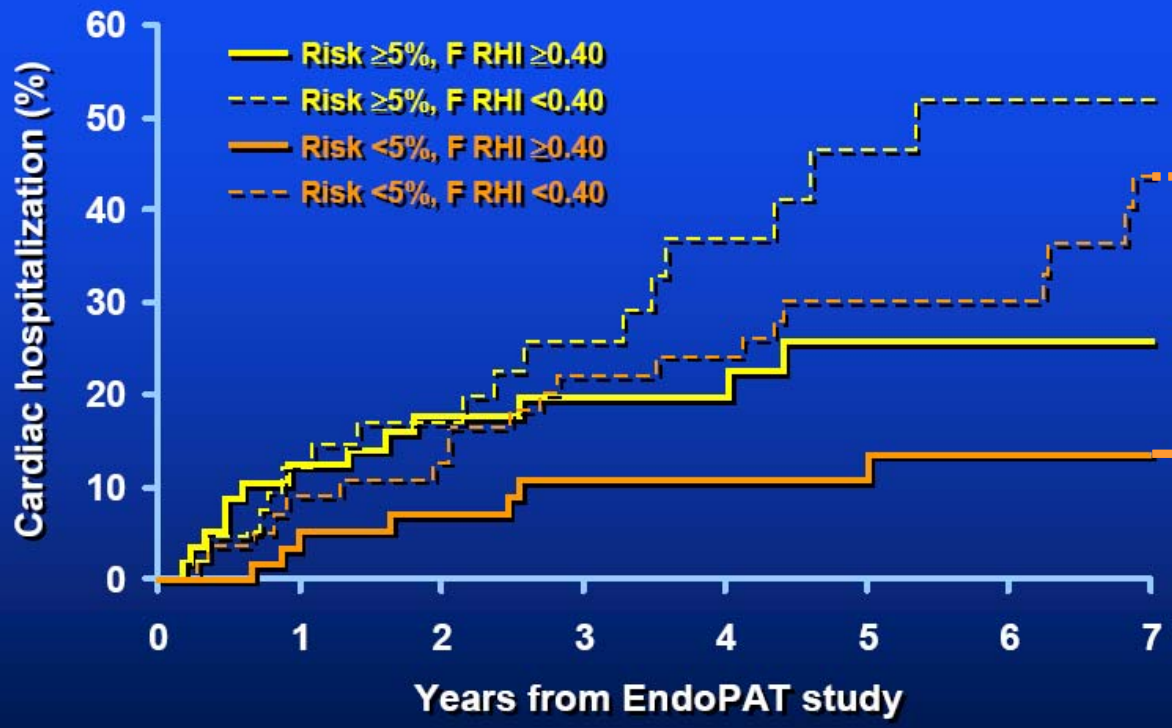
- Study designed to assess EndoPAT RHI v. Coronary Endothelial Function.
- 94 Patients without angiographic CAD
- All underwent Coronary Endothelial Function Testing with Acetylcholine.
- 39 were Normal (CBF increased by 50% or more after Ach infusion).
- 55 were Abnormal.
- EndoPAT RHI Measured in all Patients. Average RHI was 1.27 in Patients with Coronary Endothelial Dysfunction and 1.78 in those without Coronary ED.
- Conclusion: EndoPAT RHI score correlated well with coronary endothelial function testing and is therefore a valid predictive model for subsequent CVD events.

ENDOPAT AND FRAMINGHAM RISK SCORE AND CHD RISK

European J Cardiol 2010;31:1142

EndoPAT vs. Framingham Risk Score

Mayo Clinic, 2010



~300%

Low risk but <u>with</u> endothelial dysfunction

Low risk & <u>normal</u> endothelial function

n=270, Intermediate risk patients
Mayo Clinic & Tufts Medical Center

All CV Deaths were in Patients with Endothelial Dysfunction

MAYO CLINIC

ENDO-PAT AND CVD OUTCOMES

Eur Heart J 2010 ;31:1142
Am J Cardiol 2012;109:1711

- 270 patients over 7 years : ED and Framingham risk score
- Abnormal Index predicted cardiac events such as cardiac death, MI cardiac hospitalization and CABG: 48% vs 28% (p=0.03). This was independent of Framingham risk score.
- Also correlates with risk factors
- The more severe the CVD the worse the index
- Lower EP scores with ED correlate with IVUS of Coronary Arteries with more necrotic core, more calcium and higher risk of plaque rupture. (AJC)

Associations of Endopat and IVUS assessed coronary plaque morphology in CHD

Am J Cardiology 2012;109:1711

- An abnormal reactive hyperemia (ED) by Endopat is associated with plaque structure that is more prone to rupture as measured by IVUS.
- More necrotic core
- More dense calcium
- Less fibrous tissue

Endopat

1. Vasc Med 2012;17(2):79-84
2. Am Heart J 2003;146:168
3. Vasc Med 2007;12:13-16
4.J of Hypertension 2013;31:1570-74

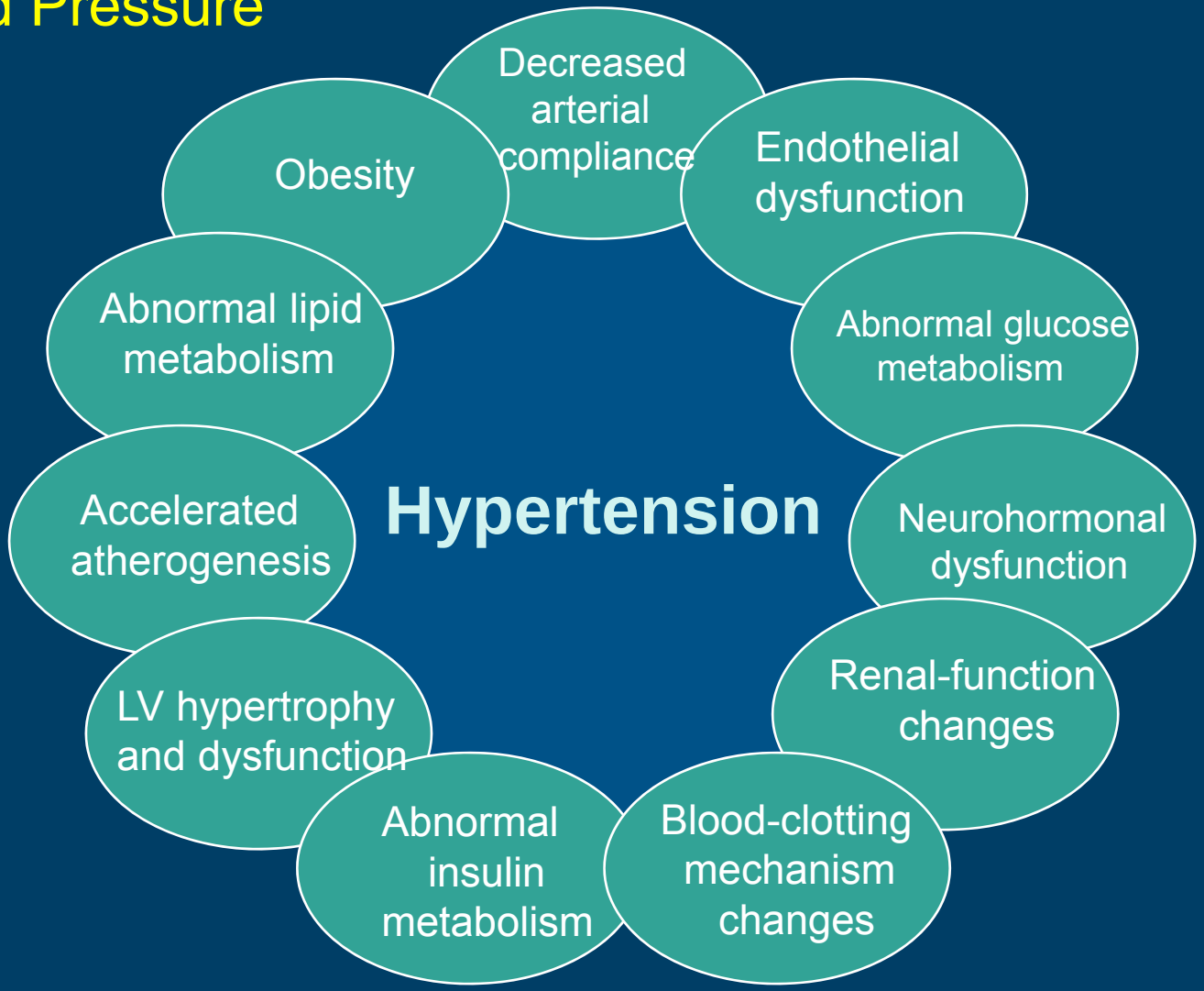
- In patients with CHD, FMD and PAT have high correlation (p< 0.001) and reproducibility on same day (18%) and between day (11%). Need 2 hours between tests to allow for endothelial recovery. (1)
- PWA, FMD and PAT have high correlations to assess vascular endothelial function. (2)
- PAT correlates with FMD and extent of CHD and presence or absence of CHD. (3)
- PAT, FMD and EDV (acetylcholine)) all correlate with each other and with endothelial function. (4)

Endothelial Dysfunction predicts CVD

J of Hypertension 2014;32:2393

- 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 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.

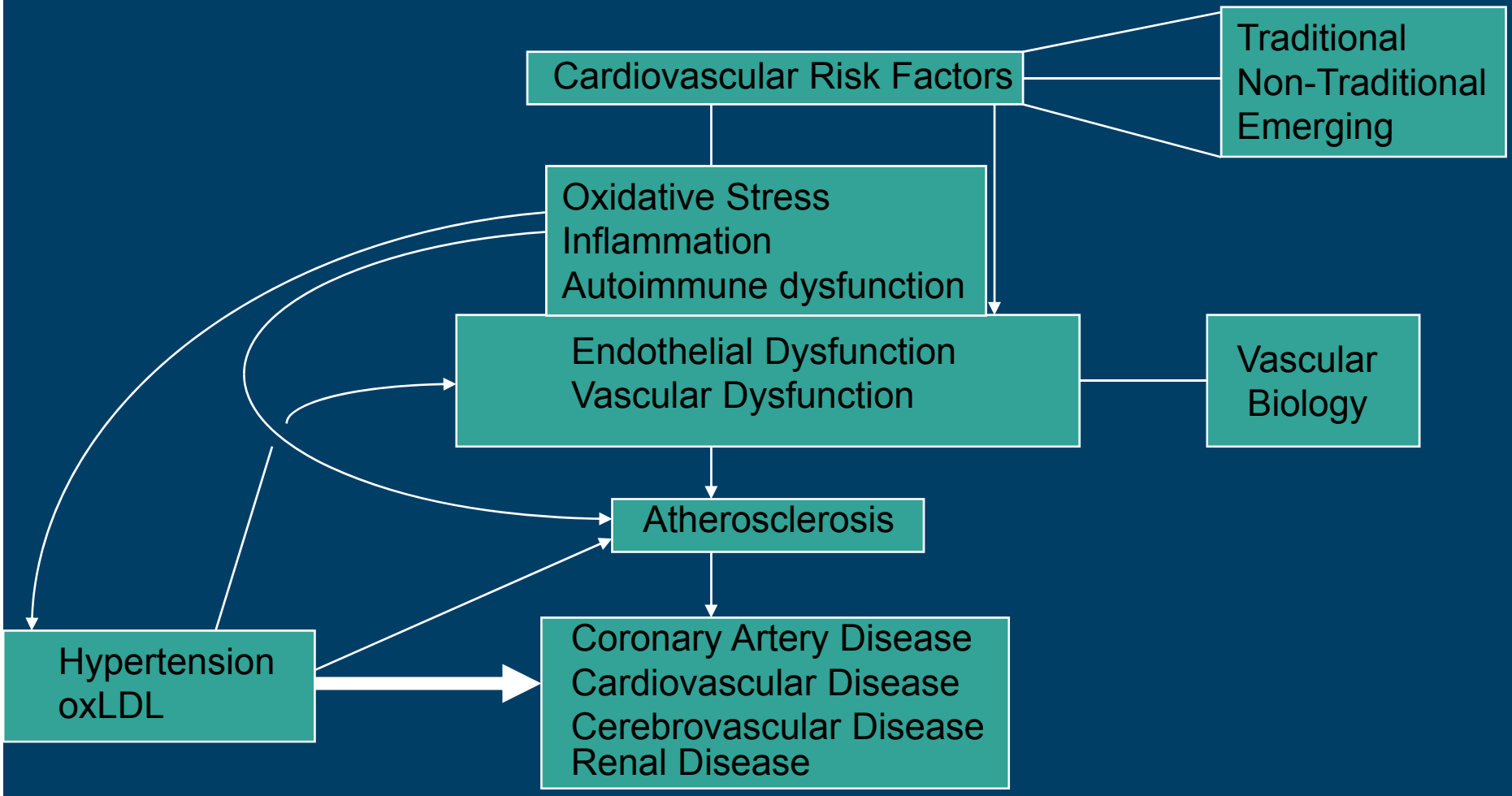
The Hypertension Syndrome - It's More Than Just Blood Pressure



Kannel WB. JAMA 1996; 275:1571-1576.
Weber MA et al. J Hum Hypertens 1991; 5:417-423. Dzau VJ et al. J Cardiovasc Pharmacol 1993; 21 (suppl 1):S1-S5

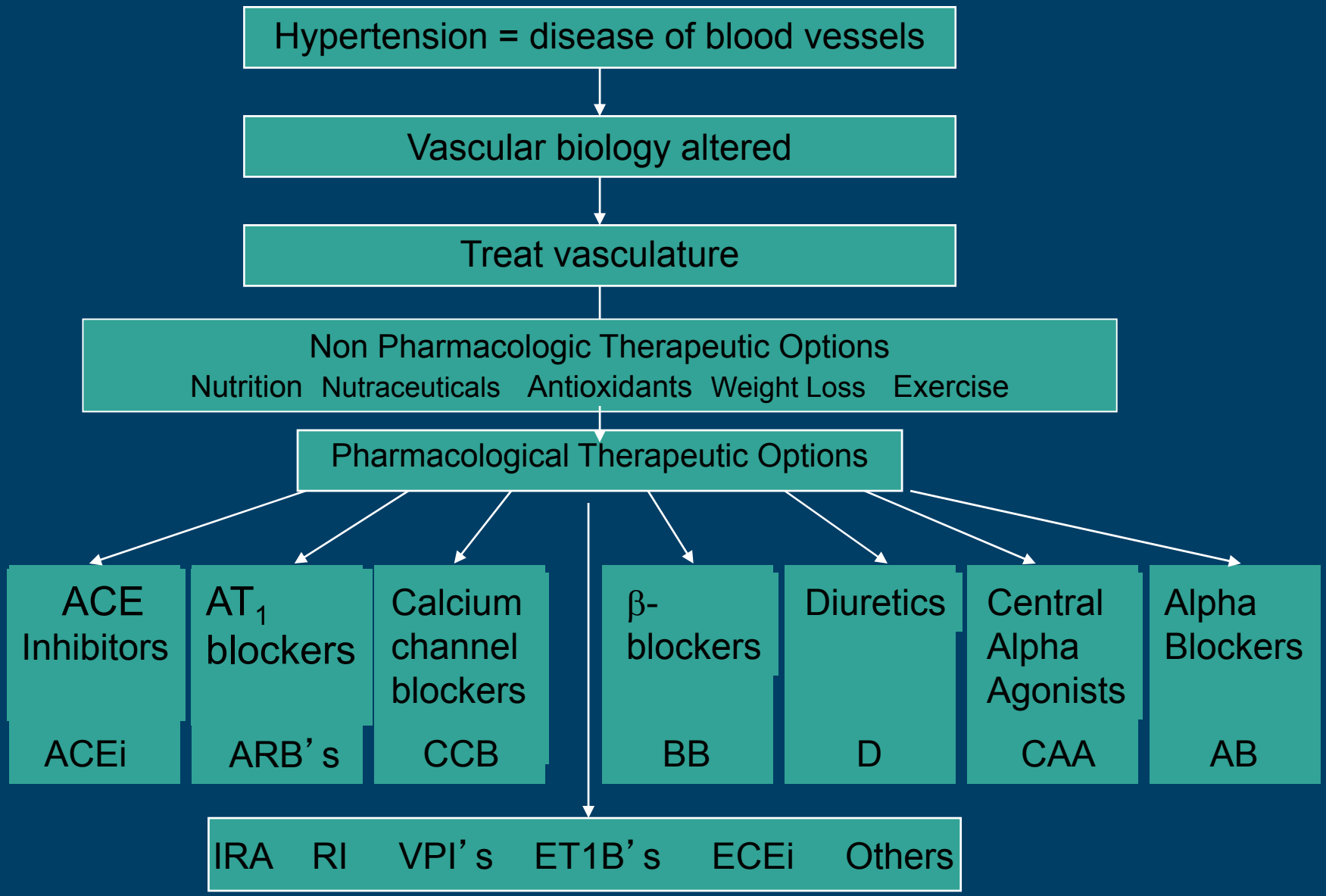
Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD

Key Concept in Risk Factors Hypertension, Vascular Biology, Finite Vascular Responses and CVD



Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD

New Treatment Approach



Vascular Biology in Clinical Practice, Oct. 2000; Mark C. Houston, MD

Weight Loss & Blood Pressure

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

- One of the most effective means to reduce BP – observational and clinical trials show positive direct relationship.
- Visceral obesity most important. Body fat reduction more important than weight reduction.
- Additive to other nonpharmacologic and pharmacologic treatment
- More effective in BP reduction when combined with exercise
- Reduces BP before and without achieving IBW
- Reduces adipokines, which increase BP and inflammation
- Role of hyperinsulinemia, insulin resistance, ↑ IVF, ↑ SNS activity, ↑ SVR, Na+ retention, PRA, Aldosterone, sleep apnea, adipokines, inflammation (hs-CRP).

