New Concepts in Cardiovascular Disease

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ABSTRACT

We have reached a limit in our ability to reduce the incidence of coronary heart disease and cardiovascular disease utilizing the traditional evaluation, prevention, and treatment strategies for the top five cardiovascular risk factors—hypertension, diabetes mellitus, dyslipidemia, obesity and smoking. Statistics show that approximately 50% of patients continue to have coronary heart disease or myocardial infarction despite traditionally defined "normal" levels of these five risk factors. A more logical and in-depth understanding is required of these top five risk factors, including, the evaluation of 24-hour ambulatory blood pressure monitoring, advanced lipid profiles, dysglycemic parameters, visceral obesity, with the effects of adipokines and of the three finite vascular endothelial responses (which include inflammation, oxidative stress and immune vascular dysfunction) to the infinite number of insults. Understanding translational cardiovascular medicine to correlate the coronary heart disease risk factors to the presence or absence of vascular injury and disease with non-invasive vascular testing will allow for early identification, prevention and treatment of coronary heart disease and cardiovascular disease.

Keywords: Cardiovascular disease; Dyslipidemia; Hypertension; Immune vascular dysfunction; Inflammation; Oxidative stress

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INTRODUCTION

Cardiovascular medicine needs a complete functional and metabolic reevaluation related to diagnosis, prevention, and integrative treatments. We have reached a limit in our ability to treat cardiovascular disease (CVD) appropriately.[1] Cardiovascular disease is a group of vascular and heart disorders which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease and deep vein thrombosis and pulmonary embolism.[2] In these states the cardiovascular system is literarily "on fire"; our present treatments are not effective at reducing this vascular inflammation. CVD remains the number one cause of morbidity and mortality in the United States.[3] $80 billion a year is spent treating CVD alone in the United States[3] and over 2200 US citizens die from stroke or myocardial infarction (MI) each day.[3–6] Coronary heart disease (CHD) includes angina, MI, ischemic heart disease, ischemic cardiomyopathy with both systolic (low ejection fraction) and diastolic congestive heart failure (CHF; normal ejection fraction with stiff and non-compliant left ventricle). Ischemic heart disease is the leading cause of death in the world responsible for approximately 17 million deaths in 2011. Of these, 41% were due to ischemic heart disease and 36% due to stroke

The traditional evaluation, prevention, and treatment strategies for the top five cardiovascular risk factors—hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, have resulted in what is now referred to as a "CHD gap".[5] Approximately 50% of patients continue to have CHD or MI despite having "normal" levels of these risk factors, as currently defined in the medical literature.[3, 6] We maintain a cholesterol-centric approach to the management of CHD,[7, 8] but do not address the basic etiologies of CHD such as inflammation, oxidative stress and immune vascular dysfunction. However, there are important details within each of these top five risk factors that are not being measured by physicians and are thus ignored in the prevention and treatment of CHD.[3] In fact, there are at least 395 other risk factors that physicians either do not know about, or they are not using appropriate techniques to identify and treat

them. Thus, it is imperative that we now begin to examine other methods to prevent and treat CVD.[3]

REVOLUTIONIZING THE TREATMENT OF CARDIOVASCULAR DISEASE

The blood vessel has three known finite responses to an infinite number of insults.[3] Those responses are inflammation (the body's response to attempt to remove the injurous stimuli and initiate healing), oxidative stress (an imbalance between reactive oxygen species and the body's ability to detoxify the reactive intermediates), and vascular immune dysfunction (related to T cell and B cell function). Tracking backwards from those three finite responses brings us to the genesis of CVD, with the goal of starting effective treatments to resolve the downstream abnormalities.

Cell membrane physiology and cell membrane dysfunction are keys to this treatment strategy. The membrane barrier between the outside and the inside of every one of our cells, such as the endothelium, enterocyte, the blood–brain barrier, or any other membrane, regulates many of the signaling mechanisms that occur from the external to the internal milieu.[3]

Any cell membrane insult such as high blood pressure (BP), low density lipoprotein (LDL) cholesterol, glucose, microbes, toxins, heavy metals or homocysteine results in a reaction diffusion wave throughout the cell membrane that disrupts the signaling mechanisms and induces membrane damage and dysfunction.[9, 10] The reaction diffusion wave means that a single injury point will be transmitted throughout the cell membrane to induce injury. One small insult becomes a heightened response (metabolic memory) to create further cell damage.[9, 10] This reaction to a foreign insult is an appropriate response by the body, but the blood vessel is injured in a cross reaction, and is really an innocent bystander in a correct but often dysregulated vascular response to these infinite insults.

In the acute setting, any vascular insult results in a correct defensive response by the endothelium. The vascular immune dysfunction, oxidative stress or inflammatory responses are usually short-lived, appropriate, and regulated.[3] However, chronic insults result in a chronic exaggerated and dysregulated vascular dysfunction with preclinical then clinical CVD due to maladaptation of various systems such as the renin-angiotensin-aldosterone (RAAS) system, sympathetic nervous system (SNS) and others.[3]

Most diseases are defined with a specific abnormal level. Hypertension is defined as systolic blood pressure >140 and/or diastolic blood pressure >90 mmHg, dyslipidemia as an LDL-cholesterol of >100 mg/dl, and glucose intolerance as a fasting glucose level of >99 mg/dl.[3, 11–13] However, it is very clear that there is a continuum of risk starting at lower levels of BP, LDL cholesterol, and glucose, as well as for most other CHD risk factors.[3] For example, we know that the BP risk for CVD actually starts at 110/70 mmHg, and that the risk of LDL cholesterol causing reduction in nitric oxide in the endothelium starts at 60 mg/dl and fasting glucose risk starts at 75 mg/dl.[3] There is a progressive continuum of risk with all of the CVD risk factors and mediators that affect the blood vessel, leading initially to functional abnormalities (endothelial dysfunction), then to structural abnormalities of the vascular and cardiac muscle and to preclinical and clinical CVD.[14, 15] In the case of LDL cholesterol, the increase in risk is non-linear, rising more steeply with increasing LDL-C concentrations.[16] Blood pressure also follows a non-linear model,[17] while glucose follows a threshold model with linear slope[18] and blood pressure.

