

Functional Medicine University's Functional Diagnostic Medicine Training Program

Module 5 * FMDT 545A

Cardiovascular Disease: A Comprehensive Approach to Evaluation and Management

By Wayne L. Sodano, D.C., D.A.B.C.I., & Ron Grisanti, D.C., D.A.B.C.O., M.S.
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Functional Medicine University's
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Module 5: FDMT 545A: Cardiovascular Disease: A Comprehensive Approach to Evaluation and Management
By Wayne L. Sodano, D.C., D.A.B.C.I., & Ron Grisanti, D.C., D.A.B.C.O., M.S.
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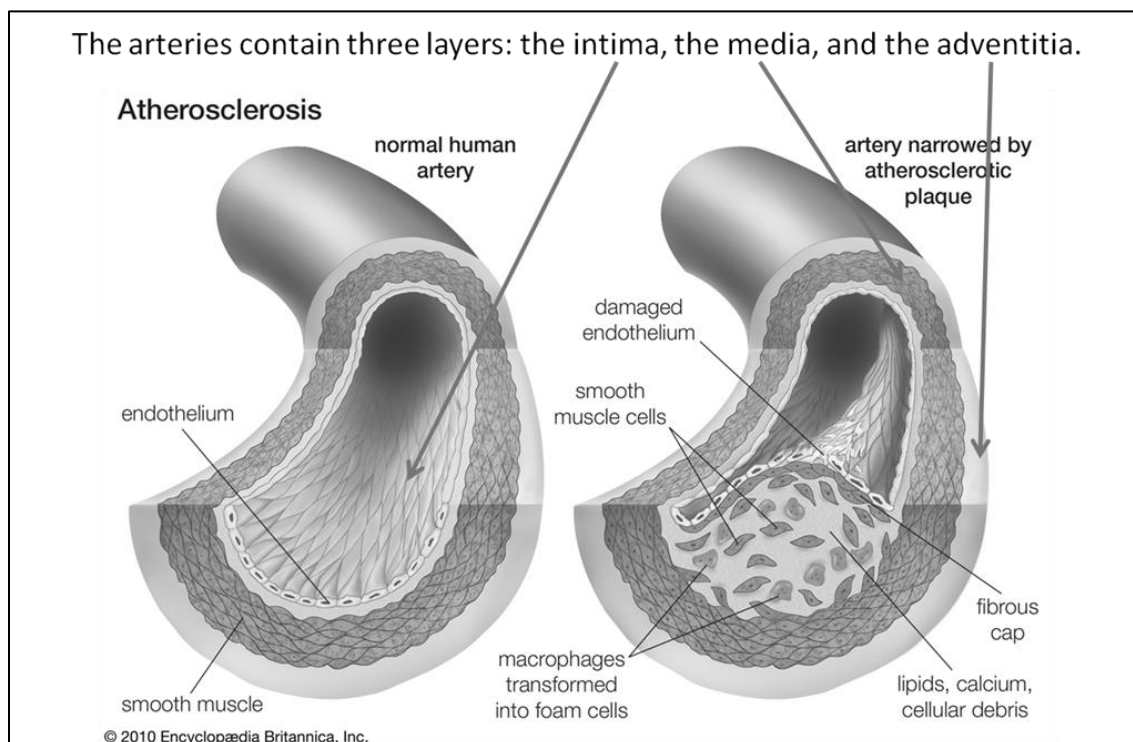
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(Required Reading): *The Atherosclerosis Time-Line and the Role of the Endothelium.* This article may be downloaded from the FMU on-line library.

2010 Update from the American Heart Association

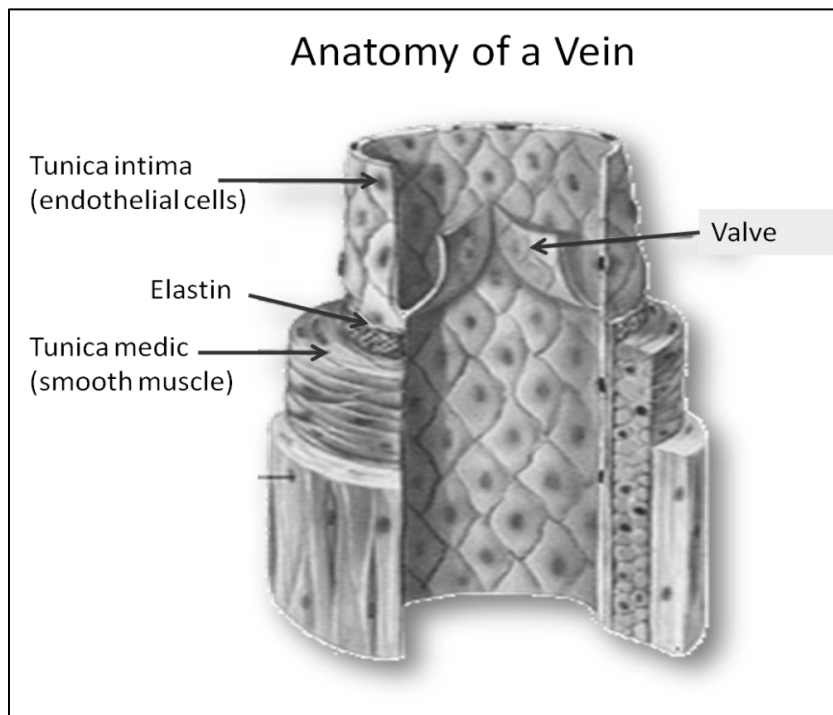
The American Heart Association, in conjunction with the Centers for Disease Control and Prevention, the National Institutes of Health, and other government agencies, gathered statistical information on heart disease, stroke, other vascular diseases and their risk factors and present them in a yearly update. A summary of the 2010 update from the American Heart Association concluded the following:

- The 2006 overall death rate for CVD was 262.5 per 100,000 (1 of every 2.9 deaths in the U.S.)
- 2300 Americans die of CVD each day (average of 1 death every 38 seconds)
- Coronary heart disease caused approximately 1 of every 6 deaths in the U.S. in 2006
- In 2006 1 in 8.6 death certificates mentioned heart failure
- Data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006 indicated that 33.6% of US adults ≥ 20 years of age have hypertension.
- Despite four decades of progress, in 2008, among Americans ≥ 18 years of age, 23.1% of men and 18.3% of women continued to be cigarette smokers. In grades 9 through 12, 21.3% of male students and 18.7% of female students reported tobacco use.
- In 2006, an estimated 17,200,000 Americans had diagnosed diabetes, representing 7.7% of the adult population. A further 6,100,000 had undiagnosed diabetes, and 29% had prediabetes, with abnormal fasting glucose levels.
- The estimated prevalence of overweight and obesity in US adults was 66.3% in 2006
- Among children 2 to 19 years of age, 31.9% are overweight and obese
- Fifty-nine percent of adults who responded to the 2008 National Health Interview Survey reported engaging in no vigorous activity



The intima surrounds the lumen of the blood vessels and is made up of a single continuous lining of endothelial cells. The endothelial cells have the capacity to perform a significant amount of metabolic reactions. The intact endothelium synthesizes regulators of thrombosis like prostacyclin, plasminogen activator, and heparin-like molecules. It produces prothrombotic molecules, and modulates blood flow and vascular reactivity. It produces vasoconstrictors like endothelin and angiotensin-converting enzyme (ACE), as well as, vasodilators, such as, nitric oxide and prostacyclin. The intimal endothelium also regulates immune and inflammatory reactions through elaboration of cytokines, adhesion molecules, and histocompatibility antigens. The media is composed of smooth muscles that dilate and constrict to accommodate blood flow and blood pressure. The media is sandwiched between an inner (internal) and outer (external) layer of elastic membrane.

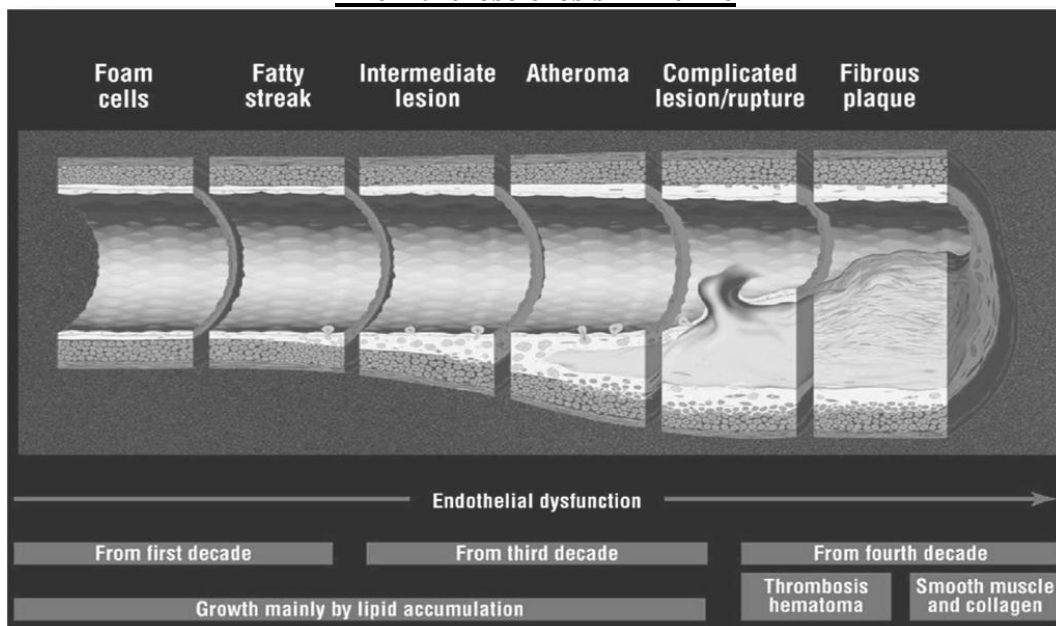
The arteries must respond to the variations that cardiac systole and cardiac diastole. The anatomy and size of the arteries vary according to their distance from the heart. The aorta and its immediate branches (pulmonary, carotid, and iliac) are highly elastic. The large arteries will course into medium-sized (muscular) arteries, like the coronary and renal arteries. The elastic recoil and smooth muscle contraction and relaxation in the media of large and medium sized arteries propagate arterial pulsatile flow. The medium arteries divide into smaller arteries and even smaller arterioles. Resistance to blood flow occurs primarily in the arterioles. Blood flows from the arterioles to the capillaries. The diameter of the capillaries is about 7 to 8 micron, about the size of a red blood cell. The capillaries have an endothelia lining, but are devoid of the tunic media.



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Unlike arteries, veins are thin-walled and highly distensible, with the capacity for up to two-thirds of circulating blood flow. The venous intima consists of a non-thrombogenic endothelium. Protruding into the lumen of the veins are valves that promote unidirectional flow. The media contains circumferential rings of elastic tissue and smooth muscle that change vein caliber in response to changes in venous pressure.