Sarcopenic Obesity is an independent risk factor for hypertension and metabolic syndrome

JASH 2013;7:420
Nutrition Research 2015: 35:1070-78

- For Hypertension
- Low LMM increases BP and arterial stiffness
- BP 12/5 mm higher in sarcopenic patients compared to normals
- Abdominal obesity and sarcopenia potentiate each other to induce hypertension
- OR is 2.48 for sarcopenia
- OR is 3.15 for visceral obesity
- OR is 6.42 for sarcopenia with visceral obesity.
- For Metabolic Syndrome: Lowest LMM had OR of 3.6 for MS compared to hightest LMM ($p < 0.001$)

Normal Weight Obesity Syndrome (NWOS) and Hypertension and Metabolic Disorders

Nutrition Reviews 2016;74:558-570

- 30 million in US have NWOS with normal BMI but high BF.
- Increased incidence of inflammation,(increase HS-CRP, IL, TNF-alpha, CAMs) oxidative stress, IR, hyperglycemia, MS, DM, hypertension, dyslipidemia, homocysteinemia, low adiponectin, high leptin, endothelial dysfunction, CVD,CHD.
- F>M incidence
- May not have other anthropometric parameters (WC, WHR, WHR, Android or gynoid fat etc.
- Various genetic associations.

Exercise & Hypertension

CANNT 2005;15:60Dtsch Med Wochenschr 2011;136:2367J Hum Hypertens 2010;24:796;Am Heart J 2012;163:666 ;*Circulation 1986; 73: 30-9*
Circirculation 1990; 81: 1560-7

- Regular aerobic exercise lowers BP significantly and reduces CHD risk.
- Need combination of aerobic and resistance training.
- Meta-analysis of 13 controlled trials: mean BP reduction 11.3/7.5 mm Hg
- Increase eNOS and NO
- Improves ED
- Increase IL-10 and reduce inflammation
- Muscle VEGF protein increased 67%.(J of Hypertens 2010;28:1176)
- Marked improvement in angiogenesis.
- 60 minutes 4 x per week with 4200 KJ for reduction in CHD and BP

Caffeine, Coffee, Hypertension, CHD and MI.

J of Hypertension 2009;27:1594;Am J Clin Nutr 2007;86:457
European J Clinical Nutrition 2007;61:796; Am J Clin Nutr 2011;94:1113
Current Opinion in Lipidology 2007;18:13;JAMA 2006;295:1135.

- Cytochrome P-450 - CYP1A2 genotype modifies the association between caffeinated coffee intake and the risk of hypertension, CVD, CHD and MI in a linear relationship. Caffeine is exclusively metabolized by CYP1A2 to paraxanthine, theobromine and theophylline.
- Chromosome 15q24.1. SNP is rs7762551 A to C. C SNP decreases enzymatic activity. Caffeine also blocks vasodilating adenosine receptors.
- Rapid metabolizers of caffeinated coffee IA/IA allele have lower BP and lower risk of MI. Hypertension .36 to .80 RR. SBP decrease 10/7 mm Hg. MI is 17%-52% reduction. About 40-45% of the population.
- Slow metabolizers of caffeine IF/IF or IA/IF allele have higher BP 8.1/5.7 mm Hg lasting > 3 hours after consumption. Have tachycardia, increased aortic stiffness and increased catecholamines. Increased hypertension 1.72 to 3.00 RR. Over age 59: MI 36% increase (2-3 cups/d) ; 64 % increase 4 cups or more/d. Under age 59: MI 24% (1 cup/d), 67%(2-cups/d) and 233%(4 or more cups/d) About 55-60% of population
- Increased aortic stiffness , increased arterial pulse wave velocity and wave reflections and vascular inflammation. Augments SBP and PP.
- Polyphenols, chlorogenic acid and dihydro-caffeic acid increase eNOS, NO, improve ED and lower BP 10/7 mm Hg at 140 mg / day (cocoa in coffee). Diterpenes in unfiltered coffee and caffeine increase risk of CHD.

Summary of BP Reductions in DASH-I &DASH-II Na^+ Diets Hypertensive Patients & Overall

		SBP (mmHg)	DBP (mmHg)
Dash-I Overall	Combo Diet vs Control Diet	-5	-3
Dash-I Hypertensive	Pts Combo Diet vs Control	-10.7	-5.2
Dash-II Overall	Combo Low Na+ DASH Diet vs Control high Na+ Diet	-8.9	-4.5
Dash-II Hypertensive	Combo Low Na+ DASH Diet vs Control high Na+ Diet	-11.5	-6.8

* = $p < 0.001$

NEJM 1997; 336: 1117-24
NEJM 2001; 344: 3-10

DASH HF (High Fat, lower CHO)

Am J Clin Nutr 2016;103:341

- DASH-HF lowered BP the same as DASH but reduced TG and VLDL and increased LDL size more without a change in LDL.
- DASH reduced LDL, HDL, Apo A-1, ILDL and large LDL particles and mean diameter.
- DASH-HF: 43% CHO, 18% protein,14% SFA,18 % MUFA, 8% PUFA, 221 mg cholesterol
- DASH: 55% CHO,17% protein,8% SFA, 12% MUFA,7% PUFA 160 mg cholesterol.
- Limiting CHO despite increased SFA improved the lipid profile with DASH –HF. More MUFA and PUFA also improved lipids.

Eating frequency predicts new onset hypertension and the rate of progression of blood pressure, arterial stiffness, and wave reflections.

Hypertens.2016 Mar;34(3):429-37.

- Cross-sectional evidence indicates that eating frequency correlates with blood pressure, hypertension, and related target organ damage. The aim of the present study was to prospectively assess eating frequency as a predictor of arteriosclerosis progression and new onset hypertension over a follow-up period of 5 years in adults without cardiovascular disease.

- Eating frequency among other dietary parameters was evaluated in 115 nondiabetic study participants from a general population sample (54±9.1 years, 45 women) at a baseline visit. Metabolic parameters known to be associated with eating frequency, markers of arteriosclerosis, including augmentation index, pulse wave velocity, SBP, and DBP were evaluated in all volunteers at baseline and after a 5-year follow-up.
- RESULTS: By applying linear mixed models analysis, it was found that a high eating frequency at baseline significantly correlated with the rate of progression of pulse wave velocity (β=0.521, P=0.004), augmentation index (β=0.503, P=0.01), SBP (β=0.694, P<0.001), and DBP (β=0.477, P=0.009) and the incidence of new onset hypertension (odds ratio=8.89, P<0.001). After adjustment traditional cardiovascular risk factors, heart rate, homeostasis model assessment index of insulin resistance and total energy intake, the associations with augmentation index, SBP, DBP, and new onset hypertension remained significant.
- CONCLUSION: In a population of nondiabetic adults without cardiovascular disease, higher eating frequency is associated with a llower rate of progression of wave reflections, blood pressure and of new onset hypertension.

Hydrogen Sulfide and Thiosulfates reduce BP

Curr Opin Nephrol Hypertension 2016;25:107

- Hydrogen Sulfide, H2S donors and thiosulfates reduce BP
- H2S is from sulfate-reducing bacteria , dietary sulfur containing amino acids and from enzymatic breakdown of homocysteine and cysteine
- Higher blood levels of sulfate and thiosulfate and polysulfides correlate with reductions in CVD and hypertension by inducing vasodilation and ROS scavenging.
- H2S reacts with NO and nitrosothiols forming thionitrous acid, nitroso-persulfide and nitroxyl which vasodilates. Also activates K channels, inhibits SNS, activates PKG1 alpha and inhibits PDE 5.
- Treatments: NaHS and H2S by cysteine, methionine, P5P, arginine, citrullene, BH4, sulfated NSAIDs, sulfated ACEI, microbiome sulfate-reducing bacteria, dietary sulfate and sulfate containing amino acids.

Sodium (Na^+) Restriction

Complementary Health Practice Review 2000; 6 : 11-19;
Circ 1998; 98: 613-17;
Current Atherosclerosis Reports 2000; 2: 521-8;
Hypertension 1989; 14: 570-7;
JAMA 1996; 275: 1590-7;
Am J Clin Nutri 1997; 65: 648-51,
Arch IM 1997; 157: 657-67;
JAMA 1998; 299: 839-46
Am J Clin Nutrition 2015;101;440

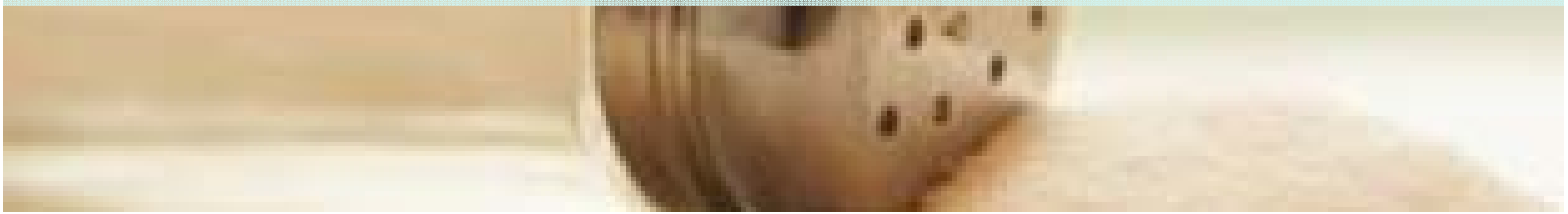
- Increase Na+ intake = Increase BP (E,O,C) and CVD, CVA, LVH, CHD, MI, Death, CRI, proteinuria, AC, Platelet Function, SNS, especially if salt sensitive
- Magnitude BP reduction directly proportional to decrease Na+ 150 mmol $\rightarrow$ 100 mmol $\rightarrow$ 50 mmol : 4-6 mmHg/2-3 mmHg

Sodium (Na^+) Restriction

Current Opin Nephrol 2011;20:37
Exper Rev Cardiovasc Ther 2010;8:821
Complementary Health Practice Review 2000; 6 : 11-19;
Circ 1998; 98: 613-17;
Current Atherosclerosis Reports 2000; 2: 521-8;
Hypertension 1989; 14: 570-7;

JAMA 1996; 275: 1590-7;
Am J Clin Nutri 1997; 65: 648-51,
Arch IM 1997; 157: 657-67;
JAMA 1998; 299: 839-46
Am J Clin Nutr. 2015 Mar;101(3):440-8.

- Improve HBP control in pharmacologic treated patients
- Reduce CVD, CHD, CHF, CVA in all subjects, especially the obese
- Reduce LVH, diastolic dysfunction, and vascular hypertrophy
- Reduce renal disease and proteinuria
- Improved effect with high K+, Mg++ and Ca++ intake (especially Na+ sensitive) (DASH I and II) (Montreal)
- Improved effect with restriction of refined carbohydrates
- Reduction in TOD is also independent of BP Reduction



Sodium - Endothelial Cells & Salt Sensitivity

Curr Opin Nephrol Hypertens 2011;20:37 Biochim Biophys Acta 2010;1802: 1193
Proc Natl Acad Sci 2009;106: 2629

- Sodium promotes cutaneous lymphangiogenesis, increases endothelial cell stiffness, reduces size, surface area, volume, cytoskeleton, deformability, and pliability, reduces eNOS and NO production, and increases TGF-b. This is increased in the presence of aldosterone which mimics these same pathophysiologic changes.
- Both dietary sodium and potassium promote functional changes in the vasculature and lymphatic system independent of BP changes. Potassium counteracts all the actions of sodium.
- Estimated that 51% of hypertensive patients are salt sensitive and 33% are salt resistant.

Salt Induced Hemodynamic Regulation is Mediated by NO

J of Hypertens 2011;29:415

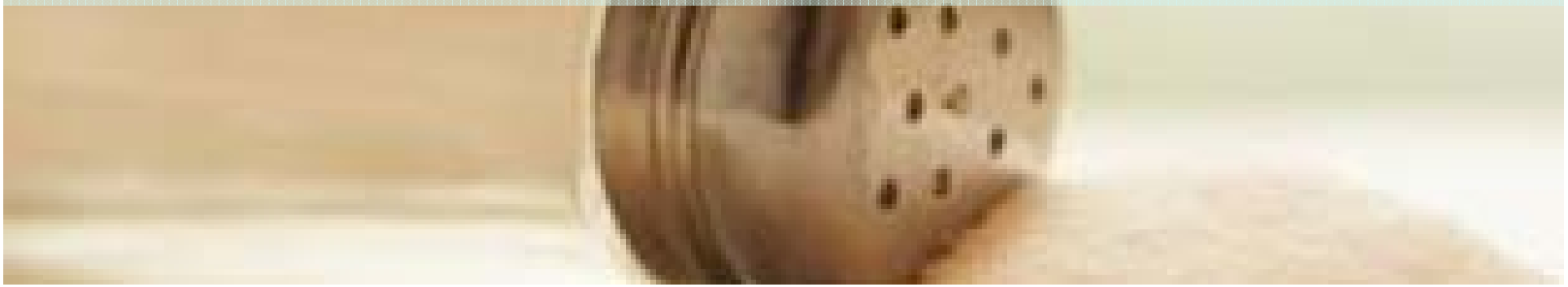
- Excess NaCl intake impairs vasodilation and increases vasoconstriction which reduces blood flow and increases BP in both normal and hypertensive patients with or without salt sensitivity.
- Decrease eNOS and NO
- Increased ADMA
- Increased oxidative stress
- Imbalance of NO and Ang-II
- Endothelial cells act as **vascular salt sensors**

Sodium & AT2-mediated Vasodilation

J Hypertens 2011; 29:1392

- High sodium intake specifically abolishes the AT2-mediated vasodilation immediately via decreased level of AT2 receptor protein and after 30 days is associated with the abolition of endothelial vasodilation.

- Loss of the AT2-mediated vasodilation increases BP and risk of stroke and CVD.



Inhibition of Intestinal Sodium Uptake Sodium/Hydrogen Exchanger Isoform 3

Curr Opin Neprhol Hypertens 2015;24:410

- Pharmacologic blockade of the apical intestinal sodium exchanger isoform 3

  (NHE 3) with tenapanor
- Reduces sodium absorption and fluid overload
- Reduces BP
- No adverse effects

Dietary Sodium and Potassium alter LV Diastolic Function and Mass (LVH)

Am J Cardiol 2015;115:1244

- An increase in dietary sodium/potassium ratio is related to an accentuation of the atrial phase LV diastolic filling in normotensive young subjects and both LVDV and LVH in prehypertensive or hypertensive patients.
- The effects are directly related to the increase in Na/K ratio in the diet.

Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events

JAMA 2011;306:2229

- J shaped curve for sodium excretion and CV events ? Confounding studies and information with design issues.
- Sodium excretion over 7 grams per day or less than 3 grams per day was associated with increased risk of CV mortality and hospitalization for CHF over 56 months.
- Over 8 grams: CV death 53%,MI 34%, stroke 48% and CHF 51 % increase
- Less than 3 grams: CV death 19 %, CHF 23% increase. RAAS activated at about 3 grams per day?.

- Is 3000 mg per day the correct daily intake????
- Higher potassium excretion was associated with a reduced risk of stroke.
  - 1.5-1.99 grams: 23 % RRR
  - 2.0-2.49 grams: 27 % RRR
  - 2.5- 3 grams: 29% RRR
  - over 3 grams: 32 % RRR

Potassium, Hypertension & CVD

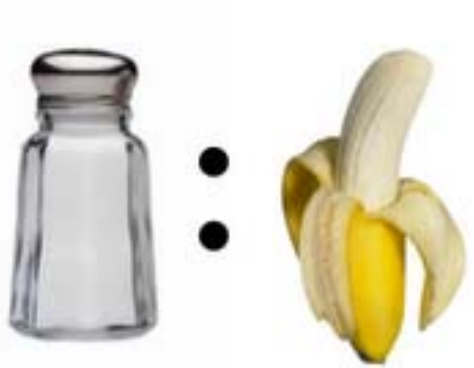
J Clin Hypertension 2008;10:3-11;Archives Int Med 2010;170:1501
J Am Society of Hypertension 2010;4:79;NEJM 2007;356:1966.
Current Hypertens Reports 2011;13:309; Arch Int Med 2010;170:1745Dietary

- Dietary potassium lowers BP in normotensives and hypertensives in a dose related response.
- 600 mg K reduces SBP 1.0 mm and DBP .52 mm Hg
- Response depends on race (B>W), sodium, magnesium and calcium intake. Higher sodium intake results in more BP reduction with potassium.
- 4.7 gm (120mmol) of potassium lowers BP 8.0/4.1 mm Hg with reduction in CVA 15% and MI 11%
- Lowers risk of CVA, CHD, MI, CHF, LVH, CVD, CRI, DM, arrhythmias.
- Reduction in CVA is both BP dependent and non BP dependent.

Sodium to Potassium Ratio Practical Recommendations

Archives Int Med 2011;171:1183

- Reduce sodium intake to 1500-2000 mg per day.
- Increase potassium intake to 5 grams per day.
- This gives a K/Na ratio of 2.5-3.3/1.
- Each 1000 mg increase in Na intake per day increases all cause mortality 20%.
- Each 1000 mg increase in K intake per day reduces all cause mortality 20%.
- Highest quartile of Na/K ratio increased CVD and total mortality by 46% compared to the lowest quartile.



