

Pathobiology Question

You are an epidemiologist working in a study of more than 3000 women (750 each of African-American, Caucasian, Japanese and Chinese), aged 50-60 years. There have been 290 "hard cardiovascular" events cumulatively (including 60 strokes) in these women, who have been followed with 10 annual visits. In the final visit and for the first time, there will be a subclinical measure of heart disease, either:

- a. An ultrasound of the carotid arteries to assess intimal-medial thickness

OR

- b. 64-slice computed tomography of the blood vessels of the heart (aorta and coronary arteries).
 1. Provide a schematic or diagram to illustrate the processes leading to the development of atherosclerosis and use this diagram to discuss the development of atherosclerosis; (expect 7-9 steps). [30 points]
 2. Compare and contrast the pathogenesis of "atherosclerosis" and "arteriolosclerosis" and discuss the relation of both these processes to the etiology of "coronary heart disease". [30 points]
 3. Use the diagram you developed in response to question 1 to discuss what aspects of the atherosclerotic process are best described by each of the two subclinical disease measures. Discuss the pros and cons of each of these two proposed measures of subclinical disease in the aforementioned study. Discuss how these pro and cons relate to the development of atherosclerosis. Note that a consideration of the age, race, and event history of the study population should be central to your answer here. The discussion should also address validity of the measures. [25 points]
 4. How might your answer to question 3 have changed if the study population were different or if your study design were different? Use specific examples to illustrate your points. [15 points]

Answers to Pathophysiology Question

Arteriosclerosis (general term)	Atherosclerosis
Chronic disease of arterial system— responsible for transport of nutrient and oxygen carrying capacity	Chronic disease
Abnormal thickening and hardening "loss of distensibility" of the vessel wall	
Smooth muscle cells (SMC) and collagen migrate into tunica intima	
Unable to respond with change in lumen size	Thickening of vessel walls caused by hardening of soft tissue deposits of fat and fibrin reducing lumen size i. e. is a hardening of an artery specifically due to an atheromatous plaque
	Subset of arteriosclerosis – often used interchangeably

Process of atherogenesis:

- A. Endothelial cell injury in vessel wall
 - injured cells unable to produce antithrombic and vasodilatory cytokines
 - send out messenger to attract macrophages
 - in process of responding to injury, overproduction of free radicals especially by macrophages
 - over production of free radicals in the presence of inadequate antioxidants results in the oxidation of low density lipoproteins (oxLDL)
 - macrophages are engulfed by macrophages, ultimately becoming foam cells
 - foam cells aggregate to form fatty streaks which is a yellow, lipid-filled smooth muscle cell (SMC)

- B. Development of fibrous plaque
 - SMC cells in the intima become more compromised
 - the development of a fibrous plaque is initiated that includes collagen, elastin fibers, and mucoprotein
 - the plaque becomes elevated from the vessel wall and intrudes into the lumen of the vessel
 - plaque includes lipids and debris from cellular necrosis resulting from inadequate blood supply
 - can occlude the arterial system

- C. Development of complex lesions and impact
 - plaque becomes calcified and more hard
 - hemorrhage develops as lesion becomes dislodged
 - dislodged lesions associated with clots and emboli
 - lead to inadequate perfusion of tissue when blood supply is occluded

Process in pathophysiology extended to cerebral aneurysms

Phase I—Pathogenetic insult—

- at bifurcation, there is a thickening of the intima composed of vascular smooth muscle cells (VSMC), elastins, and collagens
- fatty streak is initiated by trapping of LDL in the subendothelial space
- cells of the arterial wall secrete oxidative products initiate oxidation of LDL

Phase II—Endothelial dysfunction

- oxLDL inhibits the release of nitric oxide and endothelium-derived hyperpolarizing factor (EDHF), impairs endothelium-dependent vasodilation, and downregulates the expression of NO synthase.
- disturb the balance between vasodilatory and vasoconstrictive factors
- NO accounts for most of the endothelium-dependent relaxation activity
- leads to increased (accelerated) endothelial cell death (apoptosis)
- Apoptosis is accelerated by angiotensin II, oxLDL, ROS, glucose, and inflammatory cytokines
- oxLDL activates NF- κ B-like transcription factor and induces the expression of genes containing NF- κ B binding sites that initiate an inflammatory response leading to fatty streak
- apoptotic endothelial cells become procoagulant

Phase III—decrease in vasodilation, increase in monocyte and leukocyte adhesion

- leukocyte and monocyte capture and rolling are mediated by the selectin family of adhesion molecules
- P-selectin facilitates rolling
- E-selectin slows leukocyte rolling velocity
- Adhesion and sticking is mediated by leukocyte beta-integrin, and intercellular and vascular cells adhesion molecule-1 (VCAM-1), intracellular adhesion molecule (ICAM-1 and ICAM-2) on the endothelial surface.
- Process is facilitated by the presence of oxLDL, cytokines (IL-1 β and TNF α)

Phase IV—increase in vascular permeability and migration of monocyte and leukocytes

- monocytes and leukocytes migrate to the subendothelial space where they are transformed into macrophages and foam cells (lipid-laden macrophages)
- chemoattractants of the monocytes and leukocytes are: oxLDL, Lp(a), cytokines {monocyte chemoattractant protein-1 (MCP-1)—considered a key recruiter of monocytes, interleukin-1 (IL-1), TNF α , monocyte colony stimulating factor (M-CSF), platelet cell adhesion molecule-1 (PCAM-1), and degraded collagens and elastins.

Phase V—apoptosis (programmed cell death)

- formation of both stable – small lipid core covered by thick fibromuscular cap—more likely to lead to occlusion
- formation of unstable plaque—larger lipid core, thin cap, large # of inflammatory cytokines, proliferation of apoptotic cells—more likely to rupture

Phase VI—release of proteolytic enzymes that degrade and remodel the vascular ECM (similar status seen with cellular invasion, tumorigenesis, metastasis and angiogenesis)

- fibronectin indicator of the elastic lamina, disappears with early stages of an aneurysm
- breakdown of collagens in arterial wall around aneurysms
- imbalance in favor of proteolytic enzymes, marked by Il-1 and TNF α
- increased levels of PAI-1 and plasmin
- increase in matrix metalloproteinases for remodeling vascular wall
 - MMP-1 – a collagenase
 - MMP-2 is synthesized in BSMS, mesenchymal cells and macrophages (gelatinase A) and MMP-9, an elastase, produced in macrophages (gelatinase B) are elevated in aneurysm walls –they degrade type IV collagen
 - elastase (also MMP) can degrade elastin, collagen, fibronectin and laminin
- MMP is counterbalanced by binding to a family of proteins (TIMP 1-4) and may provide protection against plaque destabilization

Not all cerebral aneurysms are associated with atherosclerosis

Two measures of atherosclerotic process (subclinical measures) in women

Intimal thickening:

--ultrasound measure of the carotid arteries

Advantages in the population

- 1) provides a measure of functional status of the lumen
- 2) considered an "acceptable" hard outcome by FDA
- 3) well-validated in terms of predicting hard outcomes
- 4) provides information about atherosclerotic prior to having emboli or aneurysm
- 5) does not require radiation or chemical exposures

Disadvantage in population

- 1) has a long history of use—not considered the most contemporary measure
- 2) occurs in carotid arteries and not directly in coronary arteries where MI would be expected to have impact
- 3) best measures require experienced standardized protocol and expert reading center
- 4) modestly costly

--64-slice electron beam computed tomography

Advantages in the population

- 1) provides a measure of functional status of the presence of plaques and their relative size
- 2) provides a measure of the atherosclerotic process that is further along than IMT
- 3) considered an "acceptable" hard outcome by FDA
- 4) well-validated in terms of predicting hard outcomes
- 5) a "sexy" newer measure
- 6) measures coronary arteries where MI would be expected to have impact, but not necessarily aneurysm for stroke

Disadvantage in population

- 1) has a very short history of use—rapidly evolving technology
- 2) measures require experienced standardized protocol and expert reading center
- 3) require radiation exposures
- 4) expensive, hard to implement in many clinical center – research can compete with clinical utilization

Atherosclerosis