The Atherosclerosis Timeline

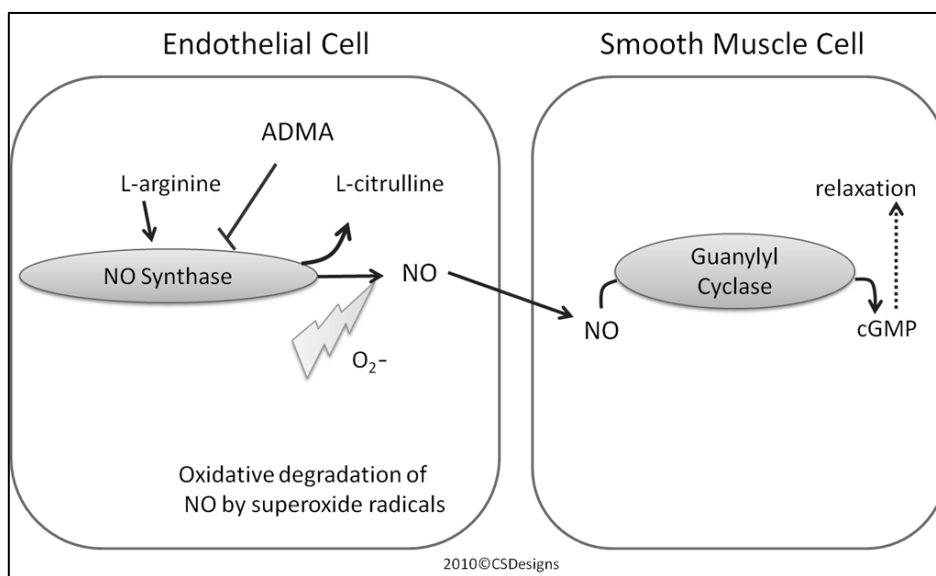


The pathological effects of atherosclerosis occur over decades, with injury to the endothelial cells initiating the process.

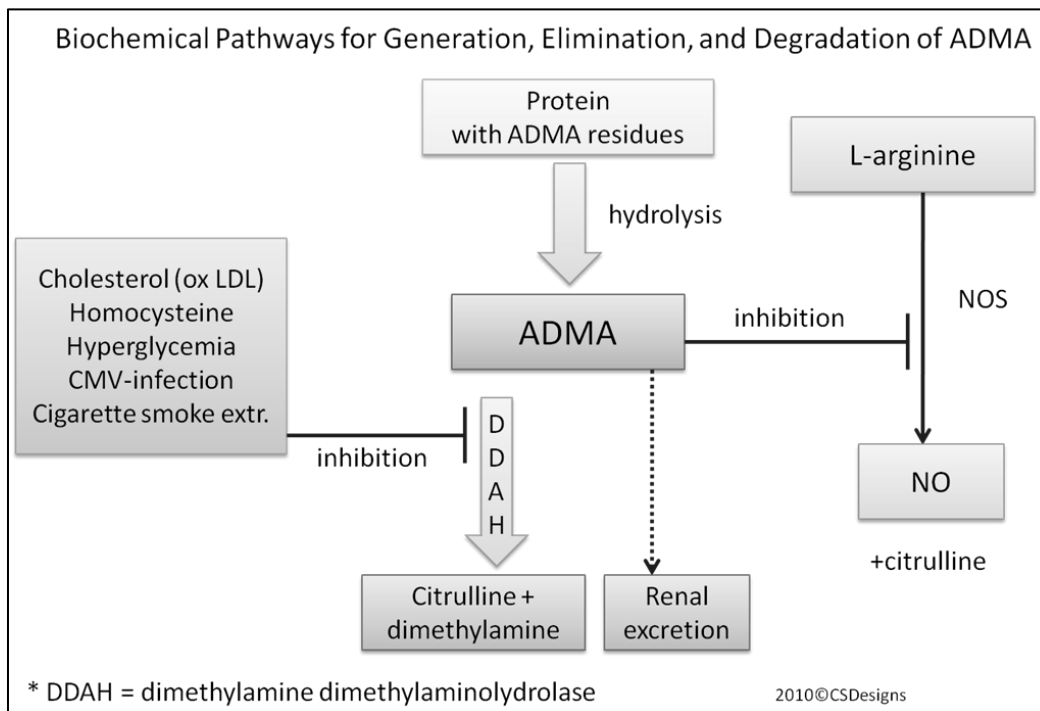
(Required Reading): *The Atherosclerosis Time-Line and the Role of the Endothelium*. This article may be downloaded from the FMU on-line library.

The systemic manifestations of atherosclerosis include:

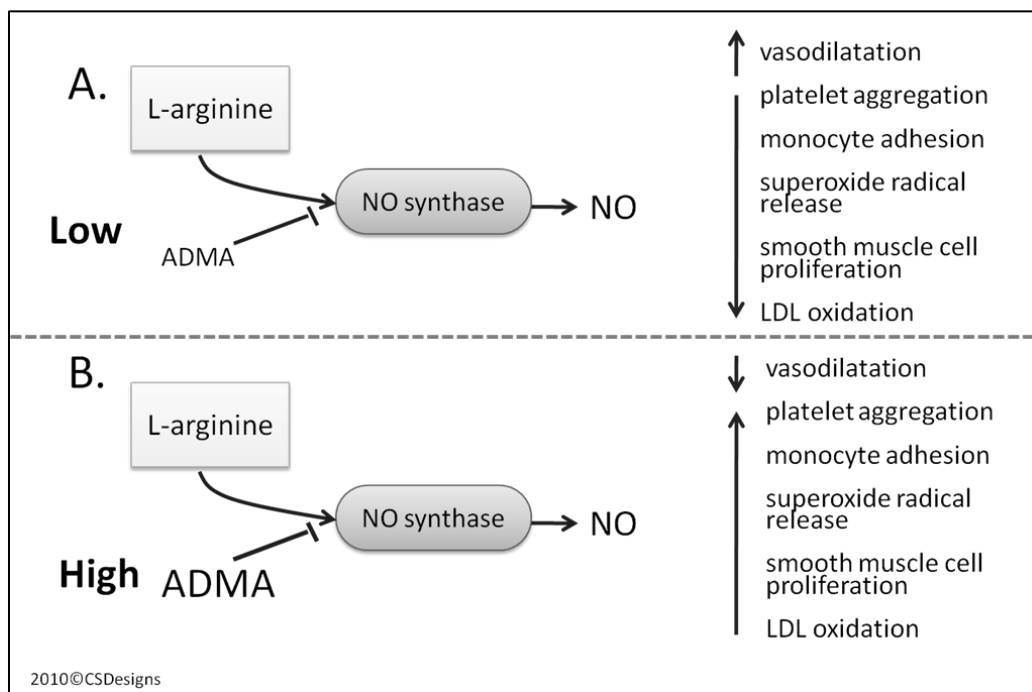
- TIA
- Ischemic stroke
- STEMI (ST segment elevation myocardial infarction)
- NSTEMI (Non-ST segment elevation myocardial infarction)
- Unstable angina pectoris
- Renovascular hypertension
- Erectile dysfunction
- Claudication
- Critical limb ischemia, rest pain, gangrene, amputation



The endothelial cells normally resist leukocyte adhesion. Normal endothelial cells produce nitric oxide from arginine via nitric oxide synthase. Nitric oxide acts as a vasodilator by increasing smooth muscle cell cyclic guanosine monophosphate levels, while at the same time inhibiting platelet aggregation and smooth muscle proliferation⁴. Abnormal vasomotor responses have been attributed to reduced bioavailability of endothelium-derived relaxing factor(s), such as nitric oxide, as a result of rapid inactivation of nitric oxide by oxidant stress or excessive generation of asymmetric dimethylarginine (ADMA) and/or increased production of vasoconstrictors⁴.



ADMA is a naturally occurring amino acid produced by methylation of specific arginine residues of certain cellular proteins. Most of the proteins that have been found to undergo significant arginine methylation are found in the nucleus. Nitric oxide cannot easily be directly measured, but the inhibitor of its formation, ADMA can be. Elevated ADMA has been associated with various cardiovascular risk factors such as lipid disorders, insulin resistance, diabetes, hypertension, PAD, renal failure, and erectile dysfunction. Factors contributing to elevated ADMA include increased oxidative stress and folic acid insufficiency. Lowering ADMA and restoring nitric oxide production can be achieved by decreasing oxidative stress, increasing antioxidants, and supplementing with L- arginine (3-6 grams/day), tetrahydrobiopterin, vitamin C, folic acid, and B-complex as well as establishing optimal essential fatty acid levels. I personally recommend performing an organic acid test as part of the evaluation and management of elevated ADMA.

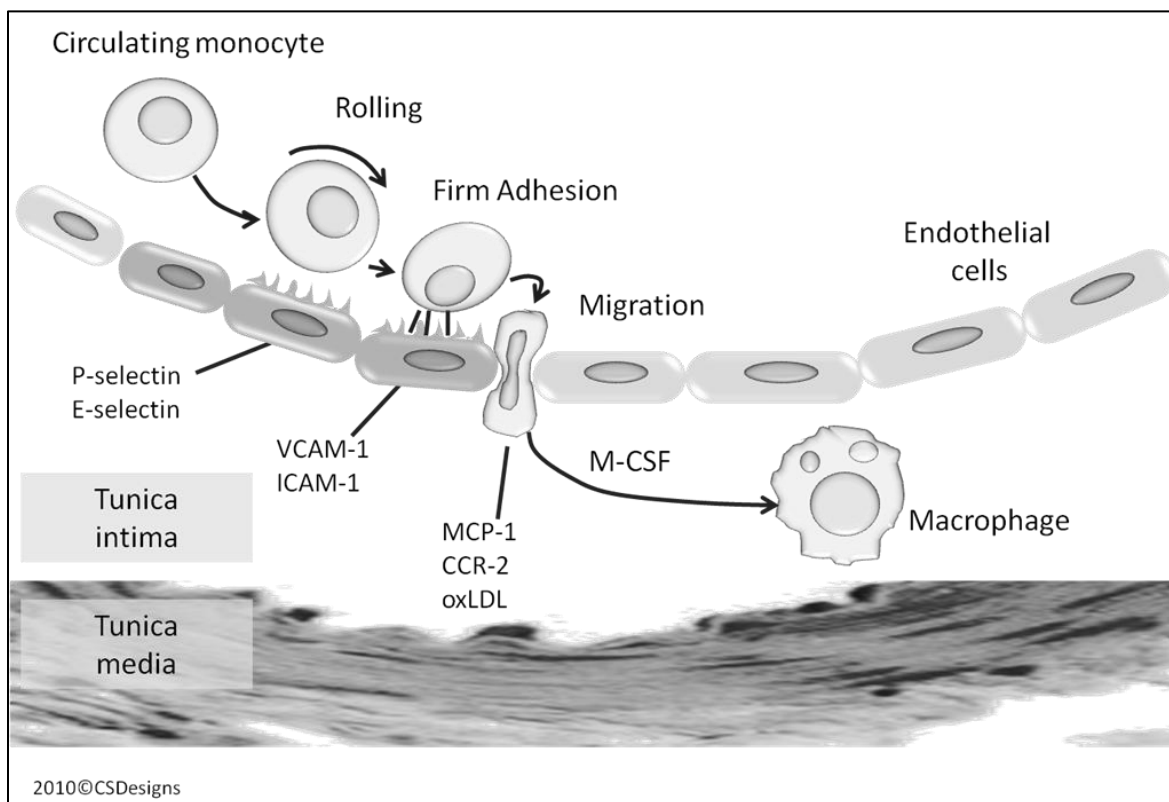


(AMDA Assay is performed by Metamatrix Labs, as well as other labs)