Magnesium (Mg^{++})

J of Clinical Hypertension 2011;13:309
J Clin Hypertension 2008;10(7 suppl 2): 3-11
Circ 1998; 98: 613-7;
Current Atherosclerosis Reports 2000; 2: 521-8;
JAMA 1992; 267: 1213-20
Am J Hypertens 1993; 6: 41-5;
Am J Hypertens 1993; 6: 920-6;
J Pak Med Assoc 1998; 48 (8): 246-50
J of Hypertension 2017;35:89

- 91 patients in DBPC Trial given 485 mg Mg++ aspartate-HCL .
- BP 2.7/3.4 mm Hg ($p<0.18$ SBP; $p<0.003$ DBP) Maximum is 5.6/2.8mmHg. Numerous randomized and observational data.
- Effective in HBP, Acute MI, Atherosclerosis, DM, dyslipidemia, LVH and IR.
- Intake of 500-1000 mg/day of chelated Mg++ (Malate). Measure RBC Mg++.
- Milk (Mg++, K+, Ca++) better than Mg^{++} alone to ↓ BP.
- Direct vasodilator: Natural CCB, regulates intracellular Ca++, Na+, K+, pH, increase PGE1, nitric oxide, improves ED and IR.
- Best with high K, low Na intake and taurine to decrease BP.
- Enhances effects of anti-hypertensive drugs.
- Improves ED, BP less progression of carotid IMT and subclinical atherosclerosis in thiazide treated patients.

Fructose and Hypertension

J of Hypertension 2015;33:912

- HFCS increases BP
- Up regulates sodium and chloride receptors that increase intravascular volume
- Increase sympathetic nervous system activity.
- Increase vasoconstrictors and block vasodilators. Increase endothelin, A-II, TX 2, ICAM, MMP 2 , metholglyoxol, uric acid and decreases NO.
- Endothelial dysfunction.

Fiber

J of Hypertension. 2015;33:897

- Soluble Fiber (Beta Glucans, Glucomannan, psyllium, Guar Gum and Guava) and oat bran lower BP and reduce need for antihypertensive medications in:
  - HBP
  - DM
  - DM + HBP
- Vuskan Study with glucomannan ↓ SBP 9.4 mmHg
- Keenan Study with oat bran ↓ BP 7.5 / 5.5 mmHg
  (40 Gm oat bran dry weight or 3 Gm B-Glucan)

Meta-analysis: Beta Glucan reduces BP 2.9/1.5 mm Hg at about 4 gms per day.

Current Atherosclerosis Reports 2000: 2: 521-8
Clin Exp Hypertens 1999; 21: 785-96
Current Atherosclerosis Reports 2000; 2: 467-75
Current Atherosclerosis Reports 2000; 2: 494-502
Diabetes Care 1999; 22: 913-19
J Fam Prac 2000; (in press)
J Am Coll Nutr 1999; 18: 529
Rev Med Suisse 2010;6: 1715

Protein

- Observational epidemiologic studies indicate a high protein intake reduces BP (non-animal > vs animal protein) in numerous populations. However, cured meat increases BP.
- Low Protein and Low Omega 3 FA intake are associated with higher BP.
- Daily intake recommended 1.0 to 1.5 grams/kg/day depending on many factors.
- Intermap Study : Inverse relationship of BP with total protein intake and non-animal protein.

Current Atherosclerosis Reports 2000; 2: 521-8
JAMA 1996; 274: 1598-1603
ISH Abstract August 20, 2000
Current Atherosclerotic Reports 2007;9:472

Protein

- Intersalt Study:
  - 10,020 subjects, worldwide had lower BP (3.0/2.5 mm Hg) with dietary protein >30% above mean vs those 30% below mean (81 gms vs 44 gms/day) This is especially true in the elderly and hypertensive patients.

- Mechanisms:
  - ACEI, reduce SNS (EPI, NE), natriuresis, inhibit Tyrosine Kinase (ERK-MAPK), reduce VSMH, reduce superoxide ion (O_2^-), reduce aldosterone

Current Atherosclerosis Reports 2000; 2: 521-8
JAMA 1996; 274: 1598-1603
ISH Abstract August 20, 2000
PLOS One 2010;5:e12102

Protein and CVD risk factors

Am J Clin Nutrition 2012;95:9-16
Nutrition Research 2011;31:907

- Lean beef at 113 to 153 grams per day with low SFA diet has favorable effects on CVD risk factors with lower TC, LDL, and Apo B.
- Reduces PGE 2 and increases PGI 2.
- Reduce inflammation

Increased Protein Intake Lowers BP

Am J Clin Nutr 2012;95:966
Curr Opin Lipidol 2013;24:65
Am J Hypertension 2014; Sept 6 epub

- 94 subjects with prehypertension and stage I hypertension
- Randomized, double blind parallel study over 4 weeks (PROPRES study)
- Compared 25% vs 15 % protein intake in isocaloric diet
- Protein was 20% pea, 20% soy , 30% egg and 30% milk-protein isolate vs maltodextin.
- Office BP 4.9/2.7 mm Hg lower in protein group (p= 0.05)

Diets Higher in Protein Predict Lower High Blood Pressure Risk in Framingham Offspring Study Adults.

Am J Hypertens. 2014 Sep 6.

- Men and women 30-54 years) without prevalent HBP, cardiovascular disease, or diabetes with 3-day dietary records (n = 1,361) were followed for a mean of 11.3 years for development of HBP.

- Higher protein intakes were associated with lower mean SBP and DBP. Both animal and plant proteins lowered BP and led to statistically significant reductions in HBP risk (hazard ratios of 0.68 and 0.51, respectively).
- Participants in the highest tertile of total protein intake had 40% less risk (95% confidence interval [CI], 0.45-0.78) of developing HBP. Beneficial effects of protein were apparent for men and women and for normal-weight and overweight individuals. Higher protein diets also characterized by higher fiber intakes led to a 59% reduction (95% CI, 0.37-0.66) in HBP risk.

- Adults consuming more dietary protein from either plant or animal sources had lower long-term risks of HBP

Dietary Protein Intake and Blood Pressure Meta-analysis

Am J Epidemiol 2012;176:S27-43

- 40 trials with 3,277 subjects
- Significant decrease in BP with increasing levels of protein intake for both animal and vegetable protein.
- BP reduction 2.27/1.26 mm Hg for vegetable protein ($p<0.001$)
- BP reduction of 2.54/.95 mm Hg for animal protein ($p<0.001$)

Dietary protein intake and risk of stroke in women
Atherosclerosis 2012;224:247

- 34.670 Swedish women
- 10.4 year followup
- Intake of total and animal protein but not vegetable protein was significantly inversely associated with risk of total stroke and cerebral infarction.
- Highest to lowest quintile of protein intake was .74 for total protein intake and .71 for animal protein.
- Highest association in women with hypertension.

Sardine Muscle (Valyl-Tyrosine): Protein

- 3 gms of Valyl-Tyrosine for 4 weeks in hypertensive patients reduced BP 9.7 / 5.3 mmHg
- Vegetable drink with sardine protein hydrolysates of Valyl-Tyrosine dipeptide in 13 weeks reduced BP 8/5 mm Hg.
- Valyl-Tyrosine is ACEI: ↓ Ang-II, ↓ Aldosterone
- No Adverse effects

J Human Hypertens 2000; 14:519-23
Fukuoka Igaku Zasshi 2002;93:208

Whey Protein

- Significant reduction in BP in animal and human studies
- Must be hydrolyzed to be effective. Rich in bioactive peptides with ACEI activity.
- Act as ACEI
  - IC 50 = .45 mg / ml for BZ
  - IC 50 = 376 mg / ml nonhydrolyzed whey protein
  - IC 50 = 1.3 x 10^{-6} for captopril
- 30 grams of hydrolyzed whey protein per day reduced BP 11 / 7 mm Hg in humans within 7 days
- 20 gms of hydrolyzed Whey Protein significantly reduced BP 8/5 mm Hg in 30 patients in 6 weeks.

J Dairy Sci 2000; 83:255-263

J Clin Hypertens 2006; 8: 775

Cardiovasc Drugs 2002;16:68

Nutrition Reviews 2015; 73: 36-50

Whey protein lowers blood pressure and improves endothelial function and lipid biomarkers in adults with prehypertension and mild hypertension: results from the chronic Whey2Go randomized controlled trial.

Am J Clin Nutr.2016 Dec;104(6):1534-1544.

Study to evaluate intact milk proteins lower 24-h ambulatory blood pressure (AMBP) and other risk markers of CVD.

DESIGN: double-blinded, randomized, 3-way-crossover, controlled intervention study. Forty-two participants were randomly assigned to consume 2 × 28 g whey protein/d, 2 × 28 g Ca caseinate/d, or 2 × 27 g maltodextrin (control)/d for 8 wk separated by a 4-wk washout.

RESULTS

- Significant reductions in 24-h BP [for systolic blood pressure (SBP): -3.9 mm Hg; for diastolic blood pressure (DBP): -2.5 mm Hg; P = 0.050 for both)] were observed after whey-protein consumption compared with control intake.
- After whey-protein supplementation compared with control intake, peripheral and central systolic pressures [-5.7 mm Hg (P = 0.007) and -5.4 mm Hg (P = 0.012), respectively] and mean pressures [-3.7 mm Hg (P = 0.025) and -4.0 mm Hg (P = 0.019), respectively] were also lowered.
- Flow-mediated dilation (FMD) increased significantly after both whey-protein and calcium-caseinate intakes compared with control intake [1.31% (P < 0.001) and 0.83% (P = 0.003), respectively].
- Although both whey protein and calcium caseinate significantly lowered total cholesterol [-0.26 mmol/L (P = 0.013) and -0.20 mmol/L (P = 0.042), respectively], only whey protein decreased triacylglycerol (-0.23 mmol/L; P = 0.025) compared with the effect of the control.
- Soluble intercellular adhesion molecule 1 and soluble vascular cell adhesion molecule 1 were reduced after whey protein consumption (P = 0.011) and after calcium-caseinate consumption (P = 0.039), respectively, compared with after control intake.

CONCLUSIONS : The consumption of unhydrolyzed milk proteins (56 g/d) for 8 wk improved vascular reactivity, biomarkers of endothelial function, and lipid risk factors. Whey-protein supplementation also

BONITO PROTEIN (Sarda Orientalis) and Marine Collagen Peptides

Cardiovasc Drugs 2002;16:68;Am J Med Sci 2010;340:360 ;Curr Pharm Dis 2009;15:3622; Nutrition Research 2001;21:1149

- Natural ACEI with numerous ACE-inhibitory peptides
- From the tuna/mackeral family
- Bonita protein reduces BP 10.2/7 mm Hg in humans over 1-3 months.
- Dose: 1.5 grams per day
- No adverse effects and cost effective

Omega-3 PUFA and Blood Pressure

J Am Society Hypertension ;2017:11:10
Current Atherosclerosis Reports 2000; 2: 508-15;Hypertension 1999; 34: 253-60
Nutrition 1998; 14: 627-33;Ann IM 1995; 123: 911-18
Hypertension 2007;50:313,Nut Res 2010;30:807;Am J Hypertension 2011 July 14 epub
Int J Hypertension 2011;8:8091

- Fish 3 x / Week lowers BP (Herring, Haddock, Atlantic Salmon, Trout)
- Fish or Fish oil + weight loss is additive to ↓ BP
- DHA better to ↓ BP. Use 3-4 grams of DHA with EPA per day with a ratio of 3 parts EPA to 2 parts DHA.
- Lowers BP 8/5 mmHg and reduces HR 6 beats per minute. 24 hr ABM inversely correlates with RBC omega 3 FA content.
- Increases HDL and HDL 2 b and changes LDL b to LDL a larger particle size and reduces LDL particle number and lowers TG up to 40%
- Reduced ALA conversion to EPA and DHA
- Improve ED. PWV and arterial compliance

Omega 3 FA and BP

1. J Complement Integr Med 2012;Oct 23 epub
2.Br J Nutr 2012;107 Suppl S 195;
3. Int J Hypertens 2011; March 8 epub
4. J Nutritional Biochem 2017;42:172

- Safflower oil 4 g/d vs fish oil 4 g/d with 1600 mg EPA and 800 mg DHA for 6 weeks. SBP reduction 6.8 mm Hg. Also reduced PP and MAP ($p<0.04$) (1).
- Meta-analysis showed that consumption of over 3 grams per day of omega 3 FA reduces BP, especially SBP significantly (2).
- 2 grams of DHA lowers BP in 38 hypertensive Scottish males significantly (3).
- Increase EPC and reduce glycation damage to EPC to lower BP and reduce ischemia. (4)
- Hypertension is inversely associated with plasma and erythrocyte levels of omega 3 FA (Int J Food Sci Nutr 2012;63:667 and Nutr Res 2010;30;807.)

Omega-6 Fatty Acids

Am J Clin Nutrition 2003;77:37-42
Addition of eicosapentaenoic acid to gamma-linolenic acid-supplemented diets prevents serum arachidonic acid accumulation in humans. Barham JB, Edens MB, Fonteh AN, Johnson MM, Easter L, Chilton FH.
J Nutr. 2000 Aug;130(8):1925-31

- LA, GLA, DGLA, AA, CLA
- GLA → DGLA → PGE_1 AND PGI_2 → vasodilate
- GLA blocks stress induced hypertension
  - ↑ PGE_1 and PGI_2
  - ↓ Aldosterone
  - ↓ Adrenal AT_1R density/affinity
  - Neurohormonal regulation (SNS, RAAS) – central + peripheral
  - Give GLA at a dose of 50% of the total omega 3 fatty acid dose.

MUFA and BP
The International Study of Macro /Micronutrients
J of Hypertension 2013;31:1144

- MUFA especially oleic acid from vegetable sources contributes to the prevention and control of adverse blood pressure levels in a general population.

Olive Oil polyphenols and BP

Am J Hypertens 2012;25:1299

- 24 women with stage I hypertension DBCO with polyphenol-rich olive oil 30mg per day for 2 months with 4 week washout
- Oleic acid and other polyphenols are responsible for BP reduction

- BP reduction 7.91/6.65 mm Hg
- Decrease ADMA
- Decrease oxLDL
- Decrease HSCRP
- Increase plasma nitrates and nitrites
- Improved FMD and ED

Extra Virgin Olive Oil Reduces Blood Pressure

Clin Nutr 2004; 23: 1113
J Agric Food Chem 2009;57:11427
Nutr Metab Cardiovasc Dis 2010:20:284
Flynn, M and Wang S. Olive Oil as Medicine: The Effect on Blood Pressure. The Report of UCD Olive Center . December 2015

- DBRC crossover study 31 hypertensive elderly patients.
- Extra virgin olive oil (EVOO) 40 grams per day vs. sunflower oil (SFO) for 4 weeks then 4 week wash out with 4 week crossover.
- SBP reduced from baseline to 136 +/- 10 mm Hg with EVOO vs 150 +/- 8 mm Hg with SFO ($p<0.01$).
- Seven other human clinical trials with 368 patients show similar results.
- The SBP is usually reduced better than DBP but depends on the total phenol content.
- Conclusions: EVOO with a total phenol content of al least 161 mg/kg at 20- 40 grams (2-4 tablespoons) per day will significantly lower BP in about 3 weeks. EVOO with 300 mg /kg of total phenols may also decrease DBP.

Effect of olive oil phenolic compounds on the expression of blood pressure-related genes in healthy individuals.

Martín-Peláez S. Eur J Nutr.2015 Dec 12. [Epub ahead of print]

- The ingestion of olive oil having different phenolic contents influences the expression of blood pressure-related genes, involved in RAAS.
- **METHODS:** A randomized, double-blind, crossover human trial with 18 healthy subjects, who ingested 25 mL/day of olive oils (1) high (366 mg/kg, HPC) and (2) low (2.7 mg/kg, LPC) in phenolic compounds for 3 weeks, preceded by 2-week washout periods. Determination of selected blood pressure-related gene expression in peripheral blood mononuclear cells (PBMNC) by qPCR, blood pressure and systemic biomarkers.
- **RESULTS:** HPC decreased systolic blood pressure compared to pre-intervention values and to LPC, and maintained diastolic blood pressure values compared to LPC. HPC decreased ACE and NR1H2 (LXRB gene expressions (Nuclear Receptor Subfamily 1 Group H Member 2 LXRB, form a subfamily of the nuclear receptor superfamily and are key regulators of macrophage function, controlling transcriptional programs involved in lipid homeostasis and inflammation) compared with pre-intervention values, and IL8RA gene expression compared with LPC.
- **CONCLUSIONS:** The introduction to the diet of an extra-virgin olive oil rich in phenolic compounds modulates the expression of some of the genes related to the renin-angiotensin-aldosterone system. These changes could underlie the decrease in systolic blood pressure observed.

