Cardiovascular Disease (CVD) Physiology

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http://noodlemaz.wordpress.com/category/science/cancer/
Outline

• Introduction
  – Serious nature of Cardiovascular Disease (CVD)
  – How to prevent CVD?

• The disease process
  – Damage and plaque development
  – Current treatments

• Control of vascular tone
  – Naturally and pharmacologically

• Current research here at Lehigh
Significance of CVD

- CVD is the leading cause of death in Western societies and Japan \(^1\)
- Treatment of patients with CVD was \(~\$444 \text{ billion}\) in 2011 \(^2\)

U.S. Death Rates per Year \(^1\)

- Heart disease
- Cancer
- Stroke (cerebrovascular diseases)
- Chronic lower respiratory diseases
- Accidents (unintentional injuries)

\(^1\)Centers for Disease Control; January 17, 2012
Projected direct and indirect costs of all CVD, 2010 to 2030 (in billions 2008$).

Heidenreich P A et al. Circulation 2011;123:933-944
CVD Risk Factors

• High blood pressure (above 120/80 mmHg)
• High serum cholesterol
  – Healthy cholesterol levels:
    • < 100 mg/dL LDL cholesterol
    • > 50 mg/dL HDL cholesterol
• Body Mass Index (BMI) > 30*
• Smoking
• Excessive alcohol consumption
• Diabetes
Metabolic Syndrome

• Excessive abdominal fat
• Atherogenic dyslipidemia
  – High triglycerides and low HDL cholesterol
• Insulin resistance or glucose intolerance
  – Body cannot properly use insulin or blood sugar
• Pro-thrombic state (pro-clotting)
• Elevated blood pressure (≥130/85 mmHg)
• Pro-inflammatory state
Obesity

- Diet
- Portion size
- Lack of physical activity
- Genetics

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

- One-third of adults and almost 17% of children and adolescents were obese in 2009-2010.

Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2009–2010

1Significant increasing linear trend by age (p < 0.01).
2Significant increasing linear trend by age (p < 0.001).

NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.

Figure 4. Trends in the prevalence of obesity among adults aged 20 and over, by sex: United States, 1999–2010

Women

Men

Significant increasing linear trend 1999–2000 to 2009–2010 (p < 0.0001).
NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.
Figure 2. Prevalence of obesity among children and adolescents aged 2–19, by sex and age: United States, 2009–2010

Age in years:  
- 2–19  
- 2–5  
- 6–11  
- 12–19

Percent

All¹
- 16.9
- 18.0
- 18.4

Boys
- 18.6
- 20.1

Girls¹
- 15.0
- 15.7
- 17.1

¹Significant increasing linear trend by age (p < 0.005).

Figure 5. Trends in the prevalence of obesity among children and adolescents aged 2–19, by sex: United States, 1999–2010

1Significant increasing linear trend 1999–2000 to 2009–2010 (p < 0.05).

Some Good News

Males 35-74

Females 35-74
So What Can You Do?

- Limit saturated fat intake (trans too)
- Consume < 200 mg/day cholesterol
- Fish may help
  - High in omega-3 fatty acids – help prevent fat build up in arteries
- Limit salt intake (<2300 mg/day)
  - Average American age 2 years and older consumes ~3,500 mg/day
- Consume vegetables and whole grains
- Diet options for lowering cholesterol
  - Plant sterols and/or soluble fiber
- Do not eat more calories than needed to maintain a healthy weight
  - Animal models indicate that caloric restriction increases longevity
- 30 mins of moderate physical activity per day
- Don’t smoke
- Limit alcohol intake
Progression of Vascular Disease

Stent

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

Medline Plus Medical Encyclopedia
Molecular Hallmarks of Atherosclerosis:
- Endothelial cell dysfunction
- Smooth muscle cell (SMC) proliferation & migration
- Inflammatory response
- Immune response

Endothelial cells become pro-thrombic
Atherosclerosis

• Leads to narrowing or blockage of arteries
  – Blocked flow to the heart
    • Myocardial infarction (heart attack)
  – Blocked flow to the brain
    • Ischemic stroke
  – Blocked flow to external tissues
    • Gangrene

http://www.tappmedical.com/atherosclerosis.htm
Statin Therapy

• Lowers serum cholesterol
  – Blocks cholesterol biosynthesis in the liver
    • Unfortunately statins target an enzyme well upstream of cholesterol, so there are many side affects of which myopathy is the most severe

• Prevents CVD:
  – Improve endothelial function
  – Modulate inflammatory responses
  – Maintain plaque stability
  – Prevent thrombus formation
Statins all decreased as a result of statin therapy.
Atherosclerosis and Blood Flow

Blood flow and other factors contributes to risk of atherosclerosis
Angiotensin is a major contraction signal that transiently increases blood pressure.

Treatments for Hypertension:
- Diuretics
- ACE inhibitors
- Beta-blockers
- Ca$^{2+}$ channel blockers

Relaxed Blood Vessel

Angiotensin II
(Ca$^{2+}$ is also important)

Contracted Blood Vessel
(Increased Blood Pressure)
Relaxation of Blood Vessels

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

Potent Vasodilator: - Nitroglycerine
Relaxation of Blood Vessels

Relaxed SMC

Contracted SMC

PDE-5 (Phosphodiesterases)
- Convert cGMP to GMP
Regulation of Contraction

- NO
- Guanylyl Cyclase
- GTP → cGMP → GMP
- SMC relaxation
- Vasodilation

Sildenafil citrate (Viagra®)

Modified from: Guiliano F. Eur Heart J 2002(4)H7-H12
Current Research at Lehigh
(Linda Lowe-Krentz Laboratory)

Aimed at understanding the development of atherosclerosis and reversing the damage
Future Therapy for Atherosclerosis

• Heparin is a soluble molecule released by mast cells at sites of infection/inflammation
• Currently used in medicine as an anti-coagulant
• Data from our lab and the literature indicates that heparin blocks SMC proliferation at the G1 phase of the cell cycle
  – Helpful in the case of atherosclerosis in which one of the problems is SMC proliferation

Understanding the relationship between atherosclerosis and blood flow

Smooth flow regions are protected against the development of atherosclerosis

Homework!

• Please watch the following video on youtube.

  - http://www.youtube.com/watch?v=fLonh7ZesKs

• It summarizes the development of CVD extremely well.
If you have further questions or are interested in learning more, please contact me at: jbs208@lehigh.edu