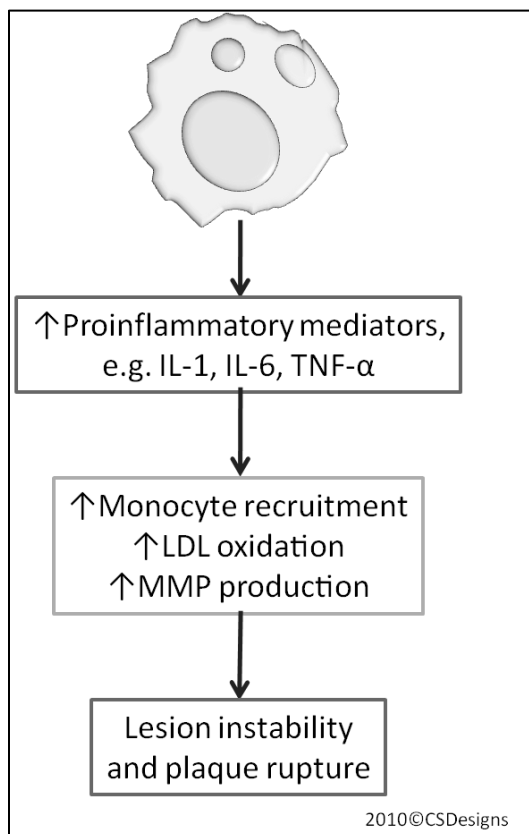
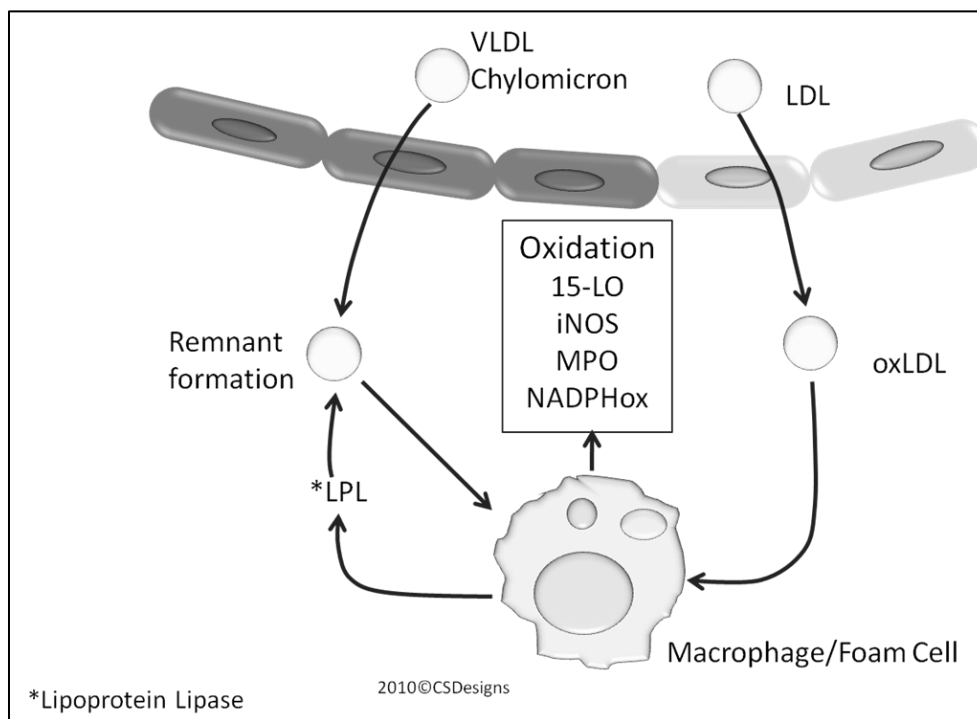
Pro-Inflammatory Stimuli That Trigger Endothelial Cells

Pro-inflammatory stimuli, such as obesity, insulin resistance, hypertension, oxidative stress, smoking, hyperglycemia, dietary factors, and infections, trigger the endothelial cells to express molecules, such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin. These molecules mediate the attachment of circulating lymphocytes and monocytes. The endothelial cells also produce chemoattractant factors, such as MCP-1 (monocytes chemoattractant protein-1) in response to modified lipoproteins and other factors. In response to the presence of inflammatory mediators, macrophages will increase the expression of scavenger receptors transforming them into foam cells.

Specialized functions of macrophages have evolved to prevent the body from infection. However, the same mechanism that enable phagocytosis of pathogens and activation of leukocytes also permit the uptake of lipoproteins and release of reactive oxygen species and immune mediators that collectively contribute to atherosclerosis.³



Foam cells are macrophages with ingested oxidized LDL. Foam cell formation from macrophages with subsequent fatty streak formation plays a key role in early atherogenesis.² During foam cell formation there is interaction of the scavenger receptor, eicosanoids and peroxisome proliferator-activated receptors (PPARs). (PPARs are a group of nuclear receptor proteins that function as transcription factors regulating gene expression. They play a role in regulation of cell differentiation, development, and metabolism)



“Macrophage-derived foam cells drive lesion progression by secreting pro-inflammatory cytokines. T lymphocytes join macrophages in the intima and direct adaptive immune responses. These leukocytes, as well as, endothelial cells, secrete additional cytokines and growth factors that promote the migration and proliferation of smooth muscles cells. In response to inflammatory stimulation, vascular smooth muscle cells express specialized enzymes that can degrade elastin and collagen, allowing their penetration into the expanding lesion.¹ “As atherosclerosis progresses, T lymphocytes, platelets and smooth muscle cells join the foam cells, expanding the size of the plaque. Thrombosis occurs with the rupture of the plaque. Plaque rupture leads to platelet activation, which progresses to the formation of blood clots.

Vasoconstrictors and Vasodilators

Vascular Endothelial Function Vasomotor Tone

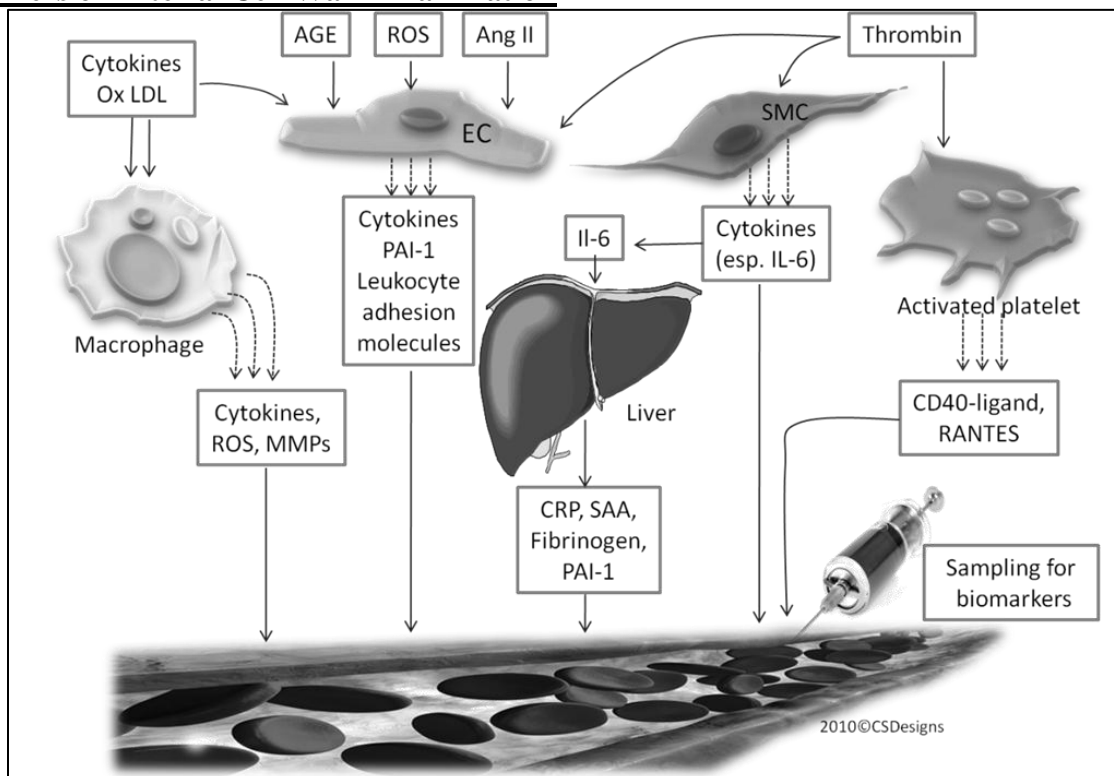
Vasodilators

- Nitric Oxide (NO)
- Prostacyclin (PGI₂)
- Endothelium-Derived Hyperpolarizing Factor (EDHF)
- Bradykinin (BK)
- Serotonin (S)
- Histamine (H)
- Substance P (SP)
- Angiotensin (1-7) (Ang 1-7)
- C-Type Natriuretic Peptide (CNP)
- Adrenomedullin (AM)
- Angiotensin (1-9) (Ang 1-9)

Vasoconstrictors

- Angiotensin-II (Ang-II)
- Endothelin-1 (ET-1)
- Angiotensin-I (Ang-I)
- Angiotensin-III (Ang-III)
- Thrombin
- Endoperoxides
- Prostaglandin 2 (PG-2)
- Prostaglandin H₂ (PG-H₂)
- Thromboxane A₂ (TxA₂)
- Serotonin (S)
- Arachidonic Acid (AA)
- Nicotine
- Angiotensin-IV (Ang-IV)
- Platelet Derived Growth Factor (PDGF)

The Biomarkers of Arterial Cell Wall Inflammation



Endothelial Activation/Dysfunction in Arthrosclerosis

Contributing Factors

- Dyslipidemia and atherogenic lipoprotein modification [elevated LDL, VLDL and Lipoprotein (a)], [LDL modification (oxidation and glycation)], [reduced HDL] – A major contributor to endothelial injury is modified LDL. LDL can be modified by oxidation, glycation, aggregation, or incorporation into immune complexes.
- Increased angiotensin II and hypertension – Angiotensin II is a potent vasoconstrictor and can contribute to atherogenesis. Angiotensin II can elicit the production of reactive oxygen species from the endothelial cells and the smooth muscle cells. It can also increase the expression of IL-6, MCP-1, and VCAM-1.
- Insulin resistance and diabetes – Hyperglycemia is associated with the formation of AGE (advance glycation end products), which leads to oxidative stress and increased production of pro-inflammatory cytokines. Insulin is a major regulator of potassium homeostasis and has multiple effects on sodium pump activity. There are several mechanisms by which insulin resistance and hyperinsulinemia *may* lead to an increase in blood pressure.
 - Increased plasma catecholamine concentration
 - Insulin stimulates the sympathetic nervous system
 - Insulin may promote renal tubular sodium resorption
 - Insulin stimulates H₂O₂ production resulting in a decrease sodium/hydrogen exchange activity in vascular smooth muscle cells and endothelial cells leading to vascular dysfunction.⁹

Ameliorating Hypertension and Insulin Resistance in Subjects at Increased Cardiovascular Risk: Effects of Acetyl-L-Carnitine Therapy (Hypertension. 2009;54)

Acetyl-L-carnitine safely ameliorated arterial hypertension, insulin resistance, impaired glucose tolerance, and hypoadiponectinemia in subjects at increased cardiovascular hypertension. The duration of the study was for 24-week study using 1 gram twice daily of acetyl-L-carnitine.

(Adiponectin is a protein expressed in white adipose tissue and may promote anti-atherogenic effects. Low serum adiponectin concentrations are associated with insulin resistance, metabolic syndrome and obesity.)

- Estrogen deficiency – Estrogen deficiency may lead to increased vascular oxidant production and enhanced angiotensin II ⁵.

