Smooth muscle pharmacology & interventional cardiology

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Classic Vascular pharmacology
- chronic
- systemic

Local Vascular pharmacology
- acute
- targeted

High blood pressure
Blood pressure control
Atherosclerosis
Endothelial Injury
Thrombus

CABG → Patient burden
PTCA → Restenosis
Stent → In-sent restenosis
Drug eluting stents
Scaffolds

Lipid lowering drugs
Platelet/SMC pharmacology
Cath lab patients / surgery

- blood pressure management
- lipid management
- Coagulation
- Diabetes

![Diagram showing blood vessels with labels: Macrophage accumulation, Formation of necrotic core, Formation of fibrous cap.]

CABG

![Diagram of a heart with blood vessels and labels: Atherosclerotic lesion, etc.]
What is PTCA?

Restenosis
Stenosis and angioplasty

Medication?

Damage
Restenosis: multi step process (lecture X)

Angioplasty:
- Widens an artery to improve blood flow.
- Following treatment, plaque build-up may return, re-closing the artery.

Monocyte attachment
Platelet adhesion

Pre-injury
- normal endothelium
- NO and prostacyclin production
- few leucocyte

Immediate response
- endothelium removed/injured
- platelet deposit/aggregation
- monocyte attachment
- SMC injury
- + bFGF release

Pre-injury to Immediate response: Monocyte attachment, Platelet adhesion

Platelet adhesion
Angioplasty injury

0-2 days
- less platelet adhesion
- leucocyte infiltration
- activation
- arterial wall oedema
- medial SMC proliferation

2-4 days
- SMC migration to intima
- continual SMC proliferation
- medial SMCs apoptosis
- synthetic SMC phenotype

Angioplasty injury

Re-endothelialization

4-10 days
- intimal SMC proliferation
- migration of endothelial cells from wound edge
- endothelial cell proliferation

10-14 days
- complete re-endothelialization by dysfunctional endothelial cells
- less intimal SMC proliferation
- more ECM elaboration

2-4 weeks
- remodeling
Restenosis

Treatment of Atherosclerosis

**STENT placement**

- Heart with coronary arteries
- Crimped stent around balloon at site of lesion
- Inflation of balloon
- Stent in position
- In-stent restenosis

Paclitaxel/Taxol

Boston Scientific

*Delivering what’s next.*
Paclitaxel/Taxol

- Anti-cancer agent
- Anti-mitotic

- As a potent stabilizer of microtubules. Microtubule disassembly is essential for the transition from the G2 to the M phase and migration
  - less SMC less leukocytes

Sirolimus/Rapamycin
-Immunosuppressant possesses anti-proliferative properties

-Stent: The metal of the stent has a soft, plastic coating. It slowly releases Sirolimus into the artery wall around the stent. Eighty percent (80%) of the sirolimus is released during the first 30 days. The rest is released by the end of 90 days.

Controlled-release, nonresorbable, elastomeric polymer coating

Paclitaxel
\(\text{C}_{47}\text{H}_{51}\text{NO}_{17}\)
MW 854
- Binding to \(\beta\)-tubulin subunit of microtubules
- Polymerization of tubulin
- Inhibition of microtubule disassembly

Sirolimus
\(\text{C}_{18}\text{H}_{21}\text{NO}_{15}\)
MW 914
- Up-regulation of p27kip1
- Inhibition of mTOR

Everolimus
\(\text{C}_{23}\text{H}_{21}\text{NO}_{14}\)
MW 958
- Up-regulation of p27kip1

Zotarolimus
\(\text{C}_{24}\text{H}_{21}\text{N}_{2}\text{O}_{12}\)
MW 966
- Up-regulation of p27kip1
**Drug eluting stents**

- Decrease rate of restenosis by 40-70% compared to BMS

- % Stenosis/total lumen diameter:
  - Sirolimus: 3.5% of diameter
  - BMS: 18.5% of diameter

  Paclitaxel: 3.3%

  BMS: 12.2%

5100 patients study


**Delayed restenosis**

- Work well for a year
- Delayed reendothelialization because of taxol/rapamycin affects endoth.
- Your vessel is never healed unless your endothelial layer regrows, and becomes functional (not dysfunctional, which is the case mostly)
- Thrombosis causes Death or MI so HUGE ANTI PLATELET THERAPY
Aspirin: should not be interrupted

Clopidogrel: no longer that day -5 to day +2 if other surgery
Normally a month of clopidogrel after PTCA or stent, now increased at 6 to 12mo

Reopro:

-Other types of surgeries need cessation of platelet therapy

Scaffolds / Resorbable stents

- Metal (Mg)
- Polymer (polylactic acid)
- Biggest advantage?
- Biggest question marks?