A Mediterranean diet supplemented with extra virgin olive oil or nuts improves endothelial markers involved in blood pressure control in hypertensive women.
Eur J Nutr.2015 Oct 8. [Epub ahead of print]

- Serum nitric oxide (NO) reduction and increased endothelin-1 (ET-1) play a pivotal role in endothelial dysfunction and hypertension.
- Non-smoking women with moderate hypertension were submitted for 1 year to interventions promoting adherence to the TMD, extra virgin olive oil (EVOO) and the other with nuts versus a control low-fat diet (30 participants/group). BP, NO, ET-1 and related gene expression as well as oxidative stress biomarkers were measured.
- **RESULTS:** Serum NO and SBP or DBP were negatively associated at baseline, as well as between NO and ET-1. DBP reduction occurred with both interventions. A negative correlation was observed between changes in NO metabolites concentration and SBP or DBP after the intervention with TMD + EVOO ($p = 0.033$ and $p = 0.044$, respectively).
- SBP reduction was related to an impairment of serum ET-1 concentrations after the intervention with TMD + nuts ($p = 0.008$). There were also changes in eNOS, caveolin 2 and ET-1 receptors gene expression which are related to NO metabolites levels and BP.
- **CONCLUSIONS:** The changes in NO and ET-1 as well as ET-1 receptors gene expression explain, at least partially, the effect of EVOO or nuts on lowering BP among hypertensive women

Olive Leaf Extract and Oleuropein

Phytomedicine 2011;18:251-8;Phytother. Res 2008;22:1239 J ethnopharmacol 2008;120:233;Circ Res 2010;107:540. J Hypertens 2008;26:223; J Pharm Belg 1996;51:69;Am J Clin Nutr 2004;80:1012;Lipids 2004;39:1233

- DBPC parallel clinical trial of 232 stage -1 hypertensive patients given oleuropein- olive leaf extract 500 mg BID for 8 weeks reduced BP 11.5/4.8 mm Hg.
- Study of 20 pairs of twins BP decreased 9/4mm Hg in 8 weeks
- Has CCB and ATR1 blocking effects.
- Olive oil and wine combined lower BP, as well as the Mediterranean diet and olive oil consumption (EPIC and SUN)

Garlic

Maturitas 2010;67:144
Nutrition Research 2014;34:106

- DBRCP Study of 50 subjects with hypertension
- 900mg aged garlic with 2.4 mg S alllylcysteine per day
- 12 weeks
- BP reduced SPB 10.2 mm Hg in patients with SBP over 140 mm Hg ($p < 0.03$)

- Need 10,000 mcg of allicin per day to have significant BP lowering effect. This is the amount in four cloves (5 grams) of garlic

Garlic and Hypertension

Exp Ther Med 2013;5:399

- 81 prehypertensive and mild hypertensive patients given 300 mg dire garlic homogenate for 12 weeks in DBRPC trial
- BP reduction 6.6-7.5 / 4.6-5.2mm Hg compared to placebo

Garlic and Hypertension

Eur J Clin Nutr 2013;67:64

- 79 patients with uncontrolled hypertension in DBRPC trial over 12 weeks.
- Aged garlic extract at one of three doses: 240mg, 480 mg, 960 mg per day.
- BP reduction 11.8 +/- 5.4 mm Hg (p=0.006) on 480 mg dose.
- Other studies show similar reductions of 7/3.8 mm Hg

  (Hypertens Res 2009;32:433)

Garlic and Hypertension :Cochrane Database

Cochrane Database Syst Rev 2012; August 15. epub

***Nutriti*ion Research 2014;34:106**

- Evaluation of prospective clinical trials indicated a average reduction in BP of 10-12/6-9 mm Hg.
- No adverse effects

Garlic and Hypertension

Heart Disease 2000; 2:3-9; Phytochemistry 1992; 31:2389-91; Planta Med 1987; 53:12-15; Econ Med Plant Res 1994; 6:55-113; Curr Med Res Opin 1994; 13:257-63
Neth J Med 2009;67:212
Ann Pharmacother 2008 ;42: 1766 and BMC Cardiovasc Disor 2008;8:13 **Nutrition Research 2014;34:106**

- Consistent dose dependent BP reduction in 10 controlled clinical trials was 8 to 16/7-9 mm Hg (Average 8.4/7.3 mm Hg in hypertensive patients.
- Cultivated garlic = Allium Sativum . Not all garlic preparations same
- AGE: Aged garlic extract has excellent CV and BP data.
- Wild uncultivated garlic = Allium Urisinum (Bear Garlic), fresh at

  1 – 4 cloves / d (5 grams)
  - High Adenosin, magnesium, flavonoids, sulfur, allicin, phosphorous and ajoenes
  - High Gamma-Glutamyl Peptides (ACEI's) (ACEI's),
  - Natural ACEI and CCB. Increase NO and bradykinin
  - Reduces NE sensitivity, ROS, TBxA2 , improves arterial compliance

Seaweed

- Wakame (Undaria Pinnatifida)
  - Most popular edible seaweed in Japan
  - ACEi activity similar to Captopril in ↓ BP in SHR
  - ↓ BP in hypertensive patients
    - ↓ SBP 14 ± 3 mmHg and ↓ DBP (5 ± 2 mm Hg) ($p < 0.01$)
    - 3.3 gms dried Wakame
    - 4 weeks study

J Nutr Biochem 2000; 11: 450-4
J Jpn Soc Clin Nutr 1998; 20: 92

Seaweed

- Ion exchange sodium-absorbing / potassium releasing seaweed preparation
  - 12-24 grams/day for 4 weeks
  - ↓ MĀP 11.2 mm Hg (p <0.001) salt-sensitive subjects
  - ↓ MĀP 5.7 mm Hg (p <0.05) salt-insensitive subjects
  - BP reduction correlated with PRA
- Mechanisms: ACEI, 771 minerals, fiber, alginate, colloid

J Nutr Biochem 2000; 11: 450-4 J Agric FoodChem2002;50:6245
J Jpn Soc Clin Nutr 1998; 20: 92
Am J Hypetens 1991;4:483
Ann Nutr Metab 2002;446:259

Vitamin C

J Clin Biochem Nutr 2007;40:141
Arzneimittelforschung 2006;56:535

- SBP , DBP and HR are inversely correlated with Vitamin C intake and plasma ascorbate levels in humans in epidemiologic, observational, cross sectional and controlled prospective clinical trials
- The higher the initial BP, the greater the response
- SBP reduced more than DBP. Improves aortic compliance
- 24 hour ABM shows daytime > nighttime decrease in BP
- BP reduction improved with concomitant use of other antioxidants such as vitamin E, lipoic acid, selenium, etc.
- Improves anti-hypertensive effects of amlodipine
- Lowers BP significantly in elderly hypertensive patients with refractory hypertension and decreases CRP, 8-isprostane and MDA. 600 mg per day over 6 months lowered BP by 20/16 mm Hg.

Vitamin D

- Vitamin D deficiency leads to insulin resistance, VSMC hypertrophy and hypertension
- Replacement of Vitamin D with or without a deficiency reduces BP in animals and humans
- BP reduced about 3.6 to 6.2/ 3.1 mm Hg but up to 13.1/7.2 mm Hg in Pfeifer female study . Best with unactivated forms of Vitamin D. Dose and serum level dependent. Only lowers BP in hypertensive patients.
- BP reduction reduced even in presence of hypercalcemia
- Markedly suppresses renin transcription by a VDR- mediated mechanism which regulates electrolytes, volume and blood pressure. Vitamin D binds to VDR then to retinoid X receptor then to DNA to alter gene expression.
- Protects Mitochondria from homocysteine induced damage (Nut Research 2017;38:52

Br J Nutr 1998; 79:315-27, J of Clinical Hypertension 2010;12:149
RecentPat Cardiovasc Dis 2011;6:345
J Clin Invest. 2002;10: 229,J Clin Endocrinol Metab 2001;86:1633
J of Hypertens 2009;27:1948 NEJM 2011;364:248,Med Clin (Barc) 2011;

Vitamin D

- BP reduction is inversely proportional to pretreatment plasma level of 25 OH D. Active 1,25 dihydoxyvitamin D signals through the Vitamin D receptor and provides vascular protection and reduces BP.
- Lowest to highest deciles of plasma 25 OH D have 1.6 to 2.3 times risk of incident hypertension

- More effective than calcium administration alone
- Reduces HR PRA, AII and VSM proliferation , improves ED, increases NO lowers ADMA, TNF alpha, decreases insulin resistance

  Reduces CHD calcification, reduces hsCRP, reduces inflammation.
- Dose: 5000 IU per day depending on many factors. 100 IU of Vitamin D3 increases serum levels by 1ng/ml
- Plasma level to about 80 ng/ml with range of 50 to 100 ng/ml as optimal (to convert ng/ml to nmol/L multiply by 2.5)
- PTH is suppressed at levels of over 30 ng/ml

Br J Nutr 1998; 79: 315-27, J of Clinical Hypertension 2010;12:149
Hypertension 2007;49:1063
Ann Intern Med 2010;152:307

Effect of Vitamin D Supplementation on BP in Blacks

Hypertension 2013;61:779
NEJM 2013;369:1991

- Dose related reduction in SBP in blacks
- Each 1ng/ml increase in Vitamin D lowered SBP by . 2 mm Hg
- 283 hypertensive patients over 6 months. The 4000 IU dose reduced SBP 4 mm Hg compared to 1.7 mm Hg increase in sBP in the placebo group
- Vit D binding protein is lower in blacks due to high prevalence of genetic polymorphisms.

Vitamin B-6 (Pyridoxine)

- Low vitamin B-6 levels are associated with hypertension in animals and humans
- Co-factor in neurotransmitter and hormone biosynthesis (NE, EPI, serotonin, GABA, kynurenine)
- Rat Models : B-6 increases cysteine synthesis from methionine
  - Cysteine is precursor of glutathione (antioxidant)
  - Cysteine neutralizes aldehydes and increases excretion
  - Glutathione neutralizes aldehydes and increases excretion
  - Decrease BP in B-6 DHT rats at 10 mg/kg/day by MAP of 24 mm Hg ($p < 0.05$)

Mol Cell Biochem 1998; 188: 137-48; J Hypertens 1996; 14: 355-63; Mol Cell Biochem 1999; 200: 155-62; Hypertens 1988; 11: 387-91
J Hypertens 1995; 13: 327-32; J Hypertens 1993; 11: 1357-62; Clin Exp Hypertens 1993; 15: 489-500

Vitamin B-6 (Pyridoxine)

- Blocks Ca^{++} influx into VSM ("CCB") – DHP – sensitive Ca^{++} channel
- B-6 reverses HBP in Ca^{++} deficient state
- Decreased FBS and RBS (improve insulin sensitivity)
- Reduces central sympathetic nervous system activity
- Decreases end organ responsiveness to glucocorticoids, mineralocorticoids

Mol Cell Biochem 1998; 188: 137-48; J Hypertens 1996; 14: 355-63; Mol Cell Biochem 1999; 200: 155-62; Hypertens 1988; 11: 387-91
J Hypertens 1995; 13: 327-32; J Hypertens 1993; 11: 1357-62; Clin Exp Hypertens 1993; 15:

Vitamin B-6

- Aybak, Arzneimittelforschung 1995;45:1271
  - 20 hypertensive subjects vs normotensive controls
  - Vitamin B-6 at 5 mg/kg/day for 4 weeks
  - Decrease SBP 14 mm Hg p <0.001
  - Decrease DBP 10 mm Hg p <0.005
  - ↓ Plasma NE (p <0.005)
  - ↓ Plasma EPI (p <0.05)
- Vitamin B-6 is a CAA, CCB, diuretic and improves insulin resistance
- Dose: 200 mg QD (short term up to 500 mg QD)

DARK CHOCOLATE AND COCOA

Am J Clin Nutr 2005;81: 611
Arch Intern Med 2007;167:626
J of Clin Hypertension 2007;9:647
JAMA 2007;298:49
BMC 2010;8:39
Am J Hypertension 2010;23:97

- 15 subjects given 100 grams of dark chocolate with 500 mg polyphenols for 15 days .
- HOMA-IR reduced ($p<0.001$)
- Reduced systolic BP by 6.4 mm Hg ($p< 0.05$) but no change in diastolic BP
- Meta-analysis of 173 patients given cocoa reduced BP 4.7/2.8 mm Hg ($p= .002$ to $.006$)
- Meta-analysis of 23 trials with 297 patients showed BP reduction of 3.2-4.5/2.0-3.2 mm Hg.

COCOA

JAMA 2007;298:49-60
J Nutr Biochem 2013;Dec 31 Epub
J of Hypertension 2015; 33:294J of Nutritional Biochemistry 2015;26:626-32

Cocoa at 30 mg of polyphenols reduced BP in human subjects with pre-hypertension and stage I hypertension at 18 weeks by 3/2 mm Hg.

Another study at 80 mg cocoa reduced BP 4.8/3.3 mm Hg, increased FMD and decreased PWV and ET-1.

BP reduction greatest in those with highest baseline BP.

Improved FMD and arterial elasticity.

Cocoa also reduces adipose tissue inflammation (TNF alpha, IL-6, iNOS, EGF, AA, LpPLA 2, COX 2 by modulating eicosanoid metabolism and metabolic endotoxemia.(improved gut barrier function and GLP-2)

Increases HDL-C (16%) , decreased oxLDL and haptoglobin, decreased monocyte adhesion (CD62L).

CoEnzyme Q-10 (Ubiquinone)

Rosenfeldt FL. J Hum Hypertens 2007;21:297 ;Molec Aspects Med 1994; 15 (Suppl): S257-S263
Molec Aspects Med 1994; 15 (Suppl): S265-S272
Nutrition Research 2017;38:1-12

- Reduced SVR and BP correlated with increase serum CoQ-10 level (↑ .97 µg/ml) (p <0.02) and pretreatment CoQ 10 levels.
- Office BP reductions average 17/10 mm Hg
- 24 hour ABM decreased 18/10 mm Hg (p <0.001)
- Meta-analysis of 12 trials with 362 patients Range BP 11-17/8-10 mm Hg
- Therapeutic plasma levels are 3.0 ng /ml
- Decrease HR 5 beats per minute
- Reduces glucose and improves IR
- BP effects occurs at 4 to 12 weeks
- BP effects are gone at 7-10 days after discontinuation

Co-Enzyme Q-10 (Ubiquinone)

Deficiency of Co Enzyme Q-10 in 39% of hypertensive patients vs. 6% of control patients

- Reduced with age, disease, oxidative stress, statins, HLP, CHD, HBP DM, aerobic exercise, atherosclerosis
- Reduces dose and number of BP medications
- Best BP reduction with lowest initial CO-Q-10
- Dose: 200 – 400 mg /day (3-5 mg /kg) Nanoparticle formulation with enhanced absorption

Alternative Med Review 1996; (I) (3):171-4
Atherosclerosis 1997; 129:119-26
Molecular Aspects Med 1994; 15:265-72 and Eur J Pharm Biopharm. 2007;67:361
Pol J Pharmacol 1994; 46 (5):457-61 and J Hum Hypertens.2007; 21:297

CO-Q-10 : BURKE STUDY
ISOLATED SYSTOLIC HYPERTENSION
SMJ 2001;94: 1112-1117

- 12 WEEK R,DB P CONTROLLED TRIAL FOR 12 WEEKS IN 83 MEN AND WOMEN WITH ISH (165/81-82MM HG)
- 60 MG CO-Q-10 BID(QGEL)
- INCREASED SERUM CO-Q-10 LEVELS BY 2.2 UG/ML($P<0.01$)
- SBP REDUCED 18 MM HG($P<0.01$)
- DBP REDUCED 2.6 MM HG(NS)
- 55% RESPONDED AND 45% DID NOT RESPOND : DEFINED AS REDUCTION IN SBP OF >4 MM HG. IN THE RESPONDERS THE AVERAGE REDUCTION IN SBP WAS 26 MM HG.
- LOW ADVERSE EFFECTS (6%)

CoQ 10 and Hypertension

Kardiologiia 2011;51:26

- Patients administered Co10 with enalapril improved 24 hr BP better than enalapril monotherapy and normalized endothelial dysfunction.

ALPHA LIPOIC ACID
HUMAN STUDY
J. Clin Hypertens 2007;9:249-55

Double-blind cross over study of 36 patients with CHD for 8 wks

200 mg lipoic acid with 500 mg Acetyl-L-Carnitine BID

RESULTS:

1. 2% Increase in brachial artery diameter
2. Patients with SHBP over 135 mm Hg had reduction in BP from 151+/- 20 to 142+/- 18 mm Hg (p<.03). No change in DBP.
3. Patients with metabolic syndrome had reduction in SBP from 139+/- 21 to 132+/-15 mm Hg (p<.03) and DBP from 76+/-8 to 73+/- 8 mm Hg (p<.06)

Lipoic Acid with ACEI in Hypertension

J Cardiovasc Pharmacol Ther 2012;17:139

- 40 patients with DM and stage I Hypertension
- Double blind cross over study with Quinapril and Lipoic Acid
- Quinapril 40 mg qd for 8 weeks vs Quinapril 40 with lipoic acid 600 mg qd for 8 weeks
- Urinary albumin decreased 30% with Q and 53 % with Q+LA, ($p < 0.005$)
- HOMA-IR decreased 19% with Q and 40% with Q + A, ($p < 0.005$). Improved insulin sensitivity.
- FMD increased 58 % with Q and 116 % with Q + A,($p <0.005$) Improved ED
- BP reduced significantly by 10 % in both groups.

ALPHA LIPOIC ACID
HUMAN STUDY

Diabetes Res Clin Pract. 2001 ;52: 175-83

Open label study of patients with diabetic nephropathy reported that long term lipoic acid at 600 mg per day for 18 months prevented the increases in BP and urine albumin compared to control patients.

Alcohol

Am J Cardiol 2010;106;1101

Am J Cardiol; 2009;1:104;Am J Cardiolol 2009; 104:932

Nutr Metab Cardiovasc Dis 2007;8:609;Ann Epidemiol 2007;17: S24

- Acute and chronic over-ingestion will increase BP and CVA risk, but smaller consumption may decrease CHD/MI risk, CVA and cancer if <20 grams/day. A "U" shaped curve. Risk reduction is proportional to intake up to this amount

- 20 grams per day or more increased BP
  - Wine (Red) 10 ounces (best)
  - Beer 24 ounces
  - Hard liquor 2 ounces

- Reducing alcohol intake will reduce BP
- 20 grams per day or less reduces CHD risk by 43%
- Mechanisms: endothelial cell mediated fibrinolysis, increases in HDL, platelet function and EPC's.