It is important to understand the concept of "translational vascular medicine." For example: do the risk factors that are measured actually translate into a vascular illness? Then, vice versa: does the absence of those risk factors actually define vascular health? At this time we often do not use functional and structural markers of vascular and endothelial dysfunction to identify the vascular effects of CHD risk factors or the presence of vascular disease. Instead, we are relying only upon risk factors or some risk factor scoring system such as Framingham or COSEHC (Consortium of Southeastern Hypertension Centers[19, 20]). We assume that if a patient has risk factors, they also have vascular disease; but if they don't have risk factors,

they may have vascular health. It is important to measure sensitive indicators of endothelial dysfunction and vascular structural disease that are induced by the insults for early detection of risk for cardiovascular events. Early detection with aggressive treatment may reduce CVD.

THE ENDOTHELIUM, ENDOTHELIAL FUNCTION, AND ENDOTHELIAL DYSFUNCTION

The endothelium is a very thin lining of vascular cells which forms an interface between the circulating blood in the lumen and the vascular smooth muscle.[3, 5, 21] When the endothelium is working correctly (endothelial function) all the blood elements and the vascular smooth muscle remain normal. However, when endothelial dysfunction occurs, the results are inflammation, oxidative stress, immune dysfunction, abnormal growth, vasoconstriction, increased permeability, thrombosis and ultimately CVD.[3, 5, 21, 22]

Figure 1 illustrates the role of LDL cholesterol in atherosclerotic plaque formation.[23] Once inside the vessel wall, LDL cholesterol becomes susceptible to oxidation and modification by free radicals and glycation.[23] Oxidized LDL and glycated LDL are toxic to the vessel wall.[23] The modified LDL is consumed by scavenger receptors (SR-A and CD-36) on macrophages to form foam cells.[24] Foam cells are not able to process the oxidized LDL or modified LDL and continue to accumulate oxidized and modified LDL, forming a plaque which may rupture and cause acute coronary thrombosis. This is the progression that needs to be interrupted. There are actually 38 different steps in this process that are important in the treatment of dyslipidemia-induced vascular disease (e.g. glucose, lipids, homocysteine, heavy metals) that are promising therapeutic targets (e.g. with ARBs, exercise, statins).[23]

Vascular disease is a balance of vascular injury (induced by contracting factors such as angiotensin II and endothelin) versus vascular repair with endothelial progenitor cells (EPCs) produced in the bone marrow.[3, 6] The infinite insults result in preconditioned and heightened "metabolic memory" responses that trigger the three known finite downstream responses that have a bi-directional communication involving endothelial dysfunction,
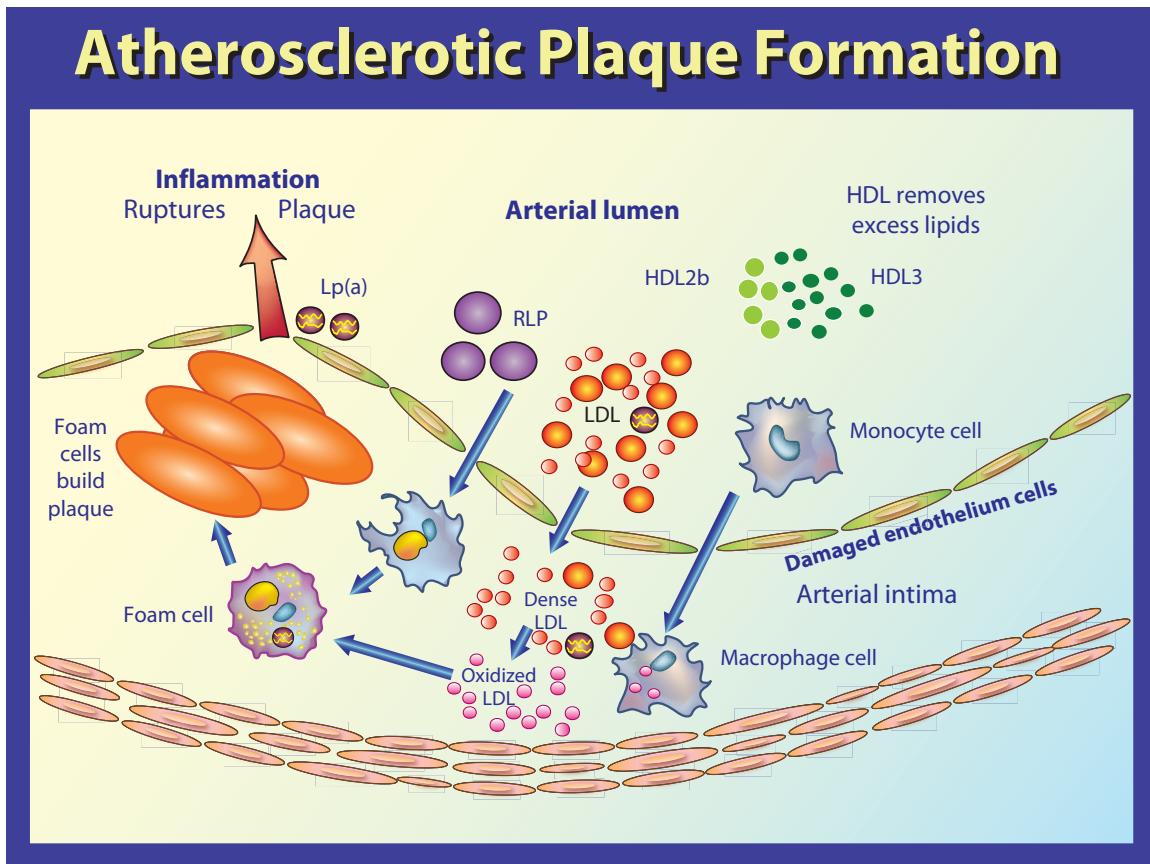
Figure 1: A simplified illustration of atherosclerotic plaque formation.