Figure 3. OCT and histology at 28 days and 2, 3, and 4 years after stent implantation. At 28 days, OCT shows preserved box appearance (A), corresponding to the voids not stained by Alcian Blue (B and C). At 2 years, OCT still shows struts as preserved box appearance (D), but the persistent voids (E) are now replaced by proteoglycan (hyaline material), which stained positively with Alcian Blue (F). At 3 years, only 2 struts at 6 o’clock remained detectable as preserved box (G). Otherwise, connective tissue cells are now infiltrated in the strut footprints (H, hematoxylin and eosin staining; I, Alcian Blue). At 4 years, struts are no longer discernible by OCT (J); the strut footprints are hardly detectable in Movat staining (K) and Alcian Blue (L) and are characterized by paucity of connective tissue cells and a small amount of calcification.
Impaired Flow-Mediated Dilation and Risk of Restenosis in Patients Undergoing Coronary Stent Implantation

Giuseppe Patti, MD; Vincenzo Passeri, MD, PhD; Rosetta Melfi, MD; Costanza Goffredo, MD; Massimo Chello, MD; Andrea D’Ambrosio, MD; Rosanna Montessuto, MD; Gennaro Di Sciascio, MD

Background—Impaired endothelial function is a key event in the atherosclerosis process and predicts future cardiovascular events in subjects with and without coronary artery disease (CAD). We performed the first prospective study evaluating whether early measurement of brachial artery endothelium-dependent dilation (flow-mediated dilation [FMD]) after coronary stenting could predict occurrence of in-stent restenosis.

Methods and Results—The study population included 156 patients with single-vessel CAD undergoing percutaneous coronary intervention (PCI) with stenting and at least 6 months of follow-up. All patients underwent ultrasound detection of brachial artery reactivity 30 days after PCI. FMD was investigated before and after 5 minutes of occlusion of the brachial artery, and nitroglycerin-mediated dilation was investigated before and after administration of sublingual nitrates. Clinical in-stent restenosis was demonstrated in 20 patients (13%), whereas 116 patients (85%) remained free of signs or symptoms of recurrent ischemia. FMD was significantly impaired in patients with restenosis versus those without restenosis (percent diameter variation 4.6±5.8% versus 9.5±6.6%, P<0.002); moreover, 4% of patients with FMD ≥7% (median value) developed in-stent restenosis versus 28% of those with FMD <7% (P=0.0001). On multivariate analysis, FMD was the strongest predictor of restenosis (OR 4.5, 95% CI 2.4 to 12.0; conversely, nitroglycerin-mediated dilation did not independently predict the risk of restenosis (OR 2.4, 95% CI 0.8 to 6.3).

Conclusions—This is the first prospective study indicating that impaired FMD independently predicts occurrence of in-stent restenosis in patients undergoing PCI. Early evaluation of endothelial function after stenting may represent a useful screening tool to stratify patients according to future risk of restenosis. (Circulation. 2005;111:267b-75.)
Diabetes

A Primary Outcome

B Death

No. at Risk
PCI CABG
PCI CABG
953 547 953 547
848 814 897 855
788 758 845 806
625 613 685 655
416 422 466 446
219 221 243 238

P=0.005 by log-rank test
5-Yr event rate: 26.6% vs. 18.7%

P=0.049 by log-rank test
5-Yr event rate: 16.3% vs. 10.9%

NEJM 367:25, 2012
Conclusion

- Restenosis – In-Stent stenosis – Delayed restenosis

- DES have a fantastic effect on restenosis and revascularization (decreased need of second procedure).

- Impaired reendothelialization

- Exam?

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