Carnitine

Clin Ther 1994;144:391;Minerva Med 1989;80:227
Drug Discov Today 2010;15:484

- Uses: DM, HBP, CHD, MI, CHF, arrhythmias, PAD, HLP
- Digesi
  - L-Carnitine 2 grams QD x 22 weeks
  - ↓ SBP 155 → 151 mm Hg (NS)
  - ↓ DBP 97.2 → 94.8 mm Hg (NS)
- Ghidini
  - L-Carnitine 1 gram BID p.o. to 38 patients
  - Hypertensive or IHD and CHF
  - Placebo controlled study x 45 days
  - ↓ HR ($p < 0.01$)
  - ↓ SBP ($p < 0.01$)
  - ↓ DBP ($p < 0.05$)
  - Lipids ($p < 0.05 – 0.001$)

Taurine

J Biomed Sci 2010;17:Suppl 1 S 6 and S 21
J Cardiovas Nurs 2006;21:9
Clin Exp Pharmacol Physiol Supple;1992;20:43
Am J Cardiovasc Dis 2011;24:574 Am J Hypertension 2011;24:574
Hypertension 2009;53:1017 Exp Clin Cardiol 2008;13:381

- Clinical Use: HBP, HLP, arrhythmias, CHD, CHF, ASCVD

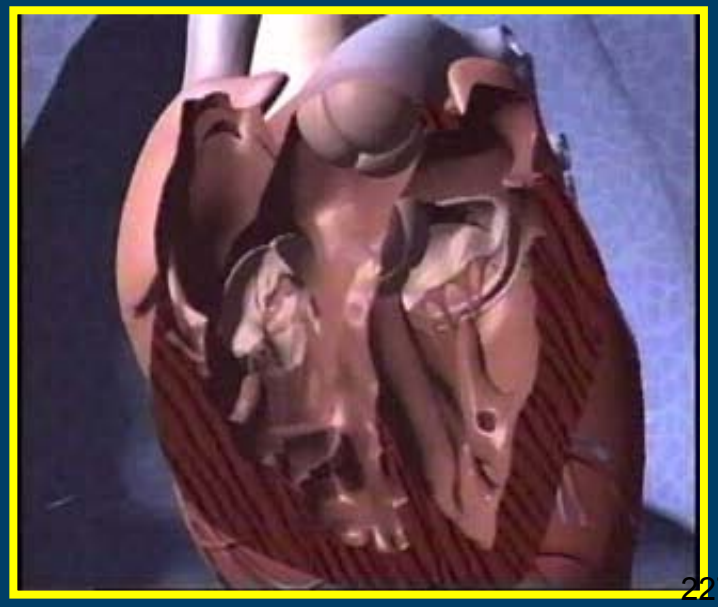
- SHR: ↓ BP 20-25% ↓ proteninuria, ↑ renal Kallifrein
  ↓ LVH ↓ Uepi + Udopamine
  ↓ SNS activity centrally

- Human Studies: Fujita. Circulation 1987;75:525
  19 hypertensive subjects
  6 grams taurine x 7 days
  ↓ BP 9/4.1 mm Hg ($p < 0.05$)

Taurine

Am J Cardiovasc Dis 2011;3:293

- Mechanisms: diuresis, ↑ Una^+, ↓ SVR,↑ ANF, ↓ homocysteine, osmoregulation, lowers lipids, anti-platelet,↑ insulin sens., ↓ SNS activity, improves Acetyl Choline responsiveness ,↑ Na^+ space, adenosine receptor opiate-mediated, improves NO/ED vasodepressor response, membrane stabilization, ↑ renal Kallikrein, ↓PRA, lowers A-II, increases kinins, decreases intracellular Ca and Na ↓ aldosterone CNS glycine response and beta receptors, antioxidant, anti-atherosclerotic and anti- inflammatory
- Dose: 3 grams BID



PYCNOGENOL

Nutrition Research .2001; 21:1251-1260
Nurition Research. 2008;28:315
Life Sci .2004; 74: 855;Hypertension Res 2007;30:775
J Cardiovasc Pharmacol Ther 2010;15:41.
Clin Appl thromb Hemosta 2006;12: 440

- Pycnogenol at 200 mg per day in 11 subjects for 8 weeks in placebo, DB, R, crossover Trial
- Reduced SBP 7 mm Hg (P < 0.05) /reduced DBP 2 mm Hg (NS)
- Reduces edema
- Decreases BP and reduces need for BP meds in DM with HBP.
- Serum thromboxane B2 levels reduced (P < 0.05)
- Cell membrane protection from oxidative stress
- Increase nitric oxide and improves ED, decrease ET-1
- ACEI action
- Increases vitamin C levels
- Reduced need for ACEI by 50%

RESVERATROL AND CENTRAL BLOOD PRESSURE

Am. J. Hypertens 2005; 18: 1161

- Subjects given 250 ml of regular or dealcoholized red wine for 2 days and wave reflections with AI, augmentation index and central and peripheral blood pressures measured.
- AI decreased 10.5% with regular red wine and 6.1 % with dealcoholized red wine
- No change in peripheral BP
- Central BP reduced by 7.4 mm Hg with regular red wine ($p=0.05$) and 5.4 mm Hg with dealcoholized red wine. ($p=0.019$)

Grape Seed Extract (GSE)

Clinical Science 2008;114:331
Abstract UCD by Siva, B. #211.1,2007
B and D Nutrition Mega Natural March 28,2007
J Am Diet Association 2011;111:1173
Metabolism 2009;58:1743

- High phenolic content in seeds (70% of total grape) activates PI3K/Akt signaling pathway through a redox sensitive mechanism resulting in phosphorylation of eNOS
- Increases nitric oxide, improves ED and lowers BP.
- 150 mg to 300 mg GSE reduced BP 11/8 mm Hg in 4 weeks ($p < 0.05$)

Pomegranate Juice and Seeds

Atherosclerosis 2001;158:195 Clin Nutr 2004;23:423
Nitric Oxide 2007;17:50 Nutr Rev 2009;67:49
Phytother Res 2010;24: S 196;Plant Foods Hum Nutr 2012;67:309 and 351.
Complement Ther Clin Pract 2011;17:113
Am J Health Syst Pharm 2011;68:1302

- Natural ACEI. Reduces activity by 36%
- Rich in tannins, anthocyanins and polyphenols.
- Lowers SBP in humans by 5% to 12%.($p<0.01$)
- Lowered BP 3.14/2.33 mm Hg on 330 ml per day in 4 weeks.
- Suppresses the postprandial increase in BP after high fat meal
- Reduces carotid IMT by 30% in one year
- Increases PON1 by 83%
- Reduces oxLDL 60-90%
- Increases eNOS and NO
- Decreases vascular inflammation, TSP and TGF-b
- Improves ED
- Decreases TBARS, increases catalase, SOD and GPX.
- Anti-hypertensive, anti-atherosclerotic, anti-oxidant and anti-inflammatory.

Folic acid therapy reduces the risk of mortality associated with heavy proteinuria among hypertensive patients

J Hypertens.2017 Jun;35(6):1302-1309

- A total of 20702 hypertensive patients without a history of major cardiovascular diseases were randomly assigned to a double-blind daily treatment of 10-mg enalapril and 0.8-mg folic acid or 10-mg enalapril alone
- All-cause mortality, a prespecified endpoint of the China Stroke Primary Prevention Trial, was the main outcome in this analysis.
- Median treatment duration of 4.5 years
- Folic acid supplementation significantly reduced the risk of all-cause mortality in patients with heavy proteinuria (6.4% in the enalapril-folic acid vs. 10.8% in the enalapril alone group, hazard ratio = 0.49; 95% CI: 0.26-0.94)
- There was no reduction in those with absent or mild proteinuria (2.8 vs. 2.9%, hazard ratio = 0.99; 95% CI: 0.84-1.17; P for interaction = 0.040).
- **Among hypertensive patients without a history of major cardiovascular diseases, folic acid therapy could reduce the mortality risk associated with heavy proteinuria by 51 %**

MELATONIN

Hypertension 2004;43: 192-197
Clin Exp Pharmacol Physiol. 2009.36: 436
J Hypertens 2009 ;27: S 17-20

- In a DB,R, PC ,XO study, chronic administration (3 weeks) of melatonin at 2.5 mg one hour before bedtime in hypertensive men ,on no anti-hypertensive medications lowered nocturnal BP by 6/4 mm Hg , reduced day-night amplitudes of SBP 15% and DBP 25 %, HR same, improved sleep, reduced cortisol levels.
- Endogenous circadian pacemaker in the SCN (supra-chiasmatic nucleus) regulates 24 biological rhythms by endocrine and autonomic mechanisms AND pineal melatonin secretion. Melatonin action is by GPCR on Mell-a and Mell-b receptors on vascular and other tissues. Also mediated by GABA(A) receptors through inhibition of plasma A-II levels.
- Hypertensive patients have altered circadian function with blunted day-nocturnal sympathetic and parasympathetic tone, reduced vasodilatation , suppressed nocturnal melatonin levels due to three neurotransmitters that are reduced by over 50%.
- Measure Urinary 6-hydoxymelatonin sulphate
- Beta Blockers reduce melatonin secretion
- Improves nocturnal dipping response

Melatonin Human BP Studies

Pedi Diabetes 2004;5:26
J Pineal Res 2004;36:262
Am J Hyperten 2005;18:1614
Am J Med 2006;119:898
Pol Arch Med Wewn 2006;115:520
Adv Gerontol 2008;21:132
Klin Med (Mosk) 2009;86:64
Klin Med (Mosk) 2009;87:46J Pineal Res 2011;50:261

- Improves nocturnal dipping
- Lowers cortisol
- Average reduction in all clinical trials on 3-5 mg at night is 6/3 mm Hg.
- Additive with ARB
- Mechanisms include GPCR on Mell a and Mell b receptors in vascular tissue, binds calmodulin, GABA receptors, inhibits A-II,increase NO and improve ED. Anti-oxidant.
- Beta blockers reduce melatonin secretion.

Melatonin in CVD

Curr Opin Lipidol 2016:27:408

- Reduces myocardial ischemia-reperfusion injury, myocardial hypoxia-reoxygenation injury, pulmonary hypertension, atherosclerosis, valvular heart disease, MI, CHF and hypertension.
- Anti-oxidant, anti-inflammatory, regulates lipids and glucose metabolism, activates SIRT-1, reduces apoptotic protiens (Ac FOX O1, Ac-p53, Ac NF-kB, BCL2 and BAX), increases BCL-2, increase Cu/ZN SOD, FGF, ILGF-1, protects MSC, lowers capase, preserves mitochondria, improves ATP synthesis, lowers insulin levels, increases adiponectin, increase NO, reduces TNF alpha
- Dose 2-10 mg per day

Sesame

J Nutr Sci Vitaminol 2009 55:87
J Med Food 2006;9:408
Mol Cancer Res 2010;8:751
Yale J Biol Med 2006;79:19
Nutr J 2011;10:82

- 60 mg of Sesamin for 4 weeks in mild hypertensive patients by 3.5/1.9 mm Hg ($p<0.04$)
- Black sesame meal 2.52 grams per day over 4 weeks in 15 subjects reduced SBP 8.3 mm Hg ($p< 0.05$).
- Additive with nifedipine
- Lowers glucose, HbA1C,TG and LDL-C
- Also suppresses NF-kappa B which reduces inflammation
- Active ingredients are sesamin ,sesamolin, sesaminol glucosides and furofuran lignans

Sesame

Unpublished data Kalliopi et al

- 30 hypertensive men on 35 grams of sesame oil for 2 months
- Decrease BP $p < 0.02$
- Decrease HR
- Increased total antioxidant capacity
- Improved AI and PWV

Sesame Oil and BP

J of Clinical Hypertension 2012;14:630

- 30 hypertensive patients treated with 35 grams of sesame oil vs control oil in acute and chronic study over 60 days
- CBP , SBP and DBP reduced significantly acutely and chronically at p = .006 and 0.016.
- Lowered HR (p= 0.017)
- Reduced arterial stiffness , AI and PWV (p= 0.017)
- Increased total antioxidant capacity (p= 0.007)
- Decrease inflammation
- Increase NO
- Decrease ET-1
- Sesamin is active ingredient

Quercetin

Nutrition Reviews 2015;72:720;Pharmacology 2002; 68:182
Phytother Res 2007;21:32;J Nutrition 2007;137:2405
Br J Nutrition 2009;103:1065

- Inhibits ACE
- Natural ACEI
- Chelates metal ions like zinc, that is present in ACE.
- Inhibits mast cells and T cells. Reduces immune dysfunction
- Reduces inflammation and oxidative stress
- Lowers BP in humans. 7/5 mmHg reduction in BP.
- Improves endothelial function, IR and lowers oxLDL.
- Reduces CHD and CVA
- 500 mg bid

Houston M. Acute effects of an oral nitric oxide supplement on blood pressure, endothelial function, and vascular compliance in hypertensive patients. J Clin Hypertens (Greenwich). 2014;16(7):524-9.

- This blinded placebo-controlled crossover study evaluated the acute effects of an orally disintegrating lozenge that generates nitric oxide (NO) in the oral cavity on blood pressure (BP) response, endothelial function, and vascular compliance in unmedicated hypertensive patients.
- Thirty patients with clinical hypertension were recruited and enrolled in a blinded placebo-controlled clinical trial in an outpatient setting. Average baseline BP in 30 patients was 144±3/91±1 mm Hg
- NO supplementation resulted in a significant decrease of 4 mm Hg in resting systolic BP (P<.003) and a significant decrease of 5 mm Hg in diastolic BP (P<.002) from baseline and placebo after 20 minutes. In addition, there was a further statistically significant reduction by 6 mm Hg in both systolic and diastolic pressure after 60 minutes (P<.0001 vs baseline).
- After a half hour of a single dose, there was a significant improvement in vascular compliance as measured by augmentation index and, after 4 hours, a statistically significant improvement in endothelial function as measured by the EndoPAT (Itamar Medical, Franklin, MA).
- A single administration of an oral active NO supplement appears to acutely lower BP, improve vascular compliance, and restore endothelial function in patients with hypertension

Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study.
Hypertension.2015;65(2):320-7

- Single dose administration of dietary inorganic nitrate acutely reduces blood pressure (BP) in normotensive healthy volunteers, via bioconversion to the vasodilator nitric oxide.
- Randomly assigned 68 patients with hypertension in a double-blind, placebo-controlled clinical trial to receive daily dietary supplementation for 4 weeks with either dietary nitrate (250 mL daily, as beetroot juice) or a placebo (250 mL daily, as nitrate-free beetroot juice) after a 2-week run-in period and followed by a 2-week washout.
- Drug-naive (n=34) and treated (n=34) patients with hypertension aged 18 to 85 years. The primary end point was change in clinic, ambulatory, and home BP compared with placebo.
- Daily supplementation with dietary nitrate was associated with reduction in BP measured by 3 different methods. Mean (95% confidence interval) reduction in clinic BP was 7.7/2.4 mm Hg (3.6-11.8/0.0-4.9, P<0.001 and P=0.050). Twenty-four-hour ambulatory BP was reduced by 7.7/5.2 mm Hg (4.1-11.2/2.7-7.7, P<0.001 for both). Home BP was reduced by 8.1/3.8 mm Hg (3.8-12.4/0.7-6.9, P<0.001 and P<0.01)
- No evidence of tachyphylaxis over the 4-week intervention period. The intervention was well tolerated
- Endothelial function improved by ≈20% (P<0.001), and arterial stiffness was reduced by 0.59 m/s (0.24-0.93; P<0.01) after dietary nitrate consumption with no change after placebo.

Effect of l-arginine, asymmetric dimethylarginine, and symmetric dimethylarginine on ischemic heart disease risk: A Mendelian randomization study

Am Heart J.2016 Dec;182:54-61.

- l-arginine is a commonly consumed dietary conditional essential amino acid found in food items and supplements, which is closely related to asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). l-arginine is thought to increase nitric oxide and be cardioprotective, whereas ADMA and SDMA may inhibit nitric oxide synthesis and increase cardiovascular disease risk. Unexpectedly, l-arginine increased mortality in a small trial. To clarify the effects of these potential targets of intervention, we assessed the risk of ischemic heart disease (IHD) by genetically determined l-arginine, ADMA, and SDMA.

- Single nucleotide polymorphisms (SNPs) contributing to l-arginine, ADMA, and SDMA, at genome-wide significance, were applied to the CARDIoGRAMplusC4D 1000 Genomes-based genome-wide association study IHD case (n=60,801, ~70% myocardial infarction)-control (n=123,504) study. We obtained unconfounded estimates using instrumental variable analysis by combining the Wald estimators for each SNP, taking into account any correlation between SNPs using weighted generalized linear regression.

- Higher l-arginine was associated with higher risk of IHD (odds ratio [OR] 1.18 per SD increase, 95% CI 1.03-1.36) and of myocardial infarction (OR 1.29, 95% CI 1.10-1.51), based on 2 SNPs from MED23. Symmetric dimethylarginine had an OR of 1.07 per SD (95% CI 0.99-1.17) for IHD based on 5 SNPs from AGXT2. Asymmetric dimethylarginine had and OR of 1.08 per SD (95% CI 0.99-1.19) for IHD based on 4 SNPs from DDAH1.
- CONCLUSION: l-arginine could possibly cause IHD. Given that l-arginine occurs in many common dietary items, investigation of its health effect is required.

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class

- Many of the natural compounds in food, certain nutraceutical supplements, vitamins, antioxidants, or minerals function in a similar fashion to a specific class of antihypertensive drugs.
- Although the potency of these natural compounds may be less and it may take longer to work than the antihypertensive drug, when used in combination with other nutrients and nutriceutical supplements, the antihypertensive effect is magnified.