- Hyperhomocysteinemia – Elevated plasma homocysteine can result from enzyme defects or vitamin deficiency. Increased homocysteine may facilitate atherothrombosis by causing endothelial dysfunction, decreased vasodilation and increased smooth muscle replication.
- Advanced age
- Infection – (see below)
- Smoking - chemical toxins/oxidative stress
- Obesity – High levels of free fatty acids leads to the formation of VLDL by the hepatocytes. Adipose tissues can also produce cytokines, such as, TNF- α and IL-6
- Oxidative stress – mitochondrial damage

Infectious Agents as Triggers of Inflammation in Atherosclerosis

There has been debate about the role of infectious agents and atherogenesis. Infectious agents might conceivably furnish inflammatory stimuli that accentuate atherogenesis⁷. It is likely that a number of stimuli are responsible for provoking and sustaining a chronic inflammatory response in the vessel wall in atherosclerosis⁴. *In vitro studies suggest that C. pneumonia can trigger proatherogenic events, such as foam cell formation, procoagulant activity, and metalloproteinase activity in monocytes probably mediated by its heat shock protein 60. Molecular antigenic mimicry between certain Chlamydia antigens and myosin has also raised the additional possibility that such antigenic mimicry could be involved in an immune-mediated vascular and myocardial injury. However, recent large-scale clinical trials have failed to demonstrate any clinical benefit of using antibiotics targeting C. pneumonia, raising questions about a link between this infection and atherosclerosis⁴.*

Potential Role of Infection in Atherothrombosis⁴

Infectious organisms implicated

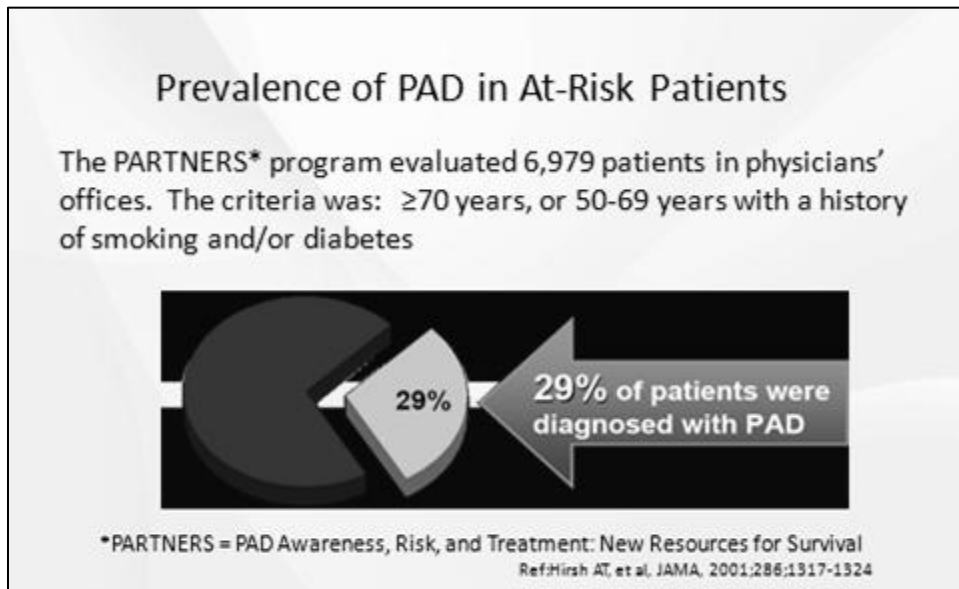
1. Viruses – herpes virus, cytomegalovirus
2. Bacteria – Chlamydia pneumoniae, H. pylori, Porphyromonas gingivalis

Mechanism(s) by which infections may contribute to atherothrombosis

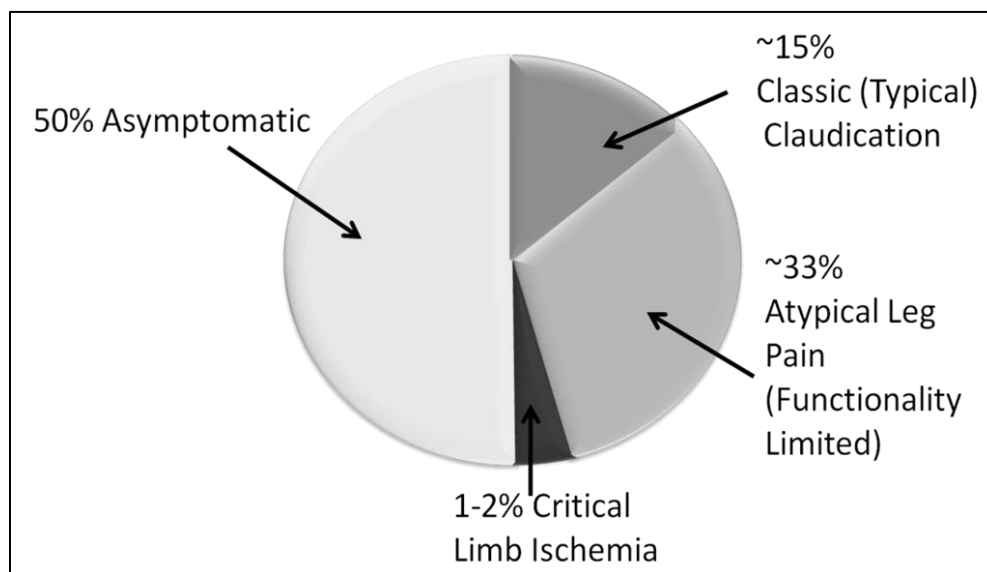
1. Direct infection of the vascular wall with endothelial injury, inflammatory recruitment, and activation (C. pneumoniae, herpes virus, cytomegalovirus)
2. Immune-mediated vascular injury through molecular mimicry (C. pneumoniae)
3. Remote infections with systemic activation of the inflammatory process (H. pylori, P. gingivalis)

(Periodontitis is a bacterial infection of the periodontal tissues. The gram-negative anaerobic bacterium *Porphyromonas gingivalis* is considered a major causative agent. One of the virulence factors of *P. gingivalis* is capsular polysaccharide.)

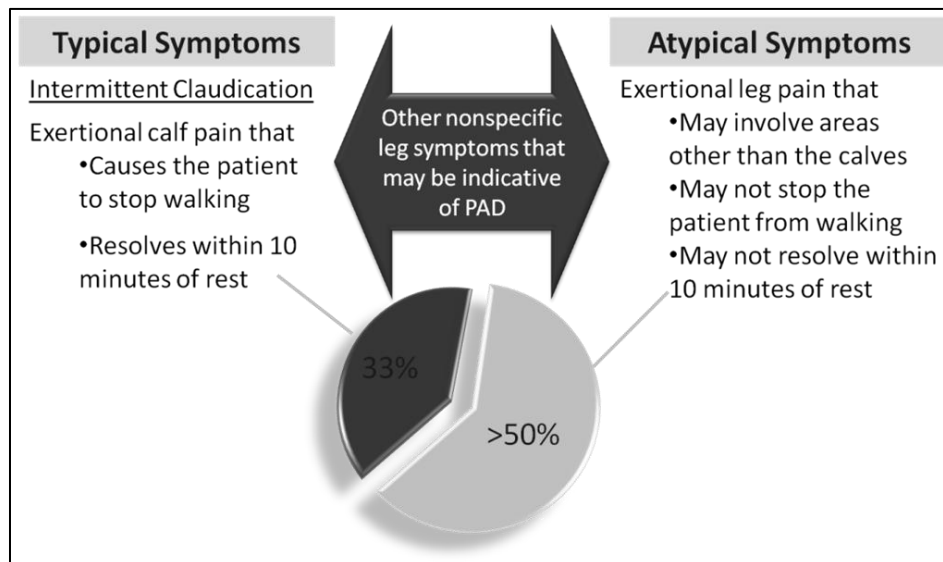
Peripheral Artery Disease (PAD)



Clinical Implications of PAD



Typical vs. Atypical Symptoms in Patients With Symptomatic PAD



The National Heart Lung and Blood Institute estimates that about (8-12 million) 5% of U.S. adults older than 65 years have lower extremity atherosclerosis, commonly known as peripheral arterial disease (PAD). Despite the high prevalence, many patients and clinicians do not immediately consider PAD as a potential cause of leg pain in older people. The disease occurs equally in men and postmenopausal women, but men are more likely to have symptoms. Once recognized, modification of risk factors and therapeutic interventions can reduce PAD progression and improve symptoms and functional status. Some argue that even asymptomatic PAD warrants aggressive treatment to reduce cardiovascular risk factors because PAD can be a harbinger of other cardiovascular problems.

Diagnosis of Peripheral Arterial Disease

- Vascular history
- Physical examination
- Non-invasive vascular laboratory
- MRA and CTA
- Traditional angiography

Physical Exam of PAD²⁰

- The absence of pedal pulses can rapidly focus the diagnosis evaluation. Palpation of arterial pulses, including the brachial, femoral, and pedal arteries, and auscultation of the abdominal aorta and femoral arteries for bruits should be done in all at-risk patients.
- The ABI is the most commonly used and most useful diagnostic test for PAD. It is a simple test that can be done in the office in less than 15 minutes. The ABI compares blood pressure in the ankle with blood pressure in the arm.
- ABI <.90 has a sensitivity of 95% and a specificity of 100% for detecting arterial narrowing >50%. An ABI <0.90% is the commonly accepted definition of PAD from the Society for Vascular Surgery.

The Edinburgh Claudication Questionnaire

(An improved version of the WHO/Rose Questionnaire for use in epidemiological surveys)

This questionnaire was tested on 300 subjects aged over 55 years attending their general practitioner, and found to be 91.3% (95% CI 88.1-94.5%) sensitive and 99.3% (95% CI 98.9-100%) specific in comparison to the diagnosis of intermittent claudication made by a physician. The repeatability of the questionnaire after 6 months was excellent (kappa = 0.76, p <0.001)²¹

The Edinburgh Claudication Questionnaire

1. Do you get a pain or discomfort in your leg(s) when you walk?

- ☐ Yes
- ☐ No
- ☐ I am unable to walk

If you answered “yes” to question (1) – please answer the following questions. Otherwise you need not continue.

2. Does this pain ever begin when you are standing still or sitting?

- ☐ Yes
- ☐ No

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3. Do you get it if you walk uphill or hurry?
- ☐ Yes
 - ☐ No
4. Do you get it when you walk at an ordinary pace on the level?
- ☐ Yes
 - ☐ No
5. What happens to it if you stand still?
- ☐ Usually continues more than 10 minutes
 - ☐ Usually disappears in 10 minutes or less
6. Where do you get this pain or discomfort? Mark the place(s) with "x" on the diagram below.



Definition of positive classification requires all of the following responses:

- 'Yes' to (1)
- 'No' to (2)
- 'Yes' to (3), and
- 'Usually disappears in 10 minutes or less' to (5); grade 1 = 'No' to (4) and grade 2 = 'Yes' to (4)

Prevention

The modifiable risk factors for PAD are the same as those for coronary and systemic atherosclerosis: smoking, hypertension, diabetes, and dyslipidemia. Strategies aimed at these risk factors to prevent atherosclerosis will reduce risk for PAD as well as other types of cardiovascular problems.