vascular smooth muscle, and cardiac dysfunction.[5, 9] Once endothelial dysfunction has developed, a smaller insult occurring at a later stage can result in a heightened response that induces more vascular damage.[5, 9] The concept of metabolic memory was demonstrated by Youssef-Elabd *et al.* who found that short-term exposure of adipose cells to uncontrolled levels of saturated fatty acids and glucose led to a long-term inflammatory insult within adipocytes.[9]

THE PATHOPHYSIOLOGY OF VASCULAR DISEASE

The major causes of vascular disease are: Oxidative stress:[25, 26] reactive oxygen species (ROS) and reactive nitrogen species (RNS) are increased in the arteries and kidneys and with decreased oxidative defenses.

- Inflammation:[26–30] this is increased in the vasculature and kidneys and includes increased C-reactive protein (CRP), leukocytosis,

increased neutrophils and decreased lymphocytes, and upregulation of RAAS in the kidney.

- Autoimmune dysfunction:[31–35] of the arteries and kidneys, which includes, increased white blood count (WBC), and involvement of CD4+ (T-helper cells) and CD8+ (cytotoxic T-cells).

These problems result in abnormal vascular biology with endothelial dysfunction and vascular smooth muscle hypertrophy and dysfunction.[5, 26] Of course, genetics, genomics, and epigenetics also play a role in the pathophysiology of vascular disease.[4]

Figure 2 offers an insight into the infinite insults that the endothelium is bombarded by. The infinite insults are divided into two major categories: biomechanical (BP, pulse pressure, shear stress, and oscillatory pressure within the arterial system— most plaques form at the bifurcation of arteries), and biochemical (e.g., nutritional factors, microbes, sterile antigens, and environmental toxins).
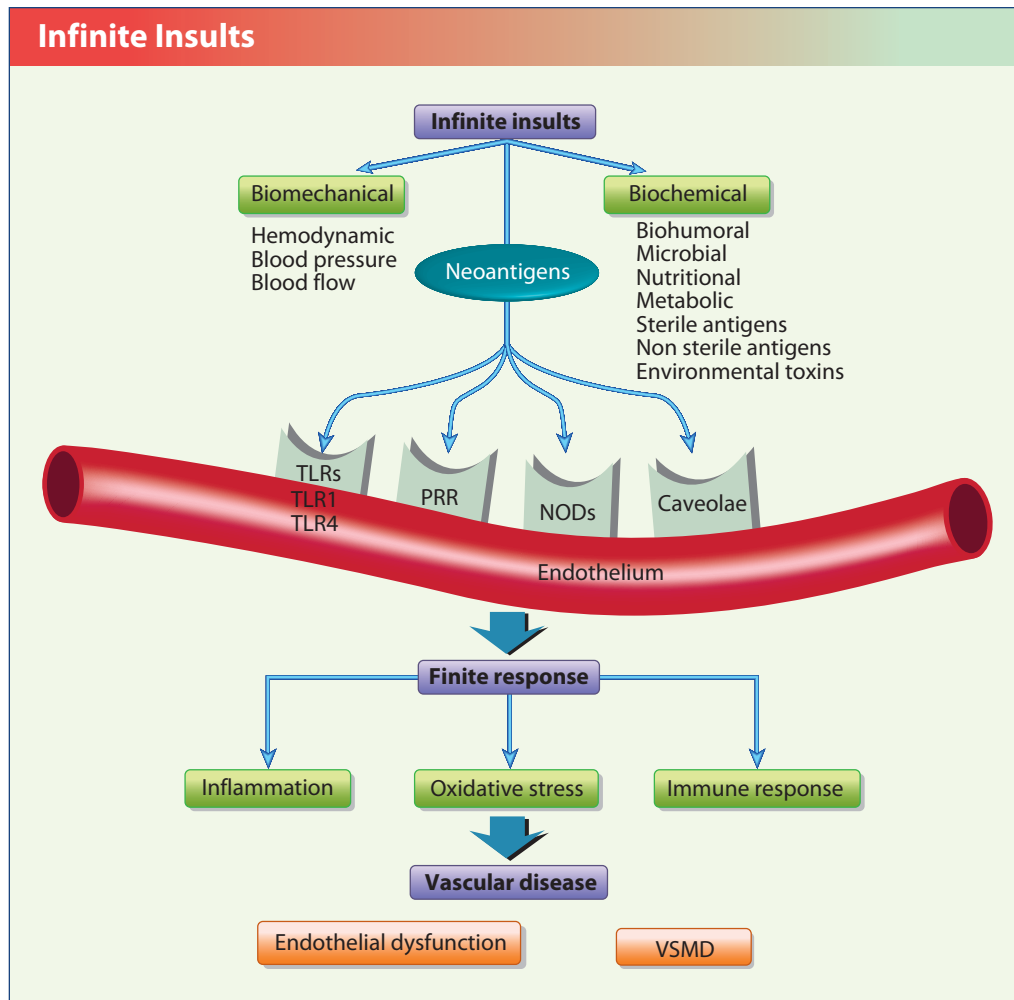
Figure 2: The endothelium is subject to an infinite number of insults but can only elicit a finite number of responses to those insults.

