Pathology of Cardiovascular Interventions

- Body and Disease 2011

This lecture is generally in chronological order; we will start with the old school treatments and move to current therapy.
Coronary Artery Atherosclerosis

- **Intervention Goals:**
  - Acute Coronary Syndromes: Treat plaque rupture and thrombosis
  - Significant Disease: Prevent development of complications
ACS: Thrombolysis

• **Goals:**
  – Restoration of blood flow
  – **Rescue ischemic myocardium**
    • Wavefront phenomenon
    • **Target:** < 6 hours from onset
      – Likely some benefit within 12 hours if significant collaterals
  – the collaterals may buy us some time if they form

• **Agents:**
  – tPA, Streptokinase, Urokinase
  – *No definite efficacy advantage of one over the others.*

Now we do catheter for thrombolysis and direct injection of the lytic agent right at the area where we want the effect to be. Catheters are used a lot in AV fistulas (used for dialysis) which are prone to clotting. They also now have a thrombectomy catheter to physically remove the thrombus. Basically catheters are getting really good, think of Inspector Gadget.
Thrombolysis: Complications

- **Hemorrhage** – ROS, PMHx, PE
- **Reocclusion**
  - No treatment of underlying cause (rupture)
  - **Up to 10% reocclusion** with 5% infarct extension
- **Reperfusion injury**
  - Flow restoration causes injury of viable myocytes.
    - Oxygen free radical generation
    - “No Reflow” phenomenon
- **Stunned Myocardium**
  - Prolonged functional impairment

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don't forget the rectal exam to look for hemorrhoids before giving thrombolytic drugs

The cells from the inflammatory response flow into area of infarct. When they get into the microcirculation they plug it up and you don’t get reprofusion on a microscopic level even though the large clot is gone.

prolonged dysfunction of the heart can persist even after reprofusion and you wont get immediate improvement.
Coronary Interventions

- **United States:**
  - Percutaneous Transluminal Coronary Angioplasty (PTCA) aka percutaneous coronary intervention
    - 1,204,000 in 2002
    - Male:female 2:1
    - Cost ~ $25,000 – $35,000
  - Coronary Artery Bypass Grafting (CABG)
    - 515,000 in 2001
    - Male:Female ~ 3:1
    - Cost - $45,000- $60,000
Balloon Angioplasty

- **Procedure**
  - Traverse plaque with guidewire
  - Balloon inflated to 6-12 ATM

- **Outcome**
  - Initially >90% of lesions reduced by >20% with resulting stenosis < 50% of vessel.

- **Desired Lesion Characteristics**
  - Length, Location, Number

Patients that don't have coronary syndromes and have significant plaque may get a balloon.

Full metal jacket = when you have stents lining over half of the coronary surface.

high pressure

good outcome

these factors may limit your success with a balloon.
Cardiac Catheterization: Duke Criteria

- Presence of a groin
- Presence of a groin substitute
- Patient slower than the cardiologist

To determine cath versus angioplasty
Angioplasty: Pathology

- **Plaque Splitting**
  - Non-distensible
  - Plaque splits at weak point
  - Split extends to media and often into media
  - Mural hemorrhage
- **Medial Dissection**
- **Endothelial Denudation**
- **Medial and Adventitial Stretch**

What does the balloon actually do?

dissection planes

squeeze endothelium to death
Angioplasty: Pathology

• Lumen Increase
  – Plaque Fracture
  – Medial and Adventitial Stretching
  – Medial Dissection
  – Plaque Stretching
  – Plaque Compression and Redistribution

• Favorable plaques:
  – Eccentric vs concentric – long term 48 vs 18%
  – Large Necrotic Cores
Angioplasty: Complications

• **Acute closure (4-9%)**
  – Procedure creates “rupture-like” state with thrombogenic surfaces
  – Medial flaps alter flow and create stasis

• **Glycoprotein IIb/IIIa receptor antagonist**
  – Abciximab (Reopro)
  – Eptifibatide (Integrilin)
  – Blocks platelet aggregation
Angioplasty: Complications

- **Late Restenosis**: 40% - primarily within 6 months
- **Neointimal Proliferation**
  - Exuberant healing response with ingrowth of smooth muscle cells from intima and media
  - Smooth muscle cells secrete extracellular matrix
    - Collagen in increasing density
    - Glycosaminoglycans
  - Leukocyte adhesion molecules – Integrins, selectins
    - Mac-1 level – chemoattractant correlates with risk of restenosis
  - Inflammation – increases injury, cytokine release

Complications after the acute phase

we are creating injury and that will create a healing response at the site on the intima, which can cause stenosis.