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009
Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

- Diuretics
  - Vitamin B-6 (Pyridoxine)
  - Taurine (diuretic, lower aldosterone)
  - Celery
  - GLA
  - Vitamin C (Ascorbic Acid)
  - K^+
  - High Gamma/Delta tocopherols and tocotrienols
  - Mg++
  - Ca++
  - Protein
  - Fiber
  - Coenzyme Q-10
  - L-Carnitine
  - Hawthorne Berry

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

- Beta Blockers (BB)
  - Hawthorne Berry
- Central Alpha Agonists (CAA) (Reduced SNS Activity)
  - Taurine
  - K^+
  - Zinc
  - Na^+ restriction
  - Protein
  - Fiber
  - Vitamin C
  - Vitamin B-6
  - Coenzyme Q-10
  - Celery
  - GLA/DGLA
  - Garlic

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

Direct Vasodilators

- Omega-3 FA
- MUFA (Omega-9 FA)
- K+
- Mg++
- Melatonin
- Soy
- Fiber
- Garlic
- Flavonoids
  Vitamin D and E
- Vitamin C
- GSE
- Coenzyme Q-10
- L-Arginine
- Taurine
- Celery
- ALA

Pomegranate
Quercetin
EVOO
Garlic

Nutrient and Nutraceutical with Calcium Channel Blocking (CCB) Activity

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009
Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

- Alpha Lipoic Acid (ALA)
- Magnesium (Mg++)
- Vitamin B-6 (Pyridoxine)
- Vitamin C
- Vitamin E : high gamma/delta E with alpha tocopherol, (↑ cytosolic Mg++ with ↓ Ca++), also diuretic
- N-Acetyl Cysteine (NAC)
- Hawthorne
- Celery
- Omega-3 fatty acids (EPA + DHA)
- Calcium
- Garlic
- Taurine
- EVOO
- Olive leaf extract

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class : ACEI

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009

Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

Angiotensin Converting Enzyme Inhibitors (ACEI)

- Garlic
- Wakame Seaweed
- Tuna protein/muscle
- Sardine protein /muscle
- Hawthorne Berry
- Bonito Fish (dried)
- Pycnogenol
- Casein
- Hydrolyzed Whey Protein
- Sour Milk and Milk peptides
- Gelatin
- EVOO
- Sake
- Omega-3 FA
- Chicken Egg Yolks
- Zein
- Dried Salted Fish
- Fish Sauce
- Zinc
- Melatonin
- Pomegranate
- Quercetin
- Berberine
- Olive leaf extract
- Taurine

Natural Anti-hypertensive Compounds Categorized by Anti-hypertensive Class: ARB

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009
Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

Angiotensin Receptor Blockers (ARB's)

- Potassium (K+)
- Taurine
- Resveratrol
- Fiber
- Garlic
- Vitamin C
- Vitamin D
- Vitamin B-6 (Pyridoxine)
- Co Enzyme Q-10
- Celery
- Gamma Linolenic Acid (GLA and DGLA)
- EVOO
- Olive leaf extract
- NAC
- Melatonin (?)

Effect of Probiotics on Blood Pressure : A Systematic Review and Meta-Analysis of Randomized, Controlled Trials.

Hypertension. 2014 Jul 21. pii: HYPERTENSIONAHA.114.03469. epub

- Human clinical trials indicated that probiotic consumption may improve BP.
- Meta-analysis of randomized, controlled trials. Nine trials were included.
- Probiotic consumption significantly changed systolic BP by -3.56 mm Hg (95% confidence interval, -6.46 to -0.66) and diastolic BP by -2.38 mm Hg (95% confidence interval, -2.38 to -0.93) compared with control groups.
- A greater reduction was found with multiple as compared with single species of probiotics, for both systolic and diastolic BP. Subgroup analysis of trials with baseline BP ≥130/85 mm Hg compared with <130/85 mm Hg found a more significant improvement in diastolic BP.
- Duration of intervention <8 weeks did not result in a significant reduction in systolic or diastolic BP.
- Subgroup analysis of trials with daily dose of probiotics $<10^{11}$ colony-forming units did not result in a significant BP change
- Consuming probiotics may improve BP by a modest degree, with a potentially greater effect when baseline BP is elevated, multiple species of probiotics are consumed, the duration of intervention is ≥8 weeks, or daily consumption dose is $\geq 10^{11}$ colony-forming units.

Take Away Points: Best Nutraceutical Supplements and Doses for Hypertension

- EVOO with high polyphenol content at 150-300 mg /kg at 2-4 tablespoons n(20-40 grams) per day or olive leaf extract 500 mg bid
- Omega 3 fatty acids with DHA, EPA and GLA at 4000 mg per day. DHA most potent. (3-4 grams per day)
- Co-enzyme Q 10 to blood level of 3 ng/ml (200 mg per day)
- Natural beet root extract supplement with nitrates/nitrites
- Whey protein at 30 grams per day
- Bonito protein at 1.5 grams per day
- Aged garlic at 600 mg bid
- Grape seed extract at 500 mg bid
- Taurine at 3000 mg bid

Clinical Trial in the Treatment of Hypertension with Nutraceutical Supplement

Integrative Medicine 2013: 12:22-29

- DBPC trial of 40 hypertensive patients with BP >140/90 mm Hg but less than 180/110 mm Hg.
- 8 week trial
- Office BP readings per AHA recommendations.
- Treated with combination of Vitamin E as magnesium ascorbate, 1000 mg, grape seed extract 150 mg, Vitamin B 6 100 mg, vitamin D 2000IU , Biotin 2 mg and Taurine 6000 mg given once per day in powdered form.
- Active treatment: Reduced SBP 144 to 128.5 mm Hg at 4 weeks ($p < 0.001$). DBP reduced from 91.86 to 80.51 mm Hg at 4 weeks ($p < 0.083$) vs placebo group. Average BP reduction 15.9/11.35 mm Hg. Sustained for duration of trial.
- No adverse effects.

Hypertension Institute Clinical Research Trial on Nutrition, Nutraceutical Supplements and Life Style in Hypertension

Houston, MC. J of Therapeutic Advances in CVD. The role of cellular micronutrient analysis and minerals in the prevention and treatment of hypertension and CVD.2010; 4:165-83

- 671 hypertensive patients with BP of 140/90 to 210/115 diastolic at baseline off medications.
- MNT of micronutrients, PRA and aldosterone were done in all patients.
- Treatment consisted of antihypertensive drugs, repletion of nutritional deficiencies, therapeutic doses of appropriate nutritional supplements, DASH 2 diet, combined aerobic and resistance exercise and ideal body weight and composition.
- Composite nutritional program.

Hypertension Institute Clinical Research Trial on Nutrition, Nutraceutical Supplements and Life Style in Hypertension

Houston, MC. J of Therapeutic Advances in CVD. The role of cellular micronutrient analysis and minerals in the prevention and treatment of hypertension and CVD.2010; 4:165-83

- Hypertensive patients had significantly more micronutrient deficiencies compared to normal patients (n=2667) $p<0.0017$ Bonferroni method
- These included biotin, serine, asparagine, calcium and vitamin D ($p < 0.0017$) and for B1, choline, insulin, magnesium, CoQ-10, lipoic acid, and total antioxidant level oxidative defense ($p<0.05$)
- Repeat testing at 6 months showed significantly improved antioxidant profile by 8.47% ($p=0.03$) and over 97% complete repletion rate of micronutrients.

Hypertension Institute Clinical Research Trial on Nutrition, Nutraceutical Supplements and Life Style Treatment in Hypertension

Houston, MC. J of Therapeutic Advances in CVD. The role of cellular micronutrient analysis and minerals in the prevention and treatment of hypertension and CVD.2010; 4:165-83

62% of the hypertensive patients over a period of 6 months average (range 4 -12 months) were able to completely taper and discontinue anti-hypertensive drugs with controlled BP of 120/80 mm Hg to 126/84 mm Hg.

- The economic implications are large. US expenditure on anti-hypertensive drugs is about 20 billion per year (10% of US expenditure on drugs).
- Drug costs alone using this program could be decreased by about 12.4 billion dollars per year.

Combination Therapy – Nutrient/Nutrient; Nutrient/Drug

- Sesame with beta blocker, diuretic, and nifedipine
- Pycnogenol with ACEI
- Lycopene with various anti-hypertensive agents
- R lipoic acid with ACEI
- Vitamin C with CCB
- NAC with Arginine
- Garlic and ACEI, diuretic, beta bloc
- Coenzyme Q-10 with ACEI and CC
- Melatonin with ARB

Anti-Hypertensive Drug Nutrient Interactions

Handbook of Food Drug Interactions CRC press 2003
Therapeutic Advances in Cardiovascular Disease 2010;4:165

Diuretics (HCTZ and chlorthalidone)

Decrease K, Mg, phosphorus, sodium, chloride, folate, B6, zinc, iodine and CoQ-10.

Increase homocysteine, calcium, glucose, insulin resistance, type 2 DM (5% per year), and creatinine. Increase incidence of renal insufficiency at year 10 by over 35%

Beta Blockers (first and second generation) decrease CoQ-10

ACEI and ARB decrease zinc

Allopurinol lowers BP and CVD

J Clin Hypertens 2013;5:435
JASH 2015;9:610; J of Hypertension 2017;35:745

- Hyperuricemia is a risk for hypertension and CVD by 3 to 5 fold. Also increases CVA, ED, CKD, IR, DM, HLP, arterial stiffness, SNS increases CRP, ROS, A-II, VSMH. Decreases prostaglandins. Urate is both an oxidant and an anti-oxidant depending on serum level.
- Hyperuricemia present in 25% of hypertensive patients and 50% on diuretics.
- Risk of hypertension starts at 6 mg/dL in men and 5 mg/dL in women.
- Allopurinol significantly reduces BP in meta-analysis: 3.3/1.4 mm Hg ($p<0.001$ and 0.04).
- Allopurinol significantly reduces CVD events.
- Allopurinol inhibits xanthine oxidase and oxidative stress.
- Lowered SBP 4.3 mm Hg and urate by 2.1 mg/dL in Black hypertensive patients on chlorthalidone at 4 weeks at 300 mg per day ($p =0.059$ (JASH 2015)
- Folate also lowers uric acid (Am J Clin Nut 201;105:882)

Effects of metformin on blood pressure in nondiabetic patients: a meta-analysis of randomized controlled trials.

J of Hypertension 2017 Jan;35(1):18-26.

Twenty-eight studies from 26 articles consisting of 4113 participants were included.
Pooled results showed that metformin had a significant effect on SBP mean difference -1.98 mmHg; 95% confidence interval -3.61, -0.35; P = 0.02P = 0.02), but not on DBP
In subgroup analysis, we found that the effect of metformin on SBP was significant in patients with impaired glucose tolerance or obesity (BMI ≥30 kg/m), with a mean reduction of 5.03 and 3.00 mmHg, respectively.

CONCLUSION:
This meta-analysis suggested that metformin could effectively lower SBP in nondiabetic patients, especially in those with impaired glucose tolerance or obesity

DIURETICS (HCTZ) AND HYPERTENSION

Am J Cardiology 2011;107:1178
J of Clinical Hypertension 2011;12:867

- **TYPE 2 DIABETES MELLITUS** and glucose intolerance: Increased risk at 5 % per year, with CHD risk equivalency and increased morbidity and mortality.
- **NEPROTOXICITY AND ESRD**: Increased risk of CRI at year 10 to 12.
- **RENAL CELL CARCINOMA**
- **ADVERSE EFFECTS ON VASCULAR INFLAMMATION**: Increase hsCRP. (VAL-MARC STUDY: Hypertension 2006 ;48:73)
- Do not reduce central arterial pressure or improve vascular function (ED) or microvascular structure,vascular remodeling or hypertrophy and do not optimally reduce CHD and MI compared to CCB, ACEI and ARB .

INDAPAMIDE VS. HCTZ

J Hypertens 2003; 21:S13-17
Am J Cardiology 2011;107:1178

- Better BP control at 1.5 mg indapamide SR vs. HCTZ 25 mg / day
- Less hypokalemia by 50%
- Minimal to no hyperglycemia or insulin resistance
- Lipid neutral
- Reduce MAU in DM / HTN
- Improve Cr and GFR, reduced ESRD
- Effective in presence of ESRD with CrCL< 15 cc per minute.
- Improves LVH more than ACEI
- Better CVD reduction in clinical trials

HCTZ

J Am Coll Cardiol 2011;57:590

- HCTZ at 12.5 to 25 mg per day reduces BP by 24 hour ABM by 6.5/4.5 mm Hg
- This is inferior to all other classes of antihypertensive agents
- This reduction in BP is similar to placebo
- There are no long term clinical trials to address CVD at this lower dose
- HCTZ is not recommended for the treatment of hypertension

Chlorthalidone

J of Clin Hypertension 2013;15:359
Hypertension 2012;59:1104
Hypertension 2012;59:1110
Annals Int Med. 2016;165:663

- 8 mg has same BP control as 25 mg HCTZ and 1.25 mg Indapamide
- 2% greater reduction in CHD/CVD events compared to HCTZ and 23 % greater reduction in CHF.
- More hypokalemia, hyperuricemia and volume depletion than the other diuretics
- Long duration of action, better nocturnal control and some pleiotrophic effects compared to HCTZ
- VA study (Diuretic Comparison Project): 13,500 patients for 3 years to compare CVD events with HCTZ vs. chlorthalidone.

Genetic Variant CYP4A11 and Hypertension Salt Sensitivity, ENaC and Amiloride

JASH 2014;8: 475;JASH 2014;8:872

- **In blacks, with resistant ,volume-dependent hypertension who are homozygous for the C allele at rs3890011 of CYP4A11, associated with BP, are resistant to spironolactone but respond to amiloride.**
- **CYP4 A11 oxidizes AA to 20 HETE which increases BP, causes vasoconstriction and natriuresis**
- **Increased activity of ENaC by loss of 20HETE inhibition induces salt sensitive resistant hypertension.**
- **Have increase urinary aldosterone/potassium ratio.**
- **Albuminuria allows plasminogen to be filtered and activated in tubules to plasmin which activates ENaC**
- **Amiloride reduces BP, attenuates the plasminogen to plasmin activation and inhibits urokinase-type plasminogen activator**
- **Amiloride 5 to 10 mg per day will lower BP average 6/3mm Hg in resistant hypertensive patients.**
- **Monitor K+.**

SUMMARY: Beta blockers: First and second generation

J of Clinical Hypertension 2011;13(12): 917
Lancet 2005;366:895 (CAFÉ trial)

- BP reduction inferior in blacks and elderly
- Do not reduce central arterial pressure adequately
- CVA reduced less than with other agents (especially ARB).
- CHD, MI and total mortality not reduced with monotherapy
- CHF reduced and prevented
- Post MI reduction and arrythmmias. Should receive non ISA-BB
- Renal protection and proteinuria reduction inferior to ACEI, ARB and CCB, but superior to diuretics
- Adverse effects high, refill and compliance rates low
- Metabolic abnormalities common, IR, DM, lipids, urate
- Lower CoQ10
- No improvement in vascular function or structure
- Increase ADMA and augmentation index

- NOTE: Nebivolol and Carvedilol are preferred beta blockers for hypertension due to favorable BP, CBP, AI, PWV ED, SVR, NO, antioxidant and other vascular and metabolic effects.

CCB AND CVA

AJH 2004;17:1817

- Meta-analysis of 103,793 subjects in 13 clinical trials
- DHP –CCB reduced CVA 10 % more than any other class of anti-hypertensive agents (95%CI .84-.96, p=0.002)
- Non DHP CCB did not have significant reduction over other anti-hypertensive agents
- The DHP-CCB have an independent effect on reducing CVA beyond their BP lowering effect.

ROLE OF CCB, ACEI and ARB IN HYPERTENSION

Houston MC. Handbook of Hypertension Wiley Blackwell Oxford UK 2009
Houston MC. What Your Doctor May Not Tell You About Hypertension 2003

- CCB (amlodipine), ACEI and ARB'S are preferred initial and maintenance therapy in most hypertensive patients as monotherapy or in selected combinations– amlodipine with ACEI or ARB
- DHP CCB are preferred over non DHP-CCB and amlodipine is the preferred DHP CCB
- ACEI and ARB are not recommended in combination at this time (ON TARGET Trial) except for reduction in proteinuria and renal protection. DRI should not be used with ACEI or ARB.
- ACEI and ARB are equivalent in reducing CV events and are interchangable (ON TARGET Trial)
- The ARB Telimisartan ameliorates the neuronal inflammatory response to IL-1beta partly through the JNK/c-Jun and NADPH oxidase pathway to reduce CND inflammation (J of Neuroinflammation 2012;9:102.)
- Higher doses of ACEI and ARB are recommended to control BP and reduce TOD (effects independent of BP reduction)
- ACEI better than ARB for CCB-induced edema.

ACE vs ARB in Clinical Trials

JASH 20159:582;JAMA 2016:176:1085
Progress in CVD 2016;58:473

ACEI may be superior to ARB in some regards

- CHD or CVD mortality or MI in hypertensive patients. 14 % reduction of MI with ACEI and 8% increase with ARB
- CHD and CVD mortality in diabetic- hypertensive patients.
- Total mortality reduced 9% with ACEI and no change with ARB.
- BP reduction, CVA reduction and CHF reduction is equal between ACEI and ARB
- ACEI in ALLLHAT reduces cardiac conduction disease more than other agents such as diuretics and CCB

ACEI and ARB in Microalbuminuria

Clinical Diabetes 2012;30:20

- ACEI and ARB reduce microalbuminuria in hypertensive patients, hypertensive diabetic patients and diabetic patients with clinically evident proteinuria.
- In addition, ACEI and ARB may decrease the time of onset of microalbuminuria in patients with Type 2 DM even under conditions of excellent blood pressure control.

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Significant natriuretic and antihypertensive action of the epithelial sodium channel blocker amiloride in diabetic patients with and without nephropathy.