NOD, nucleotide-binding oligomerization domain receptor; PRR, pattern recognition receptor; TLR, toll-like receptor; VSMD,

Endothelial cells express various receptors that determine the interaction between the insults and the downstream mediators. These include pattern recognition receptors (PRR), toll-like receptors (TLR), nod-like receptors (NLR), and caveolae.[36] The TLRs and NLRs are membrane receptors that react to external insults with appropriate intracellular signaling that usually induces inflammation, oxidative stress and immune dysfunction within the cell. The caveolae are membrane lipid microdomains that, when interrupted or stimulated, reduce nitric oxide levels, and increase BP, inflammation, dyslipidemia, oxidative stress and immune dysfunction leading to atherosclerosis. The various risk factors and

risk mediators attach to one of the receptors in the membrane and then set off a cascade of the three finite responses (inflammation, oxidative stress, and immune dysfunction), which leads to endothelial dysfunction and ultimately CVD.[36]

INTERRUPTING THE FINITE PATHWAYS

The key to the successful prevention and treatment of CVD is recognition of risk factors, modifying risk factors and interrupting pathways that connect the risk factors to the receptors discussed above.[14, 15] The TLR 1, 2 and 4 are the most common of the PRR type TLRs related to the vascular membrane

and endothelial dysfunction. TLR 2 and TLR4 are most important, but TLR2 activation may occur via a TLR1 or TLR-6 coreceptor independent pathway.[37–39] The NLRs: NOD 1 and NOD 2 are also types of PRRs that involve the vascular membrane.[39] There are many scientifically proven nutraceuticals and dietary factors that accomplish this:[40, 41]

- Curcurmin (turmeric): the PRRs, TLR 4, NOD 1 (NLR), and NOD 2 (NLR)
- Cinnamaldehyde (cinnamon): TLR 4
- Sulforaphane (broccoli): TLR 4
- Resveratrol (nutritional supplement, red wine, grapes): TLR 4
- Epigallocatechin gallate (green tea): TLR 4
- Luteolin (celery, green pepper, rosemary, carrots, oregano, oranges, olives): TLR 4
- Quercetin (tea, apples, onion, tomatoes, capers): TLR 4
- Chrysin: TLR 1
- Omega 3 fatty acids: Interrupt caveolae lipid microdomains TLRs and NODs, decrease inflammation and HS-CRP, lower BP, decrease LDL particle number (LDL P), increase LDL and high density lipoprotein (HDL) size, improve glycation parameters, decrease immune vascular dysfunction, decrease CHD plaque formation, improve CHD and CHF symptoms and outcomes

The goal is to use a systematic (dynamic systems biology), functional and metabolic medicine approach to establish cardiovascular ecology, balance, and allostasis (achieve stability through change), and minimize chronic internal and external cardiovascular stressors, mediators, and risk factors that insult the blood vessel. An attempt should be made to reduce the allostatic load, and prevent, regulate, and treat the "abnormal" downstream finite responses.

The polygenetic codes for CVD identify 30 separate loci that are associated with MI and CHD, but only a minority of those 30 loci has anything to do with the top five cardiovascular risk factors.[4] The majority of those loci deal directly with inflammatory pathways. Evaluation and treatment of only the top five risk factors and how they interact with our genome will likely not reduce CVD, and the CHD gap will persist.

Endothelial dysfunction has been hypothesized to be the link between post-prandial state and atherosclerosis and vascular disease.[42] Ingestion of sodium chloride, refined carbohydrates, and foods containing saturated fats and trans fats, lead to prolonged increases in glucose and triglycerides, vascular endotoxemia, inflammation, oxidative stress, and immune dysfunction.[9, 43] Furthermore, these responses may be perpetuated long after the original insult with a heightened continued inflammatory response (metabolic memory).[9] Fortunately, studies have shown that eating a diet rich in low-glycemic foods, monounsaturated and polyunsaturated fats, polyphenols, and antioxidants can help to prevent post-prandial endothelial dysfunction.[23] Early[44–48] evidence of CVD in the form of fatty streaks has been documented in children in the first and second decades of life (Figure 3).[3] The vascular disease is sub-clinical for 10–30 years or more prior to any cardiovascular event.[3, 4, 21] Endothelial dysfunction is the earliest functional abnormality, followed by changes in arterial compliance, stiffness, and elasticity. It is important to begin using technologies that allow earlier identification of cardiovascular dysfunction before any structural changes have occurred.

Figure 4 illustrates the vessel changes that occur as CHD progresses. On the left is a fairly normal artery. In the middle, the CHD has progressed from minimal to moderate with the subendothelium layer becoming thick, but the lumen is still the same size. This extraluminal plaque and inflammation could be observed with electron beam tomography or computed tomography (CT) angiogram but missed by conventional coronary arteriogram (Figure 5). In the image on the right in Figure 4 there is extensive extraluminal and intraluminal disease.