Functional Medicine Approach: Treatment of PAD

- Diet/lifestyle modifications (tobacco cessation)
 - Evaluate for oxidative stress
 - Evaluate for dyslipidemia
 - Blood pressure control/regulation
 - Balance glucose regulation
 - Assess for immune system dysfunction
 - Exercise
- Benefits patients with all stages of PAD, including those who have developed critical leg ischemia. For these patients, exercise provides additional benefits of helping to relieve ischemic rest pain, heal ischemic ulceration, and prevent limb loss.
 - Clinicians should recommend walking 30-40 minutes, stopping as necessary, at least 3 (preferably 4-5) times per week to improve walking distance.
 - If patient is unable to walk for a period of 30 minutes; it is recommended that they walk as far as they are able; adding a few steps each day until 30-40 minutes of walking is accomplished.

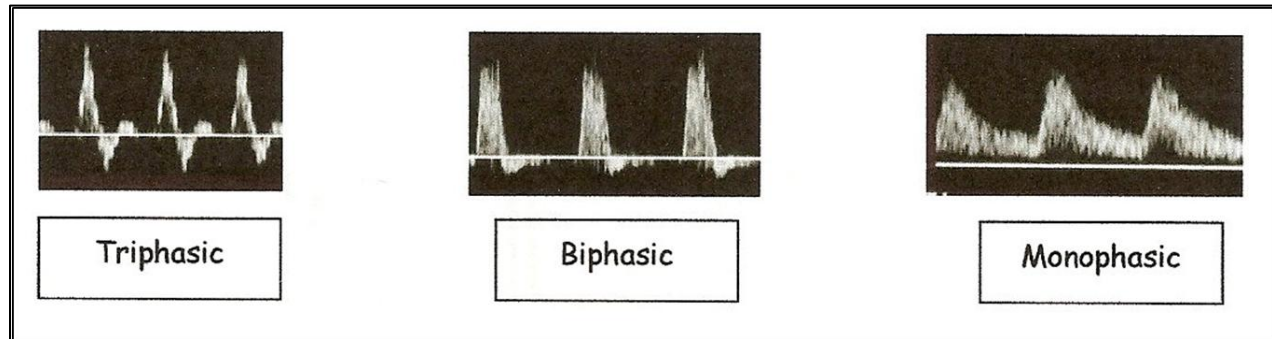
Diagnostic Studies for the Evaluation of Venous and Arterial Disease

Diagnostic Venous Tests			
Diagnostic Tests	Obstruction	Insufficiency	Location of obstruction
Continuous Wave Doppler	+	+	+/-
Duplex Ultrasound	+	+	+
Plethysmography	+	+	
D-dimer	+		
Contrast Venography	+	+	+
MRI	+		+
* Acute DVT only			

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Diagnostic Arterial Testing						
Diagnostic Test	Skin perfusion	Patency	Determine location stenosis/obstruction	Evaluate aneurysm	Monitor disease progression	Accurate in presence of non-compressible calcified arteries
ABI		+			+	-
Segmental pressures		+	+/-		+	-
Continuous wave doppler		+	+		+	+
Pulse volume recording		+	+			+
Photo-plethysmography	+	+/-				+
Transcutaneous Oximetry [Tc PO ₂]	+				+	+
Duplex scan		+	+	+	+	+
Computer tomography	+	+	+	+	+	+
MRA		+	+	+	+	+
Contrast angiography		+	+	+	+	+

Review of Doppler Waveforms

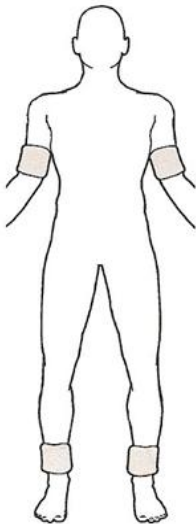
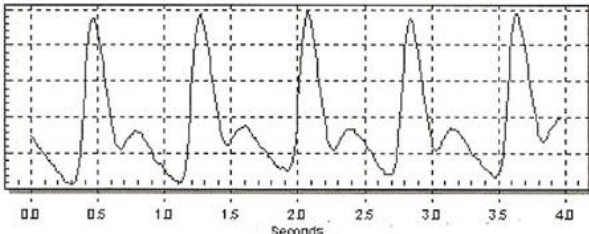
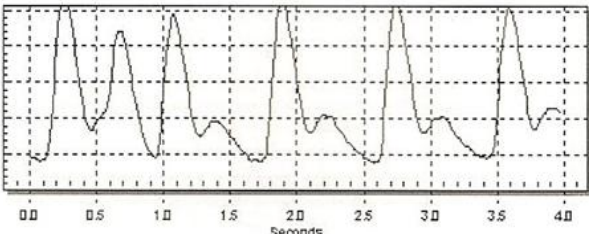


Doppler waveforms obtained from normal peripheral arteries are *triphasic* in nature and represent three distinct flow components: an initial, rapid upsweep to peak systolic velocity (PSV); a small flow reversal in early diastole; and a final forward flow in late diastole. Triphasic waveforms are normally obtained from the common and superficial femoral, popliteal, posterior tibial, and dorsalis pedis arteries in the normal non-vasoconstricted lower extremity at rest.

As the atherosclerotic disease process begins to diminish the elasticity and compliance of the arterial wall, the Doppler waveform becomes *biphasic* with a loss of the flow reversal in early diastole. Late diastolic forward flow is maintained. As the disease progresses, blood flow becomes *monophasic* with both the early and late diastolic phases absent and only the systolic forward component present.²²



Examples of ABI and Pulse Volume Record


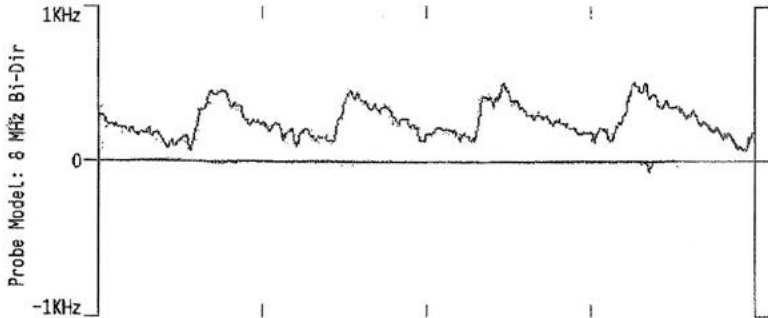
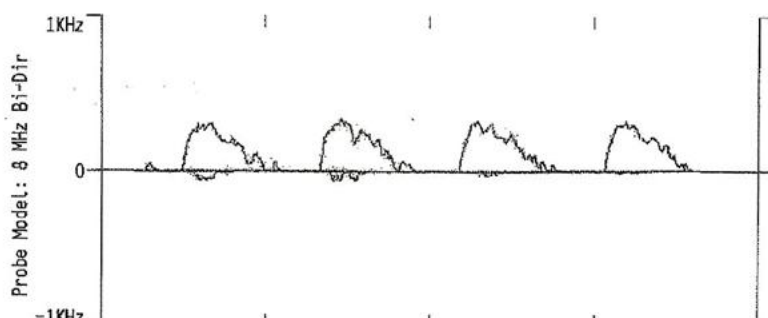
Patient Name: ABI PVR EXAM		Patient ID: 678679		Age: 45	Exam Date: 05/29/08 13:45:47
Risk Factors <input type="checkbox"/> Tobacco Use <input type="checkbox"/> Diabetes <input type="checkbox"/> Heart Disease <input checked="" type="checkbox"/> Previous CV Event MI occurred on 6/06 <input type="checkbox"/> Hyperlipidemia <input type="checkbox"/> Stroke/TIA <input type="checkbox"/> Prev. Vascular Surgery		Current Symptoms <input checked="" type="checkbox"/> Intermittent Claudication <input type="checkbox"/> Numbness, Tingling in Feet <input type="checkbox"/> Ulcerations <input type="checkbox"/> Rest Pain <input type="checkbox"/> Gangrene 3 Block Walking distance <div style="border: 1px solid black; padding: 2px; width: fit-content; margin-top: 5px;"> Location <input type="checkbox"/> Buttocks <input checked="" type="checkbox"/> Thigh <input type="checkbox"/> Calf <input type="checkbox"/> Feet </div>		ABI Severity 1.00 - 1.29 - Normal 0.91 - 0.99 - Borderline 0.41 - 0.90 - Moderate/Mild 0.00 - 0.40 - Severe	
Comments: Exam performed by Stacie					
<div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> <p>RIGHT</p> <p>Brachial</p> <p>123 mmHg</p> <p>PT</p> <p>140 mmHg</p> <p>1.13 Index</p> </div> <div style="text-align: center;">  </div> <div style="text-align: center;"> <p>LEFT</p> <p>Brachial</p> <p>122 mmHg</p> <p>PT</p> <p>145 mmHg</p> <p>1.17 Index</p> </div> </div>					
PVR X4 05/29/08 13:43:51		PVR X4 05/29/08 13:45:32			
					
Interpretation: Pressures and waveforms are normal No PAD					

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Patient Name <u>Adams, Sam</u>		ID Number <u>80421</u>	Date _____
Risk Factors <input checked="" type="checkbox"/> Tobacco Use <input checked="" type="checkbox"/> Hypertension <input checked="" type="checkbox"/> Diabetes <input type="checkbox"/> Hyperlipidemia <input type="checkbox"/> Heart Disease <input type="checkbox"/> Stroke/TIA <input type="checkbox"/> Current Age <u>63</u> <input type="checkbox"/> Previous Vasc Surgery <input type="checkbox"/> Other _____		Current Symptoms <input type="checkbox"/> Intermittent Claudication <input checked="" type="checkbox"/> Numbness, tingling in feet <input type="checkbox"/> Ulcerations <input type="checkbox"/> Other _____	
		ABI / Severity of Disease > 1.3 - Noncompressible 1.00-1.29 - Normal 0.91-0.99 - Borderline 0.41-0.90 - Mild to Moderate 0.00-0.40 - Severe <small>ACC/AHA Guidelines for Management of patients with P.A.D., 2005</small>	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> ABI Results <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="border: 1px solid black; padding: 5px; width: 45%;"> Right Arm <u>175</u> mmHg </div> <div style="border: 1px solid black; padding: 5px; width: 45%;"> Left Arm <u>154</u> mmHg </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="border: 1px solid black; padding: 5px; width: 45%;"> Right Ankle <u>80</u> mmHg </div> <div style="border: 1px solid black; padding: 5px; width: 45%;"> Left Ankle <u>53</u> mmHg </div> </div> </div> <div style="width: 50%; text-align: right;"> Left ABI $\frac{\text{Left Ankle Pressure} = 53}{\text{Higher Arm Pressure} = 175} \text{ mmHg} = 0.30$ </div> <div style="width: 50%; text-align: right;"> Right ABI $\frac{\text{Right Ankle Pressure} = 80}{\text{Higher Arm Pressure} = 175} \text{ mmHg} = 0.46$ </div> </div> <div style="text-align: center; margin: 10px 0;">  </div>			
Summit Doppler Patient Name: Patient ID: Date/Time: Notes:		<div style="display: flex; align-items: center;">  <div style="margin-left: 10px;"> <input checked="" type="checkbox"/> LEFT <input type="checkbox"/> RIGHT <input checked="" type="checkbox"/> PT <input type="checkbox"/> DP <input type="checkbox"/> BRACHIAL </div> </div>	
Summit Doppler Patient Name: Patient ID: Date/Time: Notes:		<div style="display: flex; align-items: center;">  <div style="margin-left: 10px;"> <input type="checkbox"/> LEFT <input checked="" type="checkbox"/> RIGHT <input checked="" type="checkbox"/> PT <input type="checkbox"/> DP <input type="checkbox"/> BRACHIAL </div> </div>	