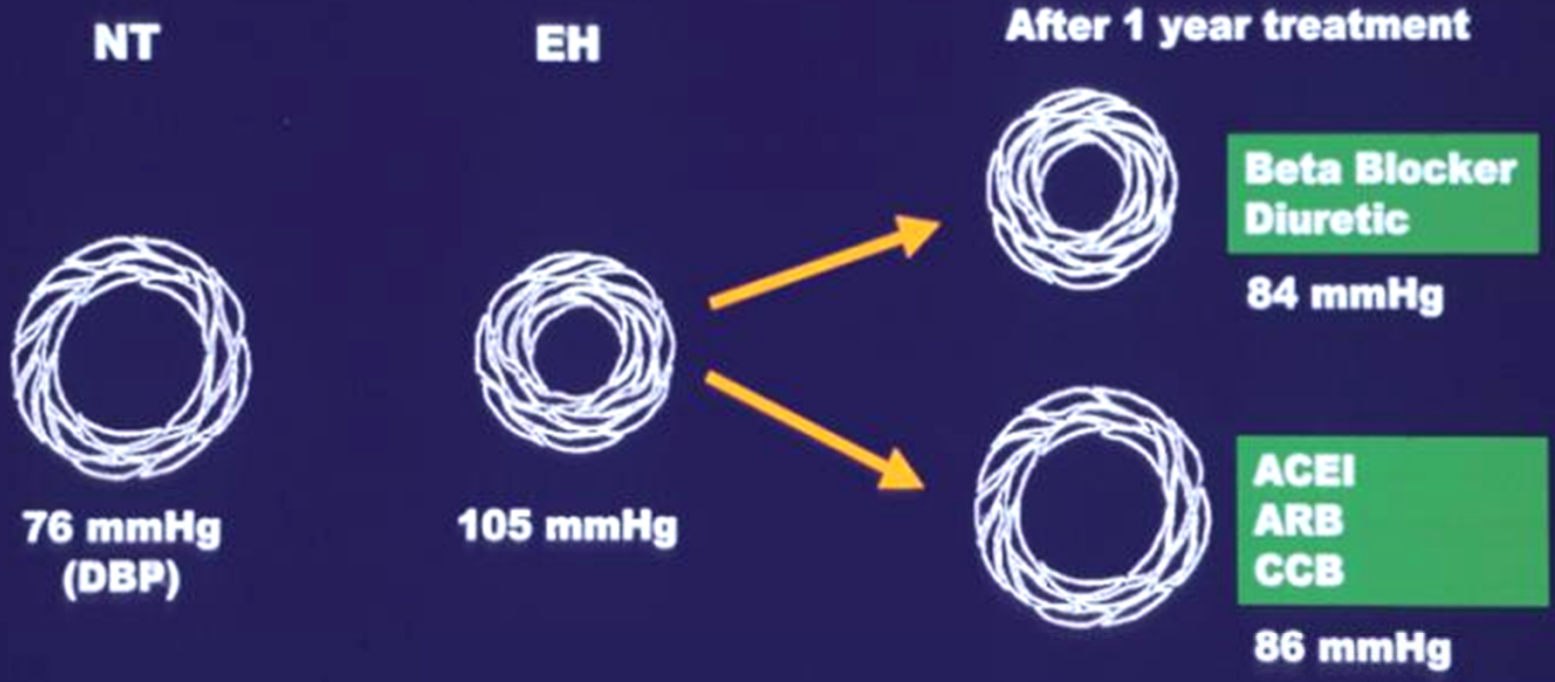
J Hypertens.2016 Aug;34(8):1621-9

- Diabetic nephropathy is associated with aberrant glomerular filtration of serine proteases such as plasminogen. Plasminogen is converted to plasmin in the urine of the diabetic neprhropathy patient. This activates the epithelial sodium channel proteolytically by urine plasmin in diabetic nephropathy and mediates renal sodium retention.

- In an open-label intervention study on type 1 diabetes patients on standardized NaCl intake (200 mmol/day) with (n = 15) and without diabetic nephropathy (control, n = 12), urinary Na excretion in response to oral amiloride (20 or 40 mg/day for 2 days) was compared.
- RESULTS: A total of 27 patients completed the study and nine diabetic nephropathy and eight control study participants were compliant (24-h urine Na excretion of 200 mmol ± 30%). Amiloride increased significantly total and fractional Na excretion in both groups. Total natriuresis and weight loss were significantly larger in the control group compared with diabetic nephropathy at day 1 of amiloride, whereas fractional Na excretion did not differ. Amiloride intervention increased plasma renin concentration only in diabetic nephropathy group; it reduced SBP in both groups, whereas DBP was reduced in diabetic nephropathy group only. Albuminuria was reduced significantly by amiloride in diabetic nephropathy group. Urine total amiloride concentration was not different between groups (12 ± 1 and 16 ± 1 μmol/l, respectively). Urine total plasminogen and active plasmin were reduced after amiloride in diabetic nephropathy.

- CONCLUSION: Amiloride increased renal Na excretion, reduced blood pressure, albuminuria, and total and active plasmin in urine. It is concluded that epithelial sodium channel is an attractive target to attain blood pressure control in long-term type I diabetes with no enhanced activity associated with nephropathy.

Anti-Hypertensive Drug Effects on Vascular Remodeling in Humans [108]



Metformin and Hypertension

J Hypertens.2017 Jan;35(1):18-26

28 studies from 26 articles consisting of 4113 participants

Metformin had a significant effect on SBP (mean difference -1.98 mmHg; 95% confidence interval -3.61, -0.35; P=0.02), but not on DBP (mean difference -0.67 mmHg; 95% confidence interval -1.74, 0.41; P=0.22

Metformin on SBP was significant in patients with impaired glucose tolerance or obesity (BMI ≥30 kg/m), with a mean reduction of 5.03 and 3.00 mmHg, respectively. Significant heterogeneity was found for both SBP (I=60.0%) and DBP (I=45.4%)..

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CONCLUSION: This meta-analysis suggested that metformin could effectively lower SBP in nondiabetic patients, especially in those with impaired glucose tolerance or obesity

ACEI and Pentoxifylline

Clin Hemorheol Microcirc 1998;18:285
J of Am Soc Hypertension 2017;11:769

- ACEI and Pentoxifylline improve BP and hemo-reholgoical status and reduce CV damage.
- Pentoxifylline reduces blood viscosity and SVR by altering RBC properties of deformability
- Also is antioxidant, anti-thrombotic and anti-inflammatory

J Hypertens. 2017 Jan;35(1):18-26.

Effects of metformin on blood pressure in nondiabetic patients: a meta-analysis of

Zhou L[1] Liu H, Wen X, Peng Y, Tian Y, Zhao L.

AUTHOR INFORMATION

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Abstract

OBJECTIVE:

To evaluate the effects of metformin on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in nondiabetic patients

CONCLUSIONS and RECOMMENDATIONS

J of Clin Hypertension 2013;15:359
Hypertension 2012;59:1104;Hypertension 2012;59:1110
J of Hypertension 2013;37:1281-1357; JASH 2015;9(4): 257-265

- Aggressive, early BP reduction for best CV decrease
- New BP goals to 120/80 mm Hg.
- 24 hour ABM and with brachial and central BP are recommended over office or home brachial BP.
- Non invasive vascular testing for function and structural abnormalities with PWV, AI, CBP, ED, AC.
- Nocturnal antihypertensive treatment is best.
- Initial therapy in most hypertensive patients should be amlodipine/ACEI or amlodipine/ARB
- Indapamide is diuretic of choice then chlorthalidone. Avoid HCTZ alone or in combination with other agents.
- Nebivolol and Carvedilol are BB of choice. Avoid other older BB for hypertension.
- Renin inhibitors (DRI) are appropriate for add treatment except to ACEI and ARB.
- Do not use ACEI with ARB.

CONCLUSIONS and RECOMMENDATIONS
JASH 2015;9(4): 257-265

- Aggressive, early BP reduction for best CV decrease
- New BP goals to 120/80 mm Hg . 24 hr ABM and central BP are recommended over office and arm BP.
- Nocturnal antihypertensive treatment.
- Initial therapy in most hypertensive patients should be amlodipine/ACEI or amlodipine/ARB
- High risk CV patients with hypertension and two other CV risk factors or those with DM should received at statin as well for initial therapy regardless of the LDL level.
- Indapamide is diuretic of choice then chlorthalidone
- Nebivolol and Carvedilol are BB of choice

PRACTICAL GUIDELINES FOR PHARMACOLOGIC TREATMENT OF HYPERTENSION ORDER OF PREFERENCE

- Amlodipine/ACEI or Amlodipine/ARB given at 6 PM (reduce edema and improve circadian/nocturnal BP control and dipping status). Dose amlodipine to 5mg/day and maximize the ARB and ACEI dose). Indapamide 1.25 to 2.5 mg Q AM
- Nebivolol (5 to 40 mg QD) or Carvedilol CR 10 to 40 mg QD)
- Spironolactone 12.5 to 25 mg QD in resistant hypertension or in low renin hypertension
- Amiloride 5-10 mg per day
- Aliskirin (DRI) 150- 300 mg QD)

Case Presentations

CASE 1

- 42 year old BM with hypertension for 10 years
- BP 160/100 mm Hg on no meds.
- Normal weight. Non smoker
- No caffeine or alcohol use
- History negative
- FH negative for hypertension. Positive for CHD
- PE shows mild hypertensive retinopathy, S3 gallop, systolic murmur
- Lab is normal except for FBS of 102 mg/dl and Vitamin D level of 24 ng/ml. HSCRP is 1.0 (normal)
- EKG: Left ventricular hypertrophy
- Plasma renin activity (PRA): 3.2 ng/ml/hour
- MNT micronutrient deficiencies: Mg, CoQ-10, Vitamin D, Vitamin C, and Vitamin B 6

What is the type of hypertension ?

1. Low Renin hypertension
2. High Renin hypertension
3. Cannot determine from the data.
4. Does not matter in regards to treatment.

The best initial treatment is:

A. Replacement of all micronutrient deficiencies and start recommended high dose therapy with CoQ-10, Vitamin B6 and whey protein.
B. DASH diet with supervised exercise program
C. Diuretic and Beta Blocker therapy
D. A and B
E. None of the above

This patient also has which of the following:

A. Metabolic Syndrome
B. Inflammatory vascular disease
C. Insulin resistance
D. None of the above

The diagnosis above is due to:

A. Obesity
B. High intake of protein and fish
C. Multiple micronutrient deficiencies
D. None of the above

Other Tests

- Evaluation for secondary causes of hypertension such as RA duplex, adrenal CT, 24 hour urines for VMA, cats, mets, 24 hydroxy corticosteroids, aldosterone and free cortisol are normal
- Insulin level is 8. HOMA is 2.04
- 24 hour ABM shows mean BP 156/96 mm Hg, non dipper, AM surges.
- ECHO shows mild LVH with diastolic dysfunction with normal EF of 60%
- EndoPAT is abnormal with score of 1.45 (normal > 2.1)
- CAPWA is abnormal: C1 AC is 7 (normal 12) and C2 AC is low at 3.2 (normal over 7). Large and small arterial vascular stiffness and loss of compliance.
- MAU is 45 with normal creatinine and GFR.
- Cardiovascular genetic profile for hypertension SNPs is negative.
- All other labs and tests are normal including his advanced lipid profile, CORUS gene expression, CAC, carotid duplex, ABI.

Case 1 Criteria to decide treatment

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

Case 1 Discussion

- Patient has high renin hypertension (HRH)
- He should be treated with nutrition (DASH 2), nutraceuticals, gradual supervised exercise initially with only walking until BP is better controlled and integrate drugs depending on the assessment criteria
- Use the nutrients and drugs that are for HRH such as ACEI, ARB, or DRI. CCB could also be used.
- His BP is significantly elevated with surges and non dipping.
- CHD risk analysis with COSHEC (23) and RASMUSSEN (13) are high
- He has preclinical testing that are abnormal such as EndoPAT and CAPWA
- He has CV TOD and should be started on ACEI or ARB. The CV TOD is retinopathy, S3 ventricular gallop, diastolic dysfunction and LVH.
- He has concomitant CVD risk factors: dysglycemia, insulin resistance and elevated HOMA.
- Studies indicate that earlier aggressive treatment will reduce future CV events.

Case 1 Discussion

- Patient has high renin hypertension (HRH) and should be treated with nutrition, nutraceuticals, exercise initially and integrate drugs depending on BP response and TOD, that work in HRH such as ACEI, ARB, or DRI.
- Replete all measured deficiencies: Mg, CoQ-10, Vitamin C, Vitamin B6 and Vitamin D.
- Omega 3 FA: Natural ACEI and CCB, lowers glucose
- GLA: Natural ARB
- Whey Protein: Natural ACEI
- Vitamin C: Natural ARB also
- CoQ-10 : Natural ARB also
- Mg: Natural CCB also
- Vitamin B 6: Natural ARB also
- Vitamin D: Reduces PRA and good treatment for HRH.
- ACEI and ARB are best drugs for HRH and reduce LVH

Case I: Treatment

- DASH 2 modified diet
- 60 minutes per day of walking with supervision starting slow and increasing as BP is controlled
- Magnesium chelates 500 mg twice per day
- CoQ-10 100 mg twice per day to blood level of 3 ug/ml
- Vitamin B6 100 mg twice per day
- Vitamin C 500 mg twice a day
- EFA (Omega 3 complex): (DHA, EPA, GLA, gamma delta E): 5 grams per day
- Hydrolyzed whey protein: 30 grams per day
- Vitamin D 3 at 4,000 IU per day to blood level 60 ng/ml
- ACEI: Quinapril 40 HS

Case I: Results

BP at 6 weeks: 134/88 mm Hg

BP at 3 months: 124/82 mm Hg

Exam and labs at 3 months

- **No murmur, retinopathy improved**
- **FBS 94 mg/dl , insulin level is 4. HOMA is 0.94**
- **Vitamin D 62 ng/dL**
- **MNT is normal**
- **24 hour ABM shows mean BP 122/78 mm Hg, dipper, no AM surges.**
- **EndoPAT score of 2.45 (normal > 2.1)**
- **CAPWA is normal: C1 AC is 13 (normal 12) and C2 AC is 8 (normal over 7).**
- **MAU is zero with normal creatinine and GFR**

Case 2

- 55 yo WF with new onset hypertension
- BP 148/94 mm Hg on no medications or supplements
- History negative
- PE normal
- Lab normal
- EKG normal
- PRA 0.20 ng/ml/hr
- Micronutrient deficiencies: GLA, lipoic acid, vitamin B6 and magnesium
- Omega 3 index is low at 2 (normal is over 8).

What is your treatment plan?

What type of hypertension does this patient have?

A. Low renin hypertension
B. High renin hypertension
C. Normal renin hypertension
D. Very high renin hypertension

What is the best type of treatment for this patient?

A. No treatment, patient is a low risk for CVD
B. Immediate treatment with ACEI or ARB
C. Replete micronutrients and start high dose nutrients that treat the mechanism of hypertension based on the PRA status.
D. Start high sodium and low potassium diet to induce the desired diuretic effect.

Name 4 micronutrients that would be best treatment options:

A. Bonito protein, whey protein, hawthorne berry and Pycnogenol
B. Omega-3 FA, vitamin B6, R-lipoic acid (with biotin) and magnesium
C. Either A or B will work in this patient
D. None of the above.

How long should you wait until rechecking the micronutrient deficiency and omega-3 deficiency?

A. One year
B. 3 months
C. 2 weeks
D. No need to check again

Case 2: Discussion

- Patient has low renin hypertension (LRH)
- Use nutraceuticals and/or drugs that work in LRH such as diuretics and calcium channel blockers (CCB)
- Replete deficiencies: GLA, lipoic acid, vitamin B 6 and magnesium
- GLA is also natural diuretic
- Lipoic acid is also natural CCB
- Vitamin B 6 is natural CCB and diuretic
- Taurine is natural diuretic
- Magnesium is natural CCB and diuretic
- Omega 3 fatty acids are natural CCB. The balanced EFA omega-3 complex also has GLA and gamma/delta tocopherol with diuretic effects

Case 2: Treatment

- Dash 2 Diet
- Combined aerobic and resistance exercise at 6 days per week at 60 minutes per session (ABCT)
- GLA 500 mg twice per day
- R-lipoic acid 100 mg per day with Biotin 2 mg per day
- Vitamin B 6 at 100 mg twice per day
- Taurine at 3 grams twice per day. Lowers BP and is diuretic
- Magnesium chelates at 500 mg twice per day
- EFA Omega 3 complex 5 grams per day

Case 2: Results

RESULTS: **BP at 6 weeks:** **126/84mm Hg**
BP at 3 months: **118/78 mm Hg**
BP at 6 months: **116/76 mm Hg**
All deficiencies are repleted and Omega index 8

Case 3

- 42 yo WM with Hypertension for 10 years treated with a diuretic (HCTZ 25 mg a day) and Beta Blocker (metoprolol 100 mg/day)
- BP is 176/104 mm Hg
- Complains of fatigue, dyspnea, ED, poor memory
- PE : 5'8, 196#, retinopathy, systolic murmur, bradycardia 48 bpm
- Lab: LDL cholesterol 142 mg/dl, dense with 1250 LDL-P, TG 340 mg/dl, HDL, 32 mg/dl and FBS is 106 mg/dl, PRA is 0.10 ng/ml/hr, K is 3.5 mg/dl and Mg is 1.0 mg/dl
- Micronutrient deficiencies: CoQ-10 and glutathione
- EKG: bradycardia, L-atrial & L-ventricular hypertrophy, unifocal PVCs
- ECHO: mitral insufficiency 2+, LAH, and LVH
- CAPWA: low C2 AC at 3.2 (normal >7)
- ENDOPAT: moderate endothelial dysfunction (1.32)(nml >1.68)

What is your treatment plan?