Lack of the proper type of imaging, ignoring the majority of the other 400 or so CHD risk factors and not properly evaluating the top five risk factors are some of the reasons for the persistence of the CHD gap.[3] For example, only a 24-hour ambulatory blood pressure monitor can identify specific BP risks for CVD such as nocturnal BP, dipping, non-dipping, BP surges, BP load and BP variability. Non-dipping is defined as a <10% reduction in BP at night. Nocturnal BP is the primary determinate of CVD related to BP measurements. The BP load is the number of BP
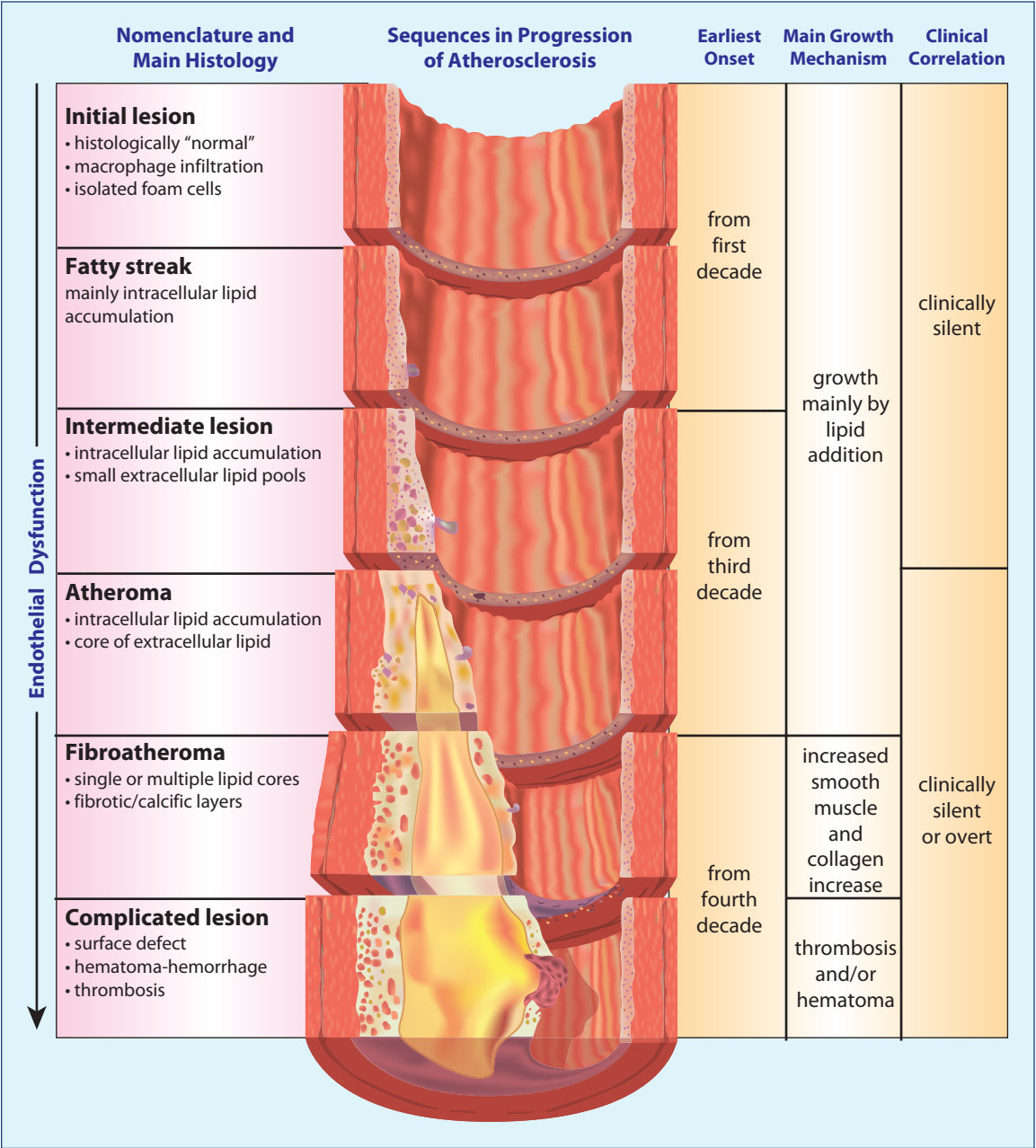
Nomenclature and Main Histology	Sequences in Progression of Atherosclerosis	Earliest Onset	Main Growth Mechanism	Clinical Correlation
Initial lesion • histologically "normal" • macrophage infiltration • isolated foam cells		from first decade	growth mainly by lipid addition	clinically silent
Fatty streak mainly intracellular lipid accumulation				
Intermediate lesion • intracellular lipid accumulation • small extracellular lipid pools		from third decade		
Atheroma • intracellular lipid accumulation • core of extracellular lipid				
Fibroatheroma • single or multiple lipid cores • fibrotic/calcific layers		from fourth decade	increased smooth muscle and collagen increase	clinically silent or overt
Complicated lesion • surface defect • hematoma-hemorrhage • thrombosis			thrombosis and/or hematoma	

(left margin label: Endothelial Dysfunction)

Figure 3: Progression of atherosclerosis.

readings >140/90 mmHg in 24 hours. The normal BP load is <15% of the total BP readings. BP surges that are high and rapid during the early morning between 3 and 9 a.m., as well as labile or variable BP will increase CVD.[21] Excessive dipping is associated with an increased risk of ischemic stroke and reverse dipping is associated with an increased risk of intracerebral hemorrhage. Nocturnal BP is more clinically important than day BP (27/15 mmHg difference is optimal).[21] Furthermore, morning BP surges (level and rapidity)

increase the risk of ischemic stroke, MI, and left ventricular hypertrophy.[21, 49] Hypertension is not a disease, it is a marker for vascular dysfunction. Therefore it is crucial that it is correctly identified. The following points should always be considered when evaluating BP:[21, 50, 51]