Low ABI Values and Mono-Phasic Blood Flow, Severe PAD, Abnormal

Hypertension

High blood pressure affects more than 65 million – or 1 in 3 American adults. About 28 percent of American adults ages 18 and older, or about 59 million people, have pre-hypertension, a condition that also increases the chance of heart disease and stroke. High blood pressure is also common among older Americans. Individuals with normal blood pressure at age 55 have a 90 percent lifetime risk for developing high blood pressure.²³

Ninety-five percent of diagnosed cases are classified as essential hypertension – yet there is epidemiologic evidence that hypertension exists almost entirely in developed countries. Much of what we call 'essential' is likely due to diet, obesity, inactivity, and stress and alcohol consumption.²⁴

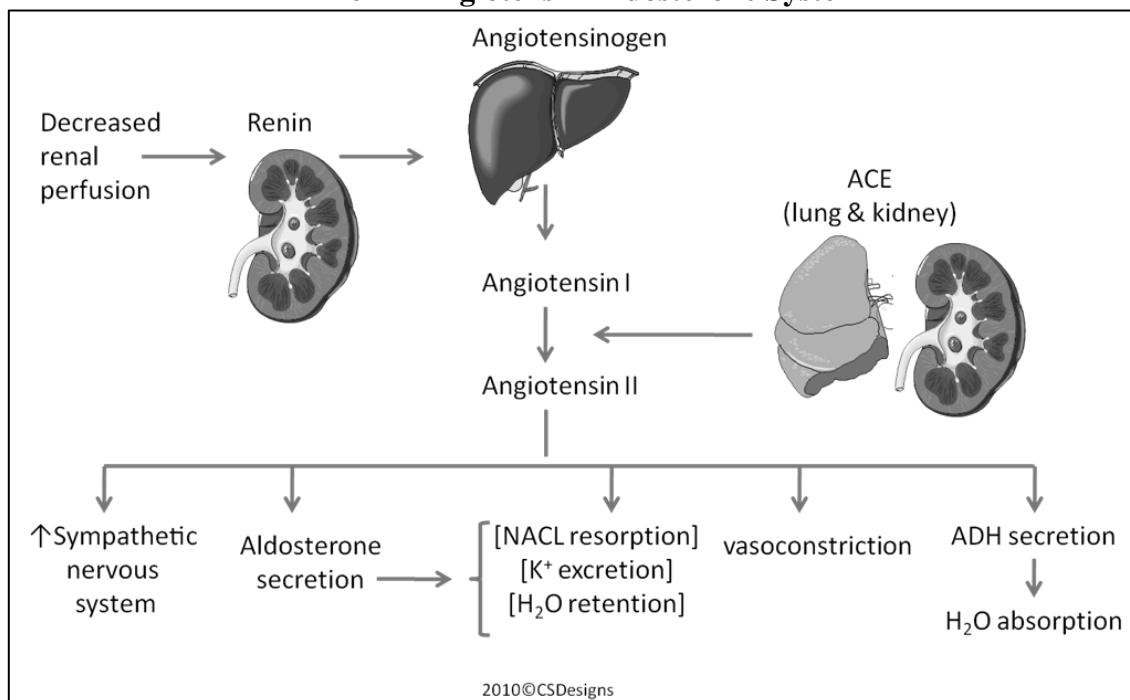
Systolic pressure is governed by:

- Cardiac action
- The elasticity and distensibility of conducting arteries
- Arteriosclerosis - Loss of distensibility → increase systolic pressure

Diastolic pressure is maintained by:

- Resistance (TONE) of arterioles
- Blood viscosity

Renin-Angiotensin-Aldosterone System



Hormone and Other Chemical Messengers That Affect Blood Pressure

- **Epinephrine and norepinephrine** – released by the adrenal glands in response to stress; increase cardiac output and constrict arterioles.
- **Aldosterone** – released by the adrenal glands as prompted by angiotensin II; causes water and salt retention.
- **Antidiuretic Hormone** – produced by the pituitary when blood pressure is very low; causes water retention and constricts arterioles.
- **Angiotensin II** – generated by the RAAS; constricts arterioles and stimulates release of ADH and aldosterone.
- **Nitric Oxide** – released by the lining of the endothelial cells of the arteries; relaxes blood vessels and improves blood flow.

Classification and management of blood pressure for adults*					
BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial Drug Therapy	
				Without Compelling Indication	With Compelling Indications (See Table 8)
Normal	<120	And <80	Encourage	No antihypertensive drug indicated	Drug(s) for compelling indications+
Prehypertension	120-139	or 80-89	Yes		
Stage 1 Hypertension	140-159	or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination	Drugs(s) for the compelling indications.+ Other antihypertensive drugs (diuretics, ACEI, as needed)
Stage 2 Hypertension	≥160	or ≥100	Yes	Two-drug combination for most~ (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)	

DBP, diastolic blood pressure; SBP, systolic blood pressure

Drug abbreviations: ACEI, angiotension converting enzyme inhibitor; ARB, angiotension receptor blocker; BB, beta blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category

~ Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

+ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg

REF: JNC

Evaluation of patients with documented hypertension has three objectives

1. To assess lifestyle & identify other **cardiovascular risk factors** or concomitant disorders that may affect prognosis and guide treatment.
 - Major Risk Factors
 - Hypertension*
 - Cigarette smoking
 - Obesity* (BMI ≥ 30 kg/m²)
 - Physical inactivity **components of the metabolic syndrome*
 - Dyslipidemia*
 - Diabetes mellitus*
 - Microalbuminuria or GFR <60 mL/min
 - Age (men >55; women >65)
 - Family history of premature cardiovascular disease (men <55; women <65)
2. To reveal identifiable causes of high BP
 - Sleep apnea - Sudden drops in blood-oxygen levels occurring during sleep apnea increases blood pressure
 - Drug-induced or related causes
 - Chronic kidney disease
 - Primary aldosteronism
 - Renovascular disease
 - Chronic steroid therapy (Cushing's syndrome)
 - Pheochromocytoma
 - Coarctation of the aorta
 - Thyroid or parathyroid disease
3. To assess the presence or absence of target organ damage and CVD.
 - Target Organ Damage
 - Heart
 - Left ventricular hypertrophy
 - Angina or prior myocardial infarction
 - Prior coronary revascularization
 - Heart failure
 - Brain - Stroke or transient ischemic attack
 - Chronic kidney disease
 - Peripheral arterial disease
 - Retinopathy
 - GFR, glomerular filtration rate

Heavy Metal Toxicity

- Cadmium - Elevated blood levels of cadmium are associated with an increased risk of hypertension.¹⁴
- Lead - Hypertension is a cardinal feature of lead nephropathy, and epidemiologic studies have shown an association between blood lead levels and blood pressure.¹⁴
- Mercury - Mercury toxicity is another cause of hypertension which can be missed unless the examiner becomes suspicious while doing a careful history and considers laboratory testing.¹⁴

Laboratory Tests

Considerations for CVD (including hypertension)

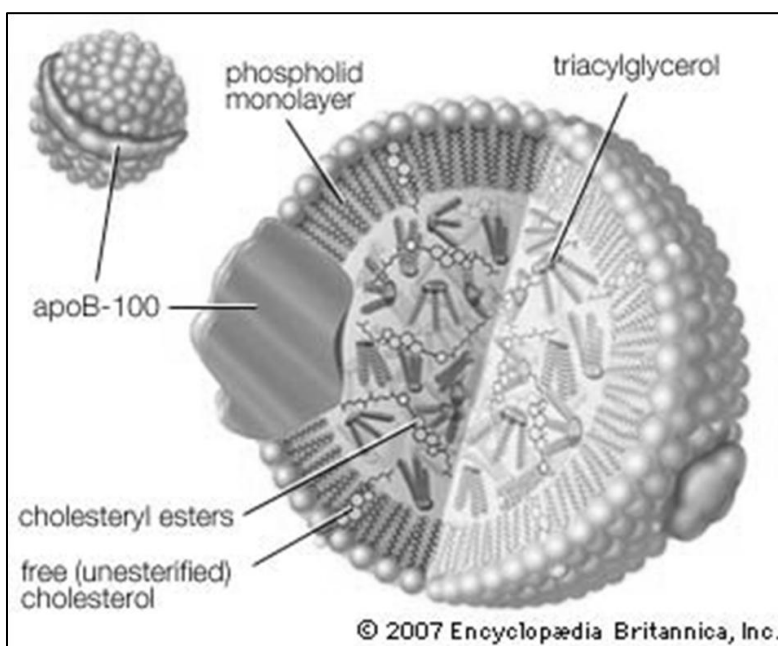
- **CMP** - To rule out evidence of renal insufficiency, hypokalemia, or hyperglycemia. Hypokalemia occurs in Cushing's disease, primary hyperaldosteronism, and renovascular hypertension. Hyperglycemia can be a manifestation of a pheochromocytoma, Cushing's disease, impaired fasting glucose due to pre-diabetes or diabetes, or increased stress. Mild renal insufficiency points toward hypertensive nephropathy, whereas marked renal insufficiency potentially suggests a secondary cause of hypertension. Increased uric acid can be a sign of oxidative stress.
- **GGT** - An increase in serum gamma-glutamyl transferase predicts the onset of metabolic syndrome and cardiovascular risk.¹⁰ GGT adsorbs into circulating LDL and can catalyze its oxidation. GGT is expressed in the arteromatous core of coronary plaques, where it colocalizes with oxidized LDL and foam cells.¹⁰ From a functional medicine perspective, hepatobiliary dysfunction may be related to cardiovascular disease via GGT.
- **Complete blood count and examination of peripheral blood smear** - Red blood cell fragments, or *schistocytes*, occur in microangiopathic hemolytic anemia resulting from malignant hypertension. Look for signs of B12 and folate deficiency (increase RDW, increased MCV, increased MCH, and increased MCHC).
- **Lipid profile**

	Chylomicron	VLDL	LDL	HDL
% Protein	1.5 – 2.5	5 - 10	20 - 25	40 – 55
% Phospholipid	7 - 9	15 - 20	15 - 20	20 – 35
% Cholesterol	1 - 3	5 - 10	7 - 10	3 – 4
% Triacylglycerol	84 - 89	50 - 65	7 - 10	3 – 5
% Cholesteryl ester	3 - 5	10 - 15	35 - 40	1 - 2

Lipoprotein Structure

The structure of lipoproteins consists of the following:

- Inner core – triacylglycerol + cholesteryl ester (The esterification of free cholesterol within the intestinal cells by acylCoA: cholesterol acyltransferase allows the cholesterol to be stored as neutral lipid in cytosolic droplets and in the packing of cholesterol into lipoprotein particles.
- Outer core – phospholipid + cholesterol
- Apolipoproteins – Apolipoproteins are proteins found in the external (outer) layer of the lipoproteins. They are important in maintaining the structural integrity and solubility of lipoproteins, playing a role in lipoprotein receptor recognition and also the regulation of certain enzymes in lipoprotein metabolism. Different types of apolipoproteins include: Apo A1, Apo A5, Apo B, Apo CII, Apo CIII, D, E. Apolipoprotein B is the main apolipoprotein of chylomicrons and LDL and is a good marker of risk of vascular disease.



Chylomicrons are produced in the intestines and transported to the liver. The liver uses the chylomicrons to produce VLDL for deliver to other tissues. VLDL has five different apolipoproteins. The apolipprotiens assist in targeting the VLDL to muscle cells and fat cells. As the VLDL travels through the body, they give up triacylglycerol and other lipids to muscle and fat cells. As the do so, they become denser and lose all but one of their apolipoproteins becoming LDLs. LDL receptors on the surfaces of the cells bind the apolipoprotein of the LDL allowing the cells to take in the LDL. The LDL in the cell merges with a lysosome. The apolipoprotein is degraded to amino acids and the cholesteryl esters are converted to cholesterol. There components can then be used by the cell.