Sort of mimic atherosclerotic plaques
Angioplasty: Complications

- **Late Restenosis**: 40% - primarily within 6 months
- **Negative Remodeling**
  - Healing of medial and adventitial stretch injury leads to late fibrosis and contraction with collagen scar maturation
  - Reduces overall vessel size

last slide was more focused on intimal healing, this is medial and adventitial

as the outer layers remodel, they can shrink the vessel
Endoluminal Stents

- **Scaffold function**
  - Compresses acute post-angioplasty intimal/medial flaps
  - Buttresses against late negative remodeling

Significant reduction in primary endpoints and restenosis versus PTCA alone
Endoluminal Stents

• Neointimalization
  – **NOT prevented by stenting**
  – Leads to in-stent restenosis

• Injury
  – Implantation of stent wires into arterial wall
  – Inflammation stimulated by stent

• Pathology
  – Initially thrombus and inflammation with subsequent covering by thickened intima with smooth muscle cells and matrix

Stents aren't perfect either...
Just shows the steps of in-stent restenosis

A Diseased Artery Pre-Stent
Atherosclerotic Plaque with Resident Macros

B Immediate Post-Stent
Endothelial Denudation, Platelet/Fibrinogen Deposition

C Leukocyte Recruitment
Cytokine Release

D Leukocyte Infiltration
SMC Proliferation/Migration

E Neointimal Growth
Continued SMC Proliferation and Macro Recruitment

F Restenotic Lesion
More ECM Rich Over Time

neointimal formation

in-stent restenosis
Stent Response

Acute

Early Neointima

Virmani
Stent Response

Arrows show where the stent actually was

all of this is neointima and has occluded about 50% of the lumen (main point of this slide: neointimal proliferation can cause significant stenosis)

the plaque didn't get squashed!!!

Internal elastic lamina

Rupture site. This is where the increase in the size of the lumen came from

He started going fast at this point, so there were things on his slide that he didn't mention from here on out.
Endoluminal Stents

- **Arterial Injury**
  - Schwartz Score: 0 – 3 based on compression and injury to IEL and media and EEL
  - Tells us how far into the wall the stent is driven and this will determine the propensity to form neointima.

The stent can go all the way through the artery wall => this procedure can be very aggressive.
Endoluminal Stents

• **Inflammation:**
  - Amount and duration reflects extent of injury
  - Kornowski Score: 0-3 based on density and extent of stent induced inflammation

Shows varying amounts of inflammation dependent on depth of stent

Lowe, et al
Endoluminal Stents

- **Long Term Results/Restenosis**
  - Correlate with stent injury and inflammation
  - Stent strut location affects reactive inflammation
  - Fibrous Plaque
    - not at much inflammation, don't press in as far
  - Medial Injury
    - obviously causes lots of inflammation
  - Lipid core penetration
    - can drive stent right into fat and cause lots of inflammation

The type of plaque also determines how far in we have to press the stent which in turn determines the amount of inflammation.
Can see stent struts in the fat portion of the plaque. Also notice that the plaque WAS NOT SQUISHED, just pushed over.
Medial Fracture

Lots of neointima formed, not even clear if the stent helped at all in the long run.

Graphs not mentioned

Farb et al
Endoluminal Stents

More inflammation comes from damaged media and lipid core penetration. More inflammation => worse outcome.

