Perspectives on the Evolution of IVUS Into a Clinical Tool

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Eras of IVUS Discovery and Usage

- Invention and validation
- Early experiences
  - Mechanisms of intervention
  - Comparisons with angiography
- Mechanisms and predictors of restenosis
  - PTCA, DCA, rotational atherectomy, and ELCA
  - BMS implantation
  - DES implantation

- Technology improvement
- Mechanisms of disease
- Progression and regression

- Clinical Utility
  - LM disease
  - Intermediate lesions
  - Unusual angiographic morphology
  - PCI optimization
    - Calcification
    - Eccentricity
    - Final lumen/stent dimensions and residual plaque burden
    - Complications
Invention and Validation

• In the beginning there were
  • InterTherapy
  • CardioVascular Imaging Systems
  • Diasonics/Mansfield
  • Endosonics
• The seminal validation studies were. . .


• Hodgson JMcB, Graham SP, Sarakus AD, et al., Clinical percutaneous imaging of coronary anatomy using an over-the-wire ultrasound catheter system. *In J Cardiac Imaging* 1989; 4: 186-93.


Mechanisms of Intervention - I

- Balloon angioplasty
  - Vessel expansion
  - Axial plaque redistribution
  - Dissection
- Stand-alone DCA
  - Plaque excision (limited by calcium, even angiographically invisible calcium)
  - Dissection
- DCA+adjunct PTCA
  - Plaque excision (limited by calcium, even angiographically invisible calcium)
  - Vessel expansion
  - Dissection
Mechanisms of Intervention - II

- **Rotational Atherectomy**
  - Limited plaque ablation
  - Significant residual plaque burden
  - Most of the lumen enlargement came with adjunct PTCA and vessel expansion
- **Excimer Laser Coronary Angioplasty**
  - Minimal plaque ablation
  - No calcium ablation
  - Fracture within calcium deposits
  - Forced vessel expansion
  - Most of the lumen enlargement came with adjunct PTCA and vessel expansion
Mechanisms of Intervention - III

- Stent implantation
  - Vessel expansion
  - Axial plaque redistribution
- Treatment of in-stent restenosis
  - DCA, RA, and ELCA all removed tissue
  - Balloon angioplasty, adjunct balloon angioplasty, or additional stent implantation additionally expanded the stent
  - Lumen of the original stent implantation procedure was rarely recovered
Lesion Calcification

Calcification

% of angiographic lesions

IVUS quadrants of calcium

Superficial calcification

% of angiographic lesions

IVUS quadrants of superficial calcium

The only predictor of IVUS calcium was angiographic calcification elsewhere in the coronary tree. (Tuzcu et al. J AM Coll Cardiol 1996;27:832-8)

Lesion Eccentricity

% of angiographic lesions

Eccentricity

1.0-3.0  3.0-5.0  5.0-7.0  >7.0

IVUS Max/Min
P&M Thickness

Yes
No

Mintz et al. Circulation 1996;93:924-931
Maximum plaque thickness spares the flow divider in nearly all cases and plaque deposition is usually opposite the sidebranch.

QCA vs IVUS MLD

Pre-PCI

Post-PCI

Post-Stent

r = 0.351

r = 0.699

r = 0.663*

*worse for >2 stents
Lesion Length

QCA lesion length (mm) vs. IVUS lesion length (mm)

IVUS-QCA lesion length = 0.6 ± 7.2 mm
Reference Lumen Sizes

IVUS (mm) vs. QCA (mm) with a correlation coefficient of $r = 0.50$

IVUS - QCA (mm) distributions

Mean and +/- 1 SD

(IVUS - QCA)/QCA (%) vs. QCA (mm)
Mechanisms of Restenosis

- Balloon angioplasty
- Atherectomy