A disease called familial hypercholesterolemia is caused by a genetic defect in the LDL receptor. The cells are unable to take up LDL, increase the serum cholesterol by a factor of three.

HDL is responsible for removing excess cholesterol from the tissues and returning it to the liver for metabolism. The transfer of cholesterol from cells to HDL requires several different cell surface proteins. One of these proteins will remove the cholesterol from the cell membrane. Other proteins will recognize the HDL and convert the cholesterol to cholesteryl esters. Defect in the gene for cholesterol removal from the cell membrane is called Tangier's disease. These individuals cannot remove cholesterol from the cells.

Lipoprotein (a)

Lipoprotein (a) is a lipoprotein subclass. Lp (a) is a low-density lipoprotein, LDL-like particle with a cholesterol rich core and a molecule of apolipoprotein B linked by a disulphide bridge to apolipoprotein A. Lp (a) competes with plasminogen for binding sites on the cell surface, decreasing plasminogen activation and inhibiting clot lysis. Plasminogen is involved in fibrinolysis (dissolving clots). Lp (a) concentrations are genetically determined and numerous studies have identified elevated Lp (a) as a risk factor for atherosclerotic disorders (atherosclerosis, cerebrovascular accidents, and coronary artery disease). Niacin can help reduce Lp(a). Diet and exercise has little effect on Lp (a) reduction. Supplementation with exogenous testosterone in men may lower serum Lp(a).

- **VAP (Vertical Auto Profile) Cholesterol Test**

The VAP test generally reports on 15 separate components of blood cholesterol. Some of the components of the test are listed below.

- Total cholesterol and all subtype measurements (e.g. directly measures LDL, HDL, VLDL)
 - Atherogenic particles - Lp(a) and APO-B100 – independent risk factors for CVD
 - LDL patterns
 - HDL₂ most protective
 - IDL (intermediate density) (↑diabetes)
 - VLDL - increased VLDL₃ increases risk of CVD
- **Urinalysis** - Look for proteinuria, hematuria, and red cell casts for evidence of a secondary cause or hypertensive nephropathy. Test for the presence microalbumin to assess for early signs of renal damage.
 - **hs-CRP** – CRP is an important independent marker for inflammation. C-reactive protein is one of the acute phase proteins that increase during systemic inflammation. High levels reflect over activity of inflammatory cytokines linked to coagulation and endothelium damage. CRP is produced in the liver by excess levels of the pro-inflammatory cytokine, interleukin-6 (IL-6). High sensitive CRP assay is a more sensitive test used to determine cardiovascular risk.
 - **Ferritin** – Ferritin is an iron-protein complex found in most tissues, but particularly the bone marrow and reticuloendothelial system (macrophage system). It is also an acute phase protein and may be increased in inflammation, malignancy and liver disease.
 - **Homocysteine** – Homocysteine is an amino acid that functions as an intermediate in methionine metabolism. It can rise in response to nutritional deficiencies of B12, folate, B6 or betaine. High levels of homocysteine have been linked to damages endothelium, increased platelet aggregation, and the formation of atherosclerotic lesions. Genetic factors such as MTHFR (methylenetetrahydrofolate reductase) polymorphisms may have a significant influence on elevated homocysteine levels.

Summary of the Causes of Elevated Homocysteine¹⁷

- Deficiency of folic acid, B6 and/or B12
- Kidney disease
- Low levels of thyroid hormones (hypothyroidism)
- MTHFR genetic mutations
- Psoriasis
- Systemic lupus erythematosus

- **Fibrinogen** – Fibrinogen plays a key role in arterial occlusion by promoting thrombus formation, endothelial injury and hyperviscosity. Fibrinogen is one of the principle blood clotting proteins and levels are increased with tissue inflammation or tissue destruction. Fibrinogen can also lead to the growth of arterial plaque formations, even without blood clot formation. Factors such as smoking, stress, oral contraceptives, and obesity can be strong modifiers of fibrinogen, potentially increasing levels.

The Four ways that fibrinogen increases risk of heart disease are as follows:

- Decreased blood flow (increasing blood viscosity)
 - Conversion to fibrin (clot promoting)
 - Binding to LDL (contributes to atherosclerosis)
 - Facilitating platelet aggregation
- **Vitamin D** – Vitamin D deficiency is associated with cardiovascular disease. The presence of vitamin D receptors on cardiomyocytes, endothelial cells and vascular smooth muscle cells suggest that vitamin D may exert a direct effect on the cardiovascular system. However, vitamin D deficiency may influence cardiovascular risk indirectly through its relationship with other traditional risk factors. Vitamin D deficiency causes insulin resistance; and studies have shown that supplementation with vitamin D may decrease the risk of diabetes. Inflammatory markers are elevated in individuals with vitamin D deficiency. Vitamin D deficiency has also been associated with dyslipidemia, most prominently hypertriglyceridemia. Finally, vitamin D deficiency is known to upregulate the rennin-angiotensin-aldosterone system (RAAS), leading to hypertension and left ventricular hypertrophy.¹¹
- **Vitamin K** – Vitamin K is a fat-soluble vitamin that functions as a cofactor in the production of blood coagulation factors (in the liver), and matrix Gla-proteins (in cartilage and vessel walls) each resulting in deposition of ionic calcium. There are two natural forms of vitamin K which differ based on the phytyl group, phylloquinone (K1), synthesized from plants and menaquinone (K2), and synthesized from bacteria.

Coronary artery calcification is an independent predictor of cardiovascular disease and CVD-related mortality. Matrix Gla protein(MGP) is a vitamin K-dependent protein that functions as a calcification inhibitor and may be integral in the regulation of human vascular mineralization.¹²

Food high in vitamin K include: kale, spinach, turnip greens, collards, Swiss chard, broccoli, parsley, and mustard greens.

Drug induced nutrient depletion of vitamin k include: High dose of salicylates, bile acid sequestrants, cephalosporins, and anti-clotting (warfarin-coumadin)

- **Testosterone** - Low endogenous testosterone is a component of the metabolic syndrome, characterized by obesity, glucose intolerance, hypertension, hypertriglyceridemia, low HDL cholesterol, a procoagulatory state, and an antifibrinolytic state. Two recent articles in 'Circulation' and 'Journal of Clinical Endocrinology' reported that older men with lower serum testosterone concentrations had a greater risk of dying than did men with higher testosterone. A clinical trial of testosterone treatment in older men, reported June 30, 2010 in the *New England Journal of Medicine* online, has found a higher rate of adverse cardiovascular events, such as heart attacks and elevated blood pressure, in a group of older men receiving testosterone gel compared to those receiving placebo. Due to these events, the treatment phase of the trial was stopped.¹³

Advanced Functional Medicine Testing

Recommended Cardiovascular Functional Medicine Tests

- Cardiovascular Health Profile (Metametrix)
- Cardio/ION Profile (Metametrix)

Individual Functional Medicine Test Considerations

- Essential Fatty Acid Analysis
- Liver Detoxification Profile
- Nutritional deficiencies
- Pathogen assessment viral/bacteria
- Hormonal testing
- Organic acid testing
- Comprehensive stool analysis
- Toxic Profile (heavy metal, persistent organic pollutants, etc.)
- RBC essential elements

Functional Medicine University's
Functional Diagnostic Medicine Training Program

Module 5: FDMT 545A: Cardiovascular Disease: A Comprehensive Approach to Evaluation and Management

By Wayne L. Sodano, D.C., D.A.B.C.I., & Ron Grisanti, D.C., D.A.B.C.O., M.S.

<http://www.FunctionalMedicineUniversity.com>

	Results		Reference Limits
<u>Lipoprotein Factors</u>			
Total Cholesterol	225 H		<= 200 mg/dL
HDL Cholesterol	120 H		30 - 85 mg/dL
LDL Cholesterol (Direct)	135 H		<= 130 mg/dL
Triglycerides	145		35 - 160 mg/dL
Lipoprotein (a)	35		<= 37 mg/dL

Lipoprotein Ratios

LDL/HDL	1.1	<= 3.3				
Total/HDL	1.9	<= 4.5				
			Male		Female	
			LDL/HDL	Total/HDL	LDL/HDL	Total/HDL
			1.0	3.4	1.5	3.3
			3.6	5.0	3.2	4.4
			6.3	9.6	5.0	7.1
			8.0	23.4	6.1	11.0
			*Adapted from the Framingham Heart Study			

Chronic Inflammatory Markers

Ferritin	97		28 - 397 ng/mL
Fibrinogen	368		175 - 425 mg/dL
c-Reactive Protein (HS)	1.8		<= 3.0 mg/L
Cardio CRP value (mg/L)	CHD Risk Level	* If the cardio CRP concentration exceeds 10 mg/L after repeat testing, the patient should be evaluated for noncardiovascular etiologies.	
<1	Low		
1-3	Average		
>3 (up to 10)*	High		

Other Important Indicators

Insulin	12.5 H		2.0 - 12.0 uIU/mL
Testosterone	845		184 - 1,171 ng/dL
Sex Hormone Binding Globulin	55		13 - 71 nmol/L
Free Androgen Index (calc.)	53.3		30.0 - 95.0
Magnesium	20 L		16 - 32 ppm packed cells

Oxidant Stress Factors

		Percentile Ranking by Quintile						
		1st	2nd	3rd	4th	5th		
		20% 40% 60% 80%					95% Reference Interval	
Homocysteine	6.1						3.0 - 14.0	nmol/mL
Coenzyme Q10	1.03						0.48 - 3.04	mg/L
alpha-Tocopherol	8.6 L						6.8 - 31.7	mg/L
gamma-Tocopherol	0.77						0.06 - 2.99	mg/L
Lipid Peroxides	0.69						<= 2.60	nmol/mL

Fibrinogen performed by Southern Clinical Laboratory
405 West Pike St., Suite A Lawrenceville, GA 30045
Lab Director: Dr. Robert David

Georgia Lab Lic. Code #067-007
CLIA ID# 11D025349

New York Clinical LFI #4578
Florida Clinical Lab Lic. #800008124

Testing Performed by Metamatrix, Inc. 3425 Corporate Way Duluth, GA 30096

Laboratory Directors
J. Alexander Bralley, PhD
Robert M. David, PhD

Minerals

Salt (sodium chloride)