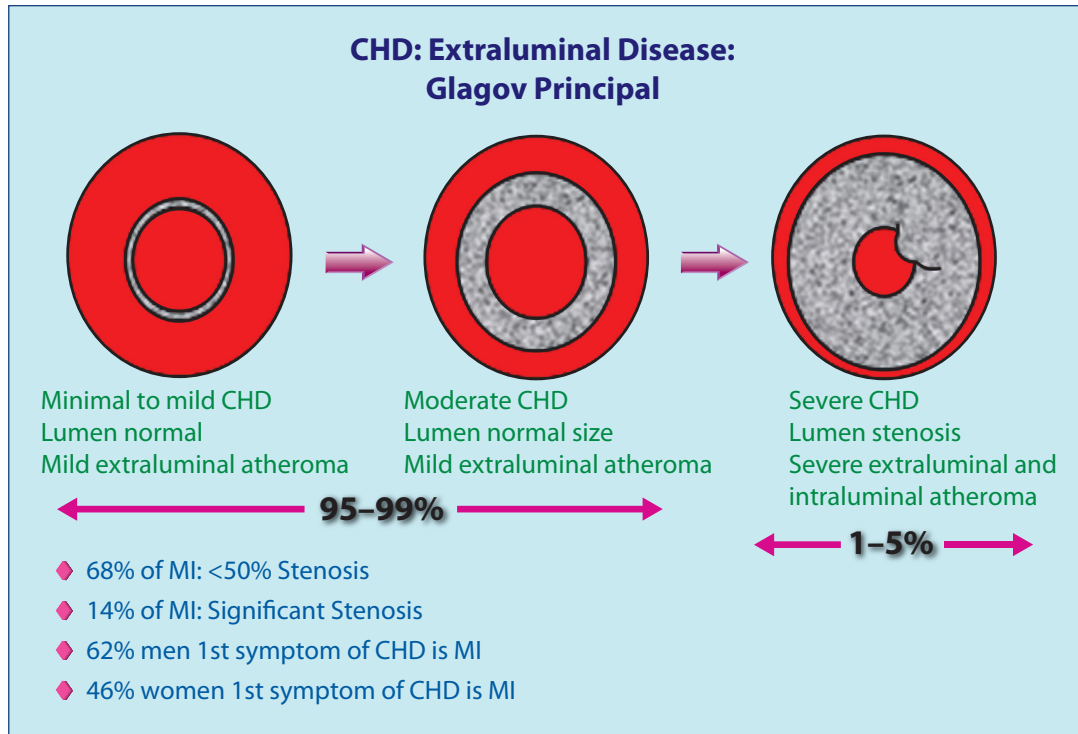• Normal BP is 120/80 mmHg, but there is a continuum of risk for CVD starting at 110/70 mmHg;

CHD: Extraluminal Disease: Glagov Principal

Minimal to mild CHD
Lumen normal
Mild extraluminal atheroma

Moderate CHD
Lumen normal size
Mild extraluminal atheroma

Severe CHD
Lumen stenosis
Severe extraluminal and intraluminal atheroma

95–99%

1–5%

- 68% of MI: <50% Stenosis
- 14% of MI: Significant Stenosis
- 62% men 1st symptom of CHD is MI
- 46% women 1st symptom of CHD is MI

Figure 4: Illustration of the vessel changes that occur as CHD progresses.

CHD, coronary heart disease.

From Nissen SE. *Manag Care.* 2002;11 (10 Suppl):8–14. Reproduced with permission.

- Each increase of 20/10 mmHg doubles cardiovascular risk);[52]
- Before age 50, the diastolic BP predicts risk best;[53]
- After age 50, the systolic BP predicts risk best);[53]
- 24-hour ambulatory BP monitoring is more accurate than office BP measurements and should be the standard of care for defining BP and CVD risk;[54, 55]

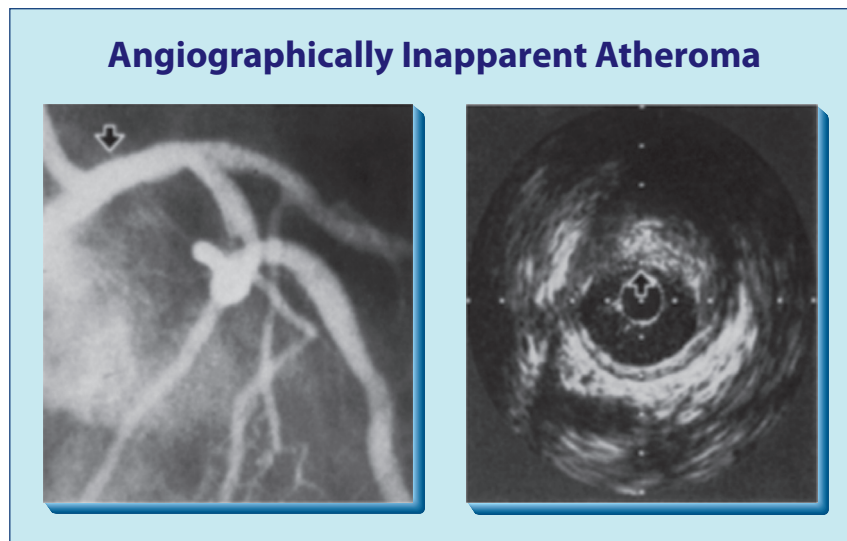**Angiographically Inapparent Atheroma**

Figure 5: Coronary heart disease that is not detectable by angiogram (left) is clearly evident using computed tomography (right).