Farb et al
Drug Eluting Stents

- Stent releases drug to prevent restenosis
  - Prevent thrombus formation?
    - More commonly via systemic therapy
  - Prevent tissue proliferation
    - Sirolimus – protein kinase binder
    - Paclitaxel – Microtubule stabilization, blocks mitosis
  - Efficacy?
    - Conor/Costar II stent pulled from development for poorer results vs sirolimus
      » Cited drug delivery issue vs efficacy
    - Est $200 million market share loss in 2008

Overall market?
Drug Eluting Stents

Take away: they work

Bare
No drug

Sirolimus
With drug

A.  
B.  
C.  
D.  

The time scale is around 6 months in these photos.

less neointima. YAY
Drug Eluting Stents

• **Efficacy**
  – Effective at limiting short and medium term restenosis
  – Long term results unclear
    • Prolonged acute phase with inflammation and thrombus
    • **Possible hypersensitivity response**

Still not sure what happens in the long term once the drugs wear off from the stent. Are we just delaying the inevitable neointimal formation?
Drug Eluting Stents

Prolonged “acute” state

Medial granuloma

Neointimal formation after the drug has worn off

hypersensitivity granuloma = bad news
Drug Eluting Stents

- **Risk of Late Thrombosis**
  - Preservation of “acute” state of surface
  - Need for prolonged antiplatelet therapy?
    - **Very late thrombosis:** >12 months
    - Slight risk of very late thrombosis compared to bare metal stents
    - ~0.2%/year excess risk of thrombosis unless **dual** antiplatelet therapy continued beyond 3-6 months
    - **Risk higher in “off-label” use** (non FDA-approved by clinical trials) Ex. Bifurcations, acute MI
      - 50-60% of stents are used off label

Study from Duke that there is a risk for thrombosis a year after the stent in certain populations

Stents not approved for these things
Sirolimus

Granulomatous reaction seen in CYPHER Stents Implanted for 28 and 90 days in Pig Coronary Arteries

His lab in the triangle showed that some of this may be due to the health state of the animals used as opposed to the actual stents.

Another example of the hypersensitivity granuloma formation.
Coronary Bypass

• **Revascularize “at risk” myocardium**
  – Left main, three vessel disease

• **Improve left ventricular function**
  – “Hibernating” myocardium
  – Ischemic valve dysfunction

• **2-3% perioperative mortality and higher short term risk than PTCA but improved long term**

"buy 2 vessel diseases for the price of one" (left main = LAD + circumflex)

Some of your heart may be living at low O2 and will be reactivated after bypass

Like the mitral valve

For patients with 2 or 3 vessel disease
Coronary Bypass: Grafts

• **Internal Mammary Artery (Thoracic Artery)**
  - **90% 5 year patency, 80% 10 year patency** – Why?
    - **Atherosclerosis is rare**
    - Generally Left IMA to LAD distribution

• **Reversed Vein Grafts - Saphenous vein**
  - **80-85% 5 year patency; 50-60% 10 year patency**

• **Other vessels:**
  - Radial artery (free graft)
  - gastroepiploic
Vein Graft Stenosis

• **Thrombosis** – acute, 15%
  – Factors include runoff obstruction, technical issues
  – Uncommon cause of perioperative mortality

• **Fibrointimal Hyperplasia**
  – Response to injury – stretch, shear - hypertension
  – Onset is relatively early

• **Atherosclerosis**
  – Tendency towards plaques with large lipid cores, thin caps and hemorrhage.
  – Less frequent fibrocalcific plaques
    • Rupture and embolization increased

*Most issues are because we are using veins as arteries*

*basically the same thing that happens with stents can happen to veins that we graft => restenosis*
Vein Graft Stenosis

• **Treatment:**
  - Percutaneous intervention – PTCA, stent
  - Redo CABG

  • Higher risk of morbidity and mortality.

If people don't change their lifestyle, they will probably need another one.
The Future

• Stent modifications
  – **Bioabsorbable stents** – release drugs through healing phase and "dissolve" to prevent stimulation of late restenosis or very late thrombosis

• Trend towards **less invasive surgery**
  – Off pump, MIDCAB, robotic CABG

• Angiogenesis
  – Stem cells – endothelial progenitor cells

• Gene therapy
  – Prevention and treatment
Damaged Hearts

• Ischemic Cardiomyopathy
  – Stem cell and myoblast therapy
  – Ventricular assist devices (VAD’s)
  – Transplantation

• Other Cardiomyopathies
  – Similar options – VAD, Transplant

• Considerations:
  – Systemic?
  – Recurrence?
  – Age? Comorbidities?
Ventricular Assist Devices

Saw this with Dr. Rogers

Thoratek
Ventricular Assist Devices

The latest wave. Implanted in the heart, no outflow cannula. The battery is still external.

For some people this is the end of their treatment, for others this is used until a transplant becomes available.

HeartWare