Case 3

- Type of hypertension can not be determined with PRA as BB decrease PRA and diuretics increase PRA.
- Replete nutrient deficiencies and electrolyte deficiencies: CoQ-10, glutathione, K+, and Mg++
- BP poorly controlled on two BP meds with side effects. Will need to taper and discontinue both drugs and start new treatment.
- Fatigue from BB and diuretic
- Dyspnea from BB
- ED from BB and diuretic
- Poor memory from BB
- Bradycardia from BB
- Obesity is exacerbated by BB
- Dyslipidemia from BB and diuretic
- Dysglycemia from BB and diuretic
- Hypokalemia and hypomagnesemia from diuretic
- Low CoQ-10 from BB and diuretic
- Low CAPWA and ED from BP, BB and diuretic

Case 3: Treatment

- DASH 2 Diet
- Combined exercise at 60 minutes per day
- Weight loss to IBW of 153 lbs
- Taper metoprolol over 6 weeks
- Taper HCTZ over 6 weeks
- Start CoQ-10 100 mg twice per day
- Whey protein at 30 gm per day, R-lipoic acid 100 mg per day, NAC 1000 mg per day, and niacinamide 1000 mg bid to increase glutathione
- Increase potassium in diet to 5000 mg per day
- Magnesium chelates 1000 mg twice per day

CASE 3

BP at 2 weeks:	145/92 mm Hg
BP at 4 weeks:	132/86 mm Hg
BP at 8 weeks:	122/82 mm Hg HR 68 b/min
BP at 4 months	120/80 mm Hg
BP at 6 months:	118/76 mm Hg

- 6 months: Off all prescription meds, weight is 164 lbs, no dyspnea, ED normal, fatigue and memory normal. Feels well. LDL is 102 mg/dl, with normal LDL and 950 LDL-P, TG 136 mg/dl, HDL 40 mg/dl, FBS 88 mg/dl. Murmur absent, retinopathy improved, no PVCs
- No nutrient deficiencies by MNT
- EKG normal
- PRA: 0.16 ng/ml/hr off all drugs. LRH
- CAPWA: C2 7.0 normal
- ENDOPAT: Normal endothelial function 2.16
- ECHO: LVH decreased. No mitral insufficiency

Case 3: Major Points

- The beta blocker & HCTZ caused all of his side effects.
- The beta blocker & HCTZ induced insulin resistance, dyslipidemia.
- Beta blocker reduced CoQ-10.
- Diuretic reduces potassium and magnesium.
- The beta blocker increased his BP as he had baseline LRH.
- Beta blockers must be tapered slowly over about 6 weeks to avoid withdrawal syndrome.
- Diuretics must be tapered over 6 weeks to avoid intravascular volume overload with sodium and water retention due to increased aldosterone.
- The beta blocker caused endothelial dysfunction and reduced C- 2 arterial compliance.
- This treatment regimen reduced BP to normal in 61% of patients over 6 months in the Hypertension Institute with complete tapering of anti-hypertensive drugs.

CASE 4

CASE 4

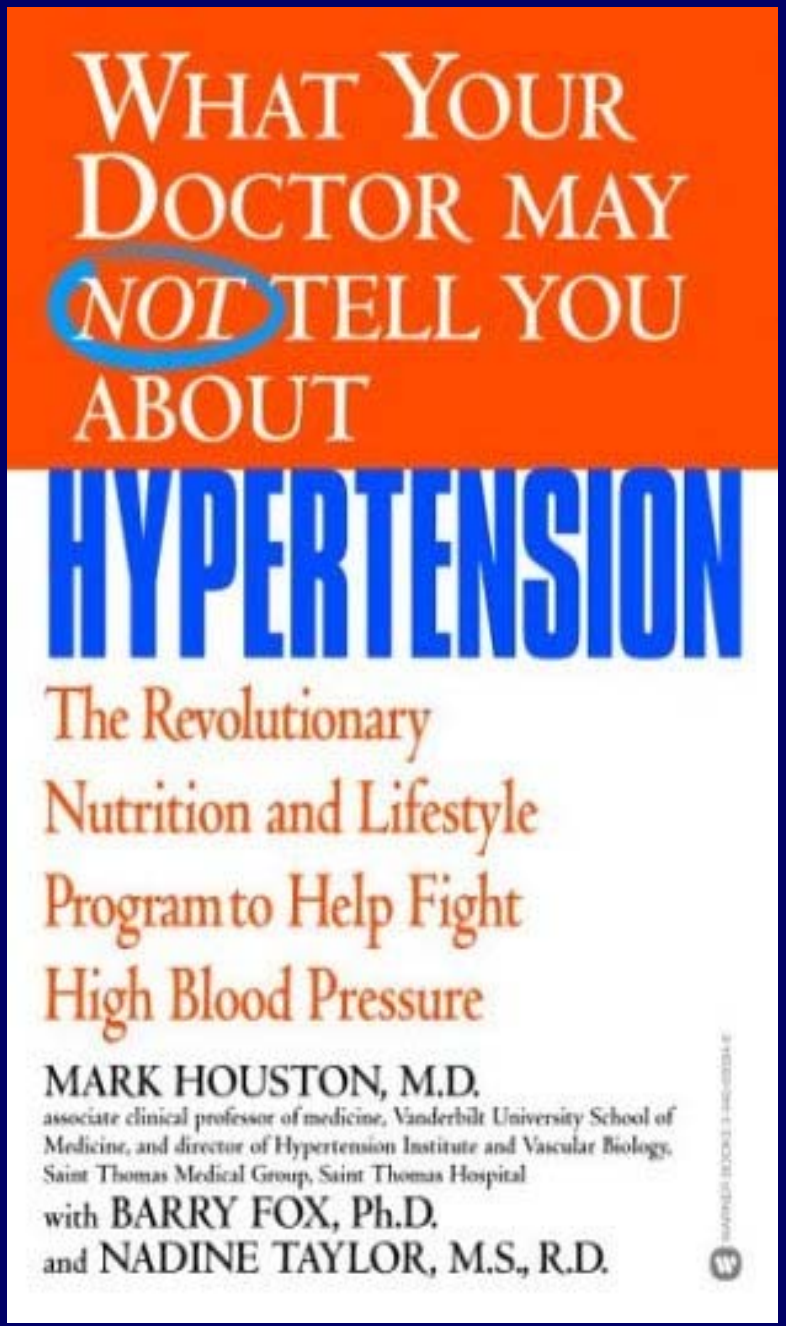
- 61 year old BF
- Hypertension for 12 years treated with amlodipine 5mg
- BP 164/96 mm Hg office and 158/ 94 on ABM
- Chest pain, GERD, fatigue
- Menopausal on black cohash
- Vitamin D 26
- Increased MPO 690
- MR, TR, PI mild on ECHO
- PVCs unifocal. 2300 in 24 hours
- PRA 0.22
- ENDOPAT 1.56 (low): ED
- Genetics: 9p21, 6p 24, CYP 11 B2, CYP 4A11, Apo C3, ACE I/D MTHFR 1298 , NOS 3, CYP 1A2.

CASE 4

- Started Aldactone 50 mg am
- Vitamin D emulsion 6000 IU/day
- Pomegranate seed ¼ cup per day
- EGCG 500 mg bid
- Magnesium Malate chelate 500 mg bid
- Omega 3 FA 3 grams per day
- Stopped caffeine
- Methylation protocol with B vitamins, SAME
- Neo 40 beet extract
- Probiotics and glutamine

CASE 4 at 2 month visit

- BP 118/ 76 mm Hg
- Vitamin D 56
- MPO normal at 390
- ENDOPAT 2.2
- No PVCs
- Murmurs absent
- All symptoms resolved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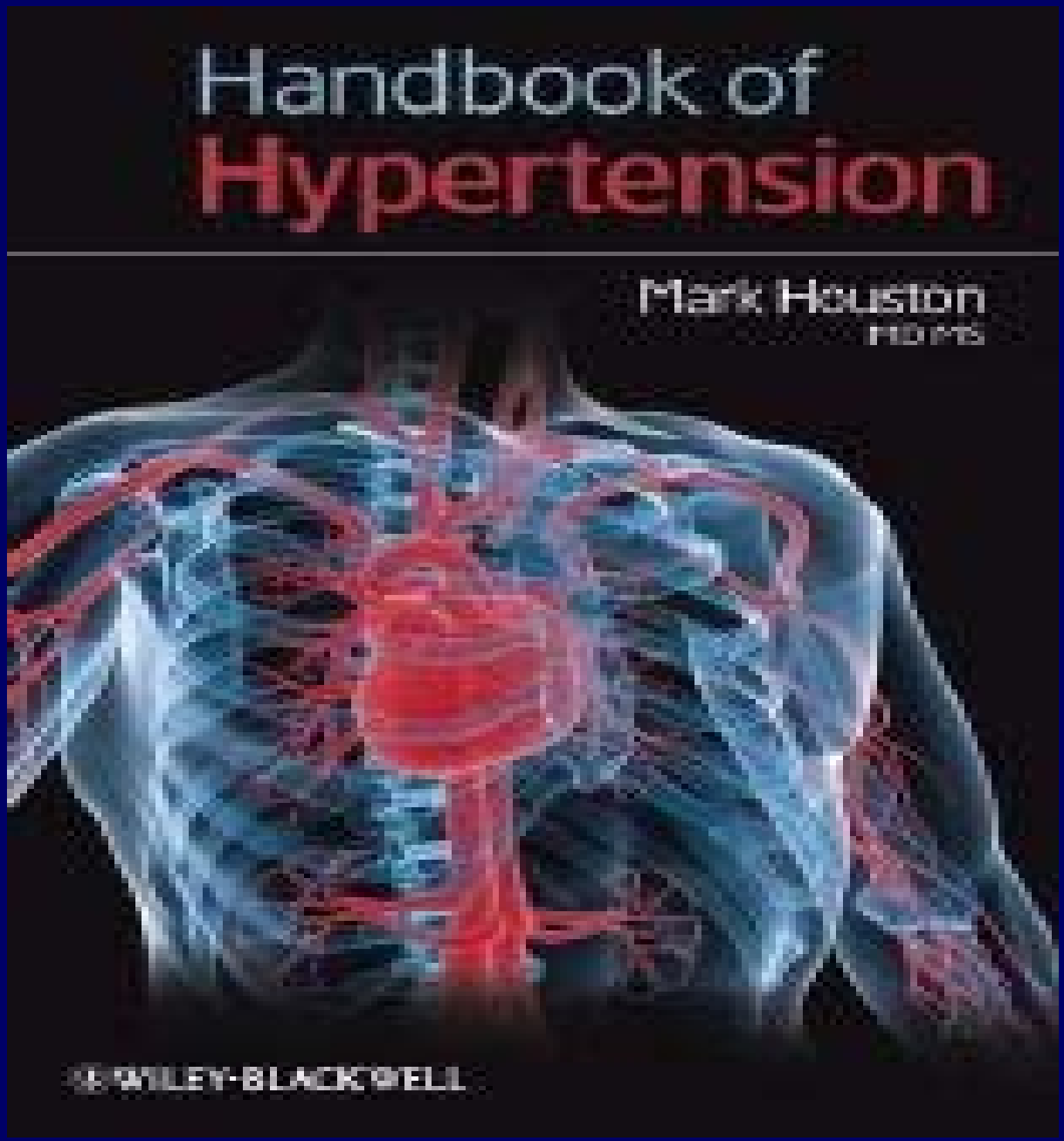
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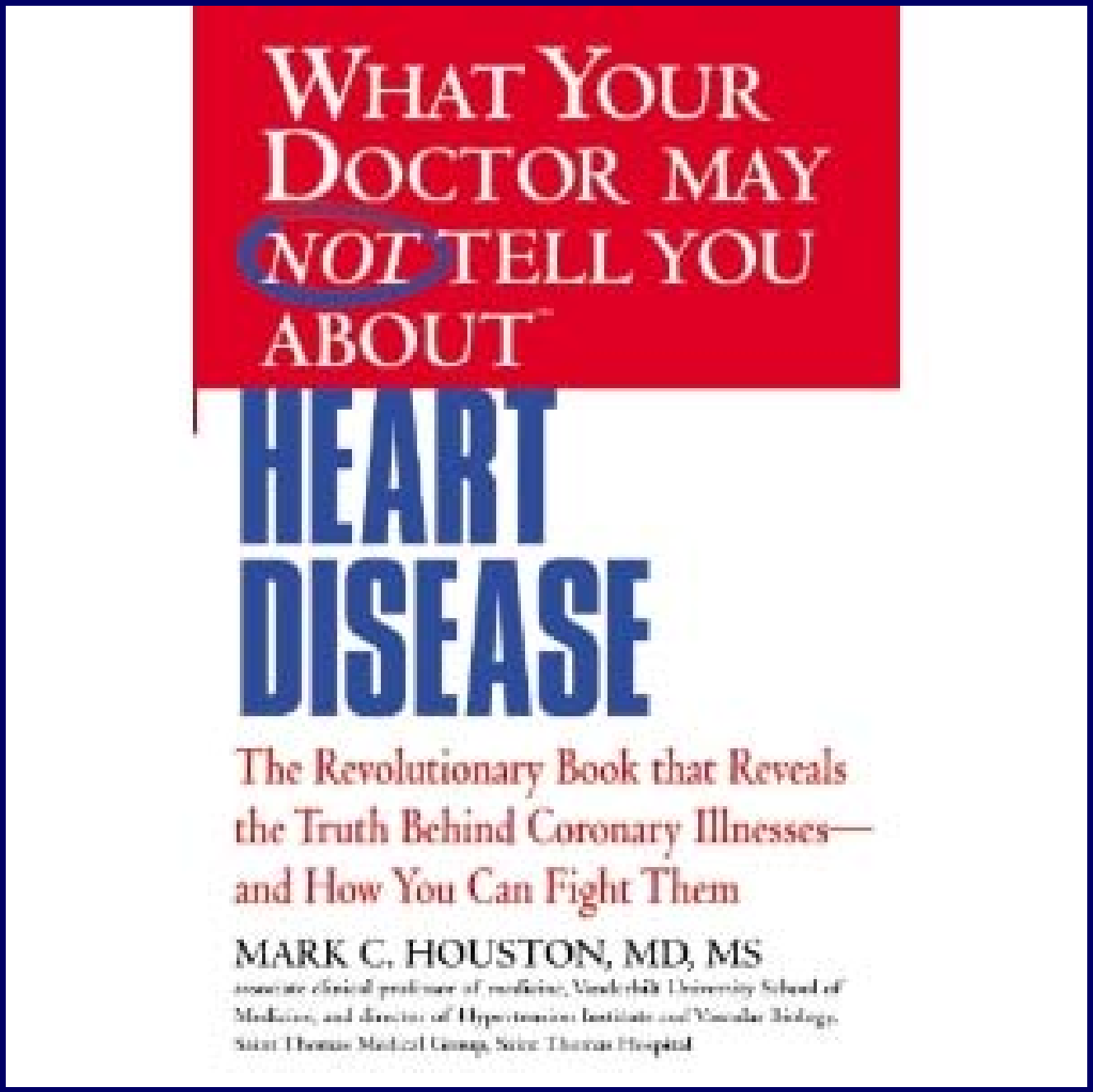
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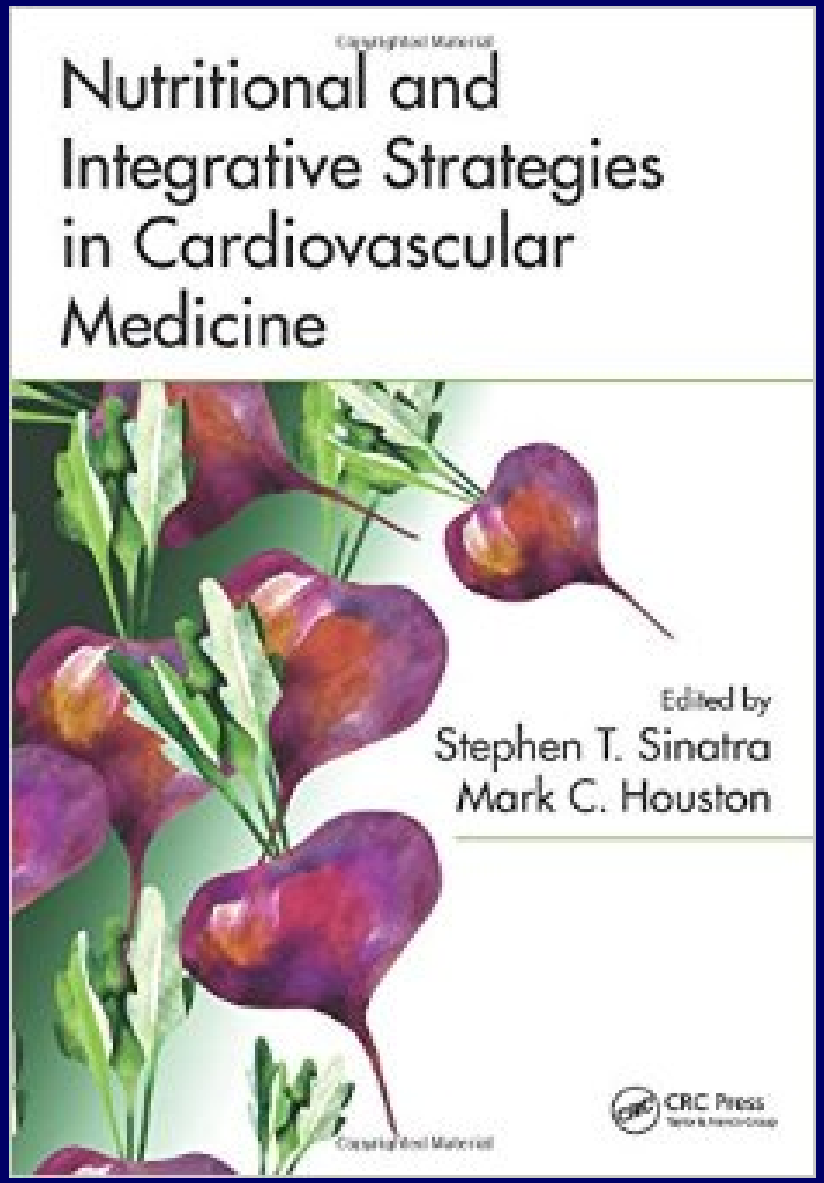
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