From Nissen SE. *Manag Care.* 2002;11 (10 Suppl):8–14. Reproduced with permission.

- Mercury cuffs are best. Electronic arm cuffs are good. Do not use wrist or finger monitors;
- BP load: this should be <15% higher than 140/90 mmHg.

Dyslipidemia is another one of the top five cardiovascular risk factors; however, proper measurement using advanced lipid profiles is not often obtained to verify risk and optimal treatment.[23, 56, 57] An advanced lipid profile, though not routinely used in routine clinical practice, is emerging in research as it measures several risk factors associated with CVD, including:

- LDL-C total
- LDL-P (particle number, drives CHD risk);
- LDL size (dense type B versus large type A);
- modified LDL (oxidized, glycated, glyco-oxidized and acetylated);
- antibodies to oxidized LDL and modified LDL;
- if apolipoprotein (APO) B is elevated;
- APO B antibodies and immune complexes;
- Lp(a);
- HDL-C total;
- HDL-P (particle number);
- HDL size (large 2b versus small type 3);
- dysfunctional HDL;
- pro-inflammatory and pro-atherogenic HDL;
- myeloperoxidase (MPO) and dysfunctional APO A;
- low APO A;
- low paraoxonase (PON)-1 and PON-2;
- increased APO-CIII;
- serum free fatty acids;
- very LDL (VLDL) and triglyceride (TG) total;
- large VLDL;
- VLDL-P particle number;
- remnant particles.

The primary factor driving cardiovascular risk related to LDL cholesterol is the number of LDL particles (LDL-P and APO B particles).[58] HDL-P (particle number) is most protective, with larger HDL type 2b providing the second most important protective mechanism.[23, 59] Larger numbers and sizes of HDL molecules are more efficient at reverse cholesterol transport, and are more protective to the vascular system in numerous other ways.
It is also important to analyze dysfunctional HDL.[23, 56, 57] Patients who have an HDL level of 85 mg/dl or more often have dysfunctional HDL that is not even protective.[56, 57] VLDL, triglycerides and remnant particles are very atherogenic and thrombogenic.[23]

Table 1: Non-invasive vascular testing for cardiovascular disease.

Non Invasive Vascular Testing
Functional Tests
Endopat (endothelial dysfunction)
CAPWA (computerized arterial pulse wave analysis)
DTM (digital thermographic monitor)
HRV: Heart Rate Variability
EKG and TMT
MCG (magnetocardiography)
Structural Tests
Carotid IMT/Duplex
EBT and CT Angiogram (CTA) with CAC scoring
Cardiac MRI (CMR)
ECHO: Rest and exercise
ABI: Rest and exercise
Other
Cardiac PET and SPECT
IVUS: Intravascular Ultrasound
Cardiac Nuclear Studies (MPI) with PET and SPECT
Coronary Angiogram

ABI, ; CT, computed tomography; EBT, EKG, ; PET, positron emission tomography; SPECT, TMT.

A fasting blood sugar (FBS) level of >75 mg/dl increases CHD by 1% per increase of 1 mg/dl, and induces endothelial dysfunction.[3] If a patient has an FBS of 100 mg/dl (often considered a normal level) the risk of CHD is increased by 25%.[3] A 2-hour glucose tolerance test (GTT) measuring >110 mg/dl increases CHD by 2% per 1 mg/dl increase in glucose.[3] The current definition of an abnormal 2-hour GTT is >140 mg/dl. If a patient's result is 140 mg/dl, which again is currently classed as "normal," CHD and MI are increased by 60%. Hyperinsulinemia is also an independent risk factor for CHD.[3] Insulin resistance creates inflammation,

reduces nitric oxide levels, and causes endothelial dysfunction and vascular disease through the mitogen activated protein kinase (MAPK) pathway, which is atherogenic and induces hypertension as opposed to the phosphatidylinositol 3-kinase (PI3K) pathway, which is anti-inflammatory, anti-hypertensive and anti-atherogenic.[3] It is important to measure all glycation parameters, including fasting glucose, 2-hour GTT, insulin levels, C-peptide and pro-insulin, depending on the clinical setting.[60]

Obesity with increased levels of inflammatory and oxidative stress-related adipokines contribute

Table 2: Other comprehensive lab tests for cardiovascular disease.

Lab Testing

- CBC with diff
- UA
- CMP 12
- Expanded advanced lipid profile
- APO B and APO AI
- Free T4, T3, TSH, RT3, thyroid antibodies
- Magnesium
- Iron, TIBC and Ferritin
- Fibrinogen
- HSCRP
- Homocysteine
- Uric acid
- Microalbuminuria
- GGTP and hepatic profile
- Myeloperoxidase (MPO)
- Cardiovascular SNP's
- Toxicology and heavy metal screen: Spot or 24 hour urine

Lab Testing

- Vitamin D3
- Fasting C peptide, AIC, insulin, proinsulin, 2 hour GTT
- PRA and Aldosterone
- Free testosterone, SHBG, estradiol, estriol
- Progesterone, DHEA and DHEAS
- B12 and folate
- AM and PM cortisol and salivary cortisol
- ADMA
- Adiponectin
- EKG and TMT and CXR
- Micro nutrient Testing
- Omega 3 index
- APO E
- Blood visosity
- Erythocyte adhesion
- Telomere test
- Gluten antibody screen
- MTHFR
- Body Impedance Analysis, waist circumference, WHR
- Rest and exercise BP and 24 hour ABM
- PFT and DEXA

ABM, ambulatory blood pressure monitoring; ADMA, ; AIC, ; APO, apolipoprotein; BP, blood pressure; CBC, ; CMP, ; CXR, ; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; DEXA, ; EKG, ; GGTP, ; GTT, glucose tolerance test; HSCRP, high sensitivity C-reactive protein; PFT, ; SHGB, sex hormone binding globulin; SNP, ; TIBC, ; TMT, ; TSH, thyroid stimulating hormone; UA, ; WHR, .