- Even though public health policy emphasizes sodium restriction as its principal recommendation, experts continue to debate sodium's role in arterial blood pressure control. A large meta-analysis of randomized controlled trials recently concluded that the evidence in the normotensive population does not support current recommendations for universal sodium restriction. Moreover, salt intake cannot usually be restricted successfully below 5 g daily on a long-term basis.¹⁴
- It does appear that moderate salt restriction (2-5 g daily) may result in about a 5 mm Hg decline, on average, in both systolic and diastolic blood pressures for perhaps half of the total population. Another estimate is that 30% of the general public, and 40-50% of hypertensive's are salt-sensitive. Conversely, in a small minority of people, moderate sodium restriction may actually increase blood pressure.¹⁴
- Other research suggests that certain populations, such as African-Americans, the elderly, and diabetics, may have a relatively high prevalence of salt sensitivity. However, the salt sensitivity noted in these groups appears to be more related to decreased ingestion of calcium and potassium than to excessive salt intake. Low magnesium intake may also be a cause of salt sensitivity.¹⁴
- Short-term, very low salt diets appear to be contraindicated in patients at risk for hypertension along with hyperinsulinemia/insulin resistance ('syndrome X'). Such patients have raised concentrations of renin and aldosterone, and salt restriction results in further increases in these variables.¹⁴
- Salt intake, however, is believed to be primarily responsible for determining how much calcium is excreted. In fact, within the usual ranges of salt and calcium intake, salt intake is more important than calcium intake in determining urinary calcium excretion. Increased urinary calcium excretion due to a high salt intake may not be adequately compensated for by increased calcium absorption; thus calcium may be reabsorbed from bone in order to maintain calcium homeostasis.¹⁴
- Because of the importance of calcium in blood pressure regulation, excess sodium intake may contribute to hypertension via its effect on calcium levels. This suggests that decreasing a high sodium intake is most likely to be effective when accompanied by an increase in a low calcium intake.¹⁴
- The evidence is very suggestive that reduction of dietary salt intake reduces target organ damage (brain, heart, kidney and vasculature) that is both dependent on the small BP reduction, and also independent of the decreased BP. However, it should be noted that higher sodium consumption has actually been associated with lower BP suggesting that nutritional deficiencies and relative serum levels or total body stores (potassium, magnesium, calcium, vitamins, antioxidants and essential fatty acids) and not excess sodium cause hypertension.¹⁵

Potassium Deficiency

- In contrast to dietary sodium, dietary potassium may have an inverse correlation with blood pressure. Many of the benefits of reduced sodium intake may actually reflect increased dietary potassium, since potassium intake usually increases when sodium intake is reduced (as when natural foods are substituted for processed foods)¹⁴
- In fact, the evidence is that the dietary sodium/potassium ratio correlates better with blood pressure than either sodium or potassium intake alone. Furthermore, in hypertensives, dietary potassium depletion has been shown to decrease sodium excretion and to increase blood pressure.¹⁴
- Another benefit of high potassium intake is its association with low calcium excretion, as adequate calcium nutrition appears important to blood pressure regulation.¹⁴
- Also, erythrocyte potassium levels have been inversely correlated with blood pressure, while potassium depletion has been shown in a double-blind crossover study to increase blood pressure in hypertensives.¹⁴
- Supplementation - From a dietary standpoint, a reasonable approach would be to replace high-sodium, low-potassium processed foods with low-sodium, high-potassium natural foods.¹⁴
- In addition, potassium may have a calcium conserving effect that would further minimize the effects of a high sodium intake. The interactions of sodium, calcium, potassium, and magnesium are more important in BP control than are isolated changes in one mineral.¹⁵

Calcium Deficiency

- Although the influence of calcium on hypertension is less widely appreciated than that of sodium and potassium, it is of at least equal importance. Calcium is the original calcium channel blocker, controlling its own influx across the cell membrane. Alterations in its metabolism may be a primary factor in the development of hypertension, leading to changes in vascular smooth muscle function and peripheral vascular resistance – they may even determine sodium sensitivity.¹⁴
- Reduced dietary calcium appears to be the most consistent nutritional correlate of hypertension; the correlation is stronger than either high dietary sodium or low dietary potassium.¹⁴
- When calcium is present in optimal concentrations, it stabilizes vascular membranes, blocks its own entry into the cells and reduces vasoconstriction. Calcium in combination with other ions such as sodium, potassium and magnesium provides ionic balance to the vascular membranes, vasorelaxation and reduced blood pressure.¹⁵

Magnesium Deficiency

- Magnesium is a potent vasodilator. A low magnesium concentration reduces production of prostacyclin (a vasodilating, anti-aggregating prostanoid), and increases release of thromboxane (a vasoconstricting, platelet-aggregating prostanoid).¹⁴
- Dietary magnesium intake is inversely related to both systolic and diastolic blood pressure.¹⁴
- Magnesium regulates both systolic and diastolic blood pressure, intracellular calcium, potassium, sodium and pH, as well as left ventricular mass, insulin sensitivity and arterial compliance.¹⁵

Specific Cardiovascular Disease Treatment Considerations

The following recommendations are in *addition to* dietary, weight reduction and exercise protocol.

High Triglycerides

- Increase soluble fiber
- Carnitine
- Balance essential fatty acids
- Optimize insulin sensitivity (chromium)
- Garlic ,onions, fenugreek seeds, guggulipid,
- Rule out thyroid dysfunction, hepatic dysfunction and diabetes
- Niacin (niacin bound to inositol – Free niacin will be slowly released into the bloodstream from inositol, helping to eliminate the side effects of high dose niacin. (monitor liver enzymes)

The two main forms of vitamin B₃ are niacin (nicotinic acid) and niacinamide. Dietary niacin is amidated to form niacinamide, the precursor of the active co-enzyme forms NAD and NADP. The amino acid tryptophan can serve as a precursor to niacin, but the conversion is dependent on adequate status of both B₆ and iron. When choosing forms of supplemental niacin, it has been suggested to consider using niacin and not niacinamide. Niacinamide inhibits certain gene expression that is related to life span and malignancy.¹⁶

High Total Cholesterol

- Oat bran, onions, garlic, beta sitosterol, artichoke leaf, dandelion root, milk thistle, fenugreek seeds, guggulipid, ginger root, and niacin (monitor liver enzymes)
- Balance essential fatty acids
- Vitamin C – Vitamin C is needed to finish converting cholesterol into bile.
- Vitamin E (mixed tocopherols)
- Same rule outs as triglycerides
- Magnesium (see abstract below)

The fenugreek diet significantly reduced fasting blood sugar and improved the glucose tolerance test. There was a 54% reduction in a 24-hour urinary glucose excretion. Serum total cholesterol, LDL and VLDL and triglycerides were also significantly reduced. The HDL fraction, however, remained unchanged.¹⁸

Comparison Of Mechanism And Functional Effects Of Magnesium And Statin Pharmaceuticals.

Rosanoff A, Seelig MS. Depart. Physiology and Pharmacology, State University of New York, Downstate Medical Center, Brooklyn, NY 11203, USA; J Am Coll Nutr. 2004 Oct;23(5):501S-505S

Abstract

Since Mg(2+)-ATP is the **controlling factor** for the rate-limiting enzyme in the cholesterol biosynthesis sequence that is targeted by the statin pharmaceutical drugs, comparison of the effects of Mg(2+) on lipoproteins with those of the statin drugs is warranted. Formation of cholesterol in blood, as well as of cholesterol required in hormone synthesis, and membrane maintenance, is achieved in a series of enzymatic reactions that convert HMG-CoA to cholesterol. The rate-limiting reaction of this pathway is the enzymatic conversion of HMG CoA to mevalonate via HMG CoA. **The statins and Mg inhibit that enzyme.** Large trials have consistently shown that statins, taken by subjects with high LDL-cholesterol (LDL-C) values, lower its blood levels 35 to 65%. They also reduce the incidence of heart attacks, angina and other nonfatal cardiac events, as well as cardiac, stroke, and total mortality. These effects of statins derive less from their lowering of LDL-C than from their reduction of mevalonate formation which improves endothelial function, inhibits proliferation and migration of vascular smooth muscle cells and macrophages, promotes plaque stabilization and regression, and reduces inflammation, **Mg has effects that parallel those of statins.** For example, the enzyme that deactivates HMG-CoA Reductase requires Mg, making Mg a Reductase controller rather than inhibitor. Mg is also necessary for the activity of lecithin cholesterol acyl transferase (LCAT), which lowers LDL-C and triglyceride levels and raises HDL-C levels. **Desaturase is another Mg-dependent enzyme involved in lipid metabolism which statins do not directly affect. Desaturase catalyzes the first step in conversion of essential fatty acids (omega-3 linoleic acid and omega-6 linolenic acid) into prostaglandins, important in cardiovascular and overall health. Mg at optimal cellular concentration is well accepted as a natural calcium channel blocker. More recent work shows that Mg also acts as a statin.**

High LDL

- Same considerations as high cholesterol and triglycerides
- Antioxidants to help prevent LDL oxidation – vitamin C and E, carotenoids and flavonoids
- Increase soluble fiber

High Lipoprotein (a)

- Genetic predisposition
- Niacin (monitor liver enzymes)
- Assess for hormonal imbalance (testosterone)

Low HDL

- Genetic factors
- Balance essential fatty acids
- Niacin (monitor liver enzymes)
- Vitamin C
- Improve insulin sensitivity (chromium, vanadium)
- Exercise

High Fibrinogen

- Balance essential fatty acids
- Garlic
- Ginger
- Licorice extract – Glycyrrhizin is a potent thrombin inhibitor and increases thrombin clotting time, fibrinogen clotting time and platelet accumulation the thrombin.¹⁹ Glycyrrhizin also has anti-inflammatory actions.

Botanical Considerations for Cardiovascular Disease²⁵

1. Alfalfa – Rich in saponins which are capable of binding to cholesterol and bile salts in the gut to prevent absorption
2. Artichoke leaf extract – known to lower triglycerides and cholesterol (inhibition of cholesterol biosynthesis possibly by influencing HMG-CoA-reductase)
3. Astragalus membranaceus – cardiogenic and antioxidant effects
4. Bilberry – reduced platelet aggregation (the mechanism is thought to be due to increased release of prostacyclin, which has a potent blood vessel dilating and anti-aggregatory activities)
5. Bromelain – fibrinolytic activity (taken on an empty stomach)
6. Curcumin (the yellow pigment in turmeric) – may inhibit pathological changes of atherosclerosis and restenosis. (anti-inflammatory effects and anti-proliferation effects, reduced lipid peroxidation, inhibit platelet aggregation)
7. Gamma-oryzanol (rice bran oil) – may improve lipid profile
8. Garlic and Onions (sulfur-containing compounds- allicin) – may reduce LDL and cholesterol, increase fibrinolytic activity and inhibit platelet aggregation
9. Ginger – may inhibit platelet aggregation
10. Ginkgo biloba – may be effective in reducing fibrinogen level, plasma viscosity, and oxidative damage to LDL (may modulate glutathione redox cycle in vascular endothelial cells)
11. Green tea (polyphenols) – exerts significant antioxidant effects and may help prevent LDL oxidation as well as lower cholesterol
12. Gugulipid (extract of the oleoresin of the mukul myrrh tree) may improve lipid profile and prevent LDL oxidation
13. Hawthorne (contains procyanidin flavonoids) may improve myocardial function, reduce LDL, and act as an antioxidant
14. Licorice - reduce LDL (may cause water and sodium retention)
15. Oligomeric proanthocyanidins (grape seed extract, OPCs, pycnogenol, procyanidins) – potent antioxidants, may inhibit platelet aggregation
16. Psyllium – soluble fiber, cholesterol lowering effects
17. Silymarin – inhibition of LDL oxidation

In Summary

In summary, it is important to understand the vascular biology and the role it plays in cardiovascular disease and hypertension. A comprehensive approach to the treatment and management of cardiovascular disease must be employed to achieve a successful outcome. Oxidative stress, gastrointestinal dysfunction, sugar dysregulation, immune system imbalance, hormonal imbalance, lifestyle (diet and exercise), and environment toxins can singularly, or in combination, initiate and perpetuate cardiovascular disease. Once again, the functional medicine practitioner must integrate the patient history, the physical exam and lab tests, formulating a precise treatment plan, and not just prescribe the supplements, botanicals or pharmaceuticals that only address certain aspects of the disease.

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