Cardiovascular disease physiology

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Content

• Introduction – The number 1 killer in America
  – Some statistics
  – Recommendations

• Cardiovascular diseases
  – Damage
  – Current treatments

• Control of vascular tone (hypertension)

• Some vascular research at Lehigh
Cardiovascular disease (CVD) and other major causes of death: total, <85 years of age, and ≥85 years of age.
https://www.nhlbi.nih.gov/health-topics/coronary-microvascular-disease
Some Good news.

In many western developed countries, deaths from coronary heart disease have decreased steadily as treatment options have improved, and as people have made lifestyle changes.

In the 1970s, the overall US rate was closer to 450 deaths per 100,000
Cardiovascular disease prevalence

![Cardiovascular Disease Prevalence Graph]

Projected total (direct and indirect) costs of total cardiovascular disease by age (2012 $ in billions).

Projected direct costs of total cardiovascular disease by type of cost (2012 $ in billions).

Risk Factors

• High blood pressure (above 120/80 mm Hg)
• Serum cholesterol [high LDL cholesterol and low HDL, or high total cholesterol]
• Body Mass Index (BMI) [above 30]
• High triglycerides
• Smoking
• Drinking
• Diabetes (high blood sugar)
Prevalence (unadjusted) estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals among US children aged 12 to 19 years, National Health and Nutrition Examination Survey 2009 to 2010 (#s updated to 2014).

Age-standardized prevalence estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals among US adults aged ≥20 years, National Health and Nutrition Examination Survey 2009 to 2010.

Dietary recommendations

Max score is 50
Fruits/Veg. aim for 4.5 c/day
Fish aim for 2+ servings/week
Sodium aim for less than 1500 mg/day
Sugar beverages less than 36 oz/week
Grains 3 or more 1 oz servings/day
Metabolic Syndrome

- Central obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
- Insulin resistance or glucose intolerance (the body can’t properly use insulin or blood sugar)
- Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- Raised blood pressure (130/85 mmHg or higher)
- Proinflammatory state

http://stateofobesity.org/adult-obesity/
Obesity

- Diet
- Portion size
- Physical Activity
- Genes

- Fat as an endocrine tissue
  - Makes leptin – lowered desire to eat, more use of stored fat
  - Makes inflammatory signaling molecules
  - Decreases synthesis of signals that in turn cause a decrease in blood pressure
  - with the result being increased blood pressure

Ob/ob mouse from “Nutritional Science”
Progression of Vascular Disease

- Normal cross-section of artery
- Tear in artery wall
- Fatty material is deposited in vessel wall
- Narrowed artery becomes blocked by a blood clot

- Statins
- Aspirin

MedlinePlus Medical Encyclopedia
Atherosclerosis

- Leads to narrowing/blocking of arteries
  - Blocked flow to the heart
    - Myocardial Infarction (heart attack)
  - Blocked flow to the brain
    - Ischemic Stroke

Bypass
Atherosclerosis Locations

Smooth Flow Region

“Non-Sticky” ECs

Intact Endothelium

Disturbed Flow Region

“Sticky” ECs

Inflamed vasculature

“Leaky” Endothelium

Flow, along with other factors, contributes to risk.

Meron Mengistu
Hypertension

• Angiotensin is a major contraction signal that increases blood pressure transiently

Diuretics, Ace inhibitors, β-blockers, Calcium channel blockers
Relaxation of blood vessels

- NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP

![Diagram showing cGMP and Nitroglycerin]
But cGMP is typically rapidly degraded by proteins called PDEs

PDE3 is primarily in cardiac muscle
PDE6 is primarily in the retinas
PDE5 is primarily in vascular smooth muscle
Sildenafil citrate

• Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
• Therefore in vascular smooth muscle cells cGMP remains elevated longer.

• Viagra is a trade name for sildenafil citrate
Model of Heparin Receptor Mediated Anti-growth Effects in VSMCs and Anti-inflammatory Effects in Endothelial cells

Questions:
Identification of the Receptor
a. Protein identity
b. Validation
c. Heparin binding ability
1. Does the signal go through eNOS? Yes, and Ca^{2+} Channels are involved in both vascular smooth muscle and endothelial cells.
2. What are the inflammatory targets in endothelial cells?
3. What are the functions in an animal? See the next slides.

Pugh, et al JBC 2016
A. 7 day old larva
B. Trunk vessels at 7 days
C. Liver vasculature, 5 day larva
D. Full length view of TG(fli1:EGFP) fish
E. Tail fin with merged transmitted light
F. Tail fin microvasculature in adult
G. Blood vessels associated with surface scales

Lawson and Weinstein, 2002
Developmental Biology 248:307
And what about angiogenesis?

Farwell, et al. Frontiers in Physiology 2017
Developmental Angiogenesis

Also, cell proliferation is maintained. Cell to cell adhesion is decreased.

Field, et al., submission 2019
Where do scientists go from here?

• Can research dissociate components of diet from their effects on heart disease?
• What types of communication/education can lead to improved activity levels, diet, etc?
• Current treatment of vascular diseases is increasing life-span, but at significant cost. Can we slow development of vascular disease and increase the time until expensive interventions are required?