Box 1

Finite Response Testing: Blood Inflammation

- HS-CRP
- TNF-alpha
- Interleukins IL-6, IL 1b
- MPO (myeloperoxidase)
- Lp-PLA 2
- Fibrinogen and Ferritin
- ESR
- Omega 3 Index
- Homocysteine
- Waist circumference, visceral obesity % fat and total body fat

ESR, ; HS-CRP, high sensitivity C-reactive protein; IL, interleukin; Lp-PLA, ; TNF, tumor necrosis factor.

Box 2

Finite Response Testing: Blood Immune Vascular Dysfunction

- Thyroid Antibodies
- IL 1b, 4, 6, 10, 12, 17
- IgG, IgE and IgA
- TNF alpha
- C4a, C3a, C3 and C4
- Tlymphocyte subsets
- Total and epitope specific IgE and IgG-type 4
- NKC percent
- CBC with diff
- ELISA-ACT
- ACTH/Cortisol ratio
- MMP-9 and MMP-2
- Infectious disease profile with IGM and IGG antibodies such as H Pylori, CMV, EBV, Lyme, Mycoplasma, HSV, Chlamydia, Hepatitis A, B, C

ACTH, adrenocorticotropic hormone; CBC, ; CMV, ; EBV, Epstein Barr virus; ELISA-ACT, enzyme-linked immunosorbent assay-; HSV, herpes simplex virus; Ig, immunoglobulin; IGG, ; IGM; IL, interleukin; MMP, matrix metalloprotease; NKC, ; TNF, tumor necrosis factor.

to CHD. Measurement of not just body weight, but body mass index and body composition with visceral fat and lean body mass will help predict CHD risk.[60]

Fortunately, there are a number of non-invasive tests to determine vascular pathology before it actually starts.[3] Emerging technologies, particularly EndoPAT, a post-brachial artery study, which is very accurate at assessing endothelial function and diagnosing endothelial dysfunction, computerized arterial pulse wave analysis (CAPWA) for endothelial function and arterial compliance, carotid intimal medial thickness (IMT), magnetic cardiography (MCG), and cardiac CT angiograms for calcium score deserve

Box 3

Finite Response Testing: Oxidative Stress

- **Ox LDL and glycated LDL**
- **MPO**
- **GGT**
- **GSH and GSH/GSSG (reduced/oxidized ratio)**
- **MDA (malondialdehyde)**
- **TBARS (Thiobarbituric acid reactive substances)**
- **F2 isoprostane and 8-OHdG (deoxguanosine)**
- **Hexanoyl Lysine (ELISA) and lipid hydroperoxide: Lipids Ox**
- **Protein Carbonyl**
- **SOD 1 and 2 and Catalase**
- **LP_PLA 2**
- **WBC with diff**
- **Uric acid**
- **Haptoglobin**
- **Oxidative Defense: TAS (total antioxidant status), Spectrox**

GGT, ; GSH/GSSG, glutathione/oxidized glutathione; Lp-PLA, ; MPO, ; WBC, white blood count.

consideration (Table 1).[3, 21, 60–63] The EndoPAT is a cost effective[64] and noninvasive test that identifies early endothelial dysfunction to predict future CVD and CHD. Further research is needed prior to wide implementation.[64] This test, in addition to 24-hour BP, advanced lipid testing, and glycation measurements, provide cost-effective ways to evaluate several key biomarkers associated with risk in the cardiovascular patient. Numerous other CHD risk factors are listed below in Table 2. Some of the most neglected and important CHD risk factors to evaluate include gender-specific hormones, thyroid function, toxins, homocysteine and vitamin D.

CONCLUSIONS

The top five cardiovascular risk factors, as they are currently defined, are not an adequate explanation for CHD. In order to close the CHD gap, the top five risk factors must be better defined while assessing the other 395 risk factors and mediators. Early detection and aggressive prevention and treatment of vascular disease are needed before any structural changes occur. To do this we need to utilize new laboratory techniques, such as the advanced lipid profiles,

24-hour BP monitoring, and specific tests to identify inflammation (such as HS-CRP), oxidative stress (such as oxidized LDL and myeloperoxidase), and immune vascular dysfunction. In addition, vascular translational medicine will need to be evaluated with new imaging technologies, such as EndoPAT, CAPWA, carotid IMT, MCG and CT angiogram.

In order to truly revolutionize the treatment of CVD, new therapies will need to involve management of the pathophysiologic risk factors, mediators and their downstream effects, as well as the finite vascular responses. This will be achievable by using a combination of targeted personalized treatments with genomics, proteomics, metabolomics, nutrition, nutraceutical supplements, vitamins, minerals, anti-oxidants, anti-inflammatory agents, anti-immunological agents, and pharmacologic agents. Future studies must begin to measure all of the pertinent risk factors that have been reviewed here to correlate their direct relationship with CHD. Only by addressing all of these factors will we be able to decrease or halt subsequent vascular damage.

DISCLOSURE OF INTERESTS

Dr. Houston has nothing to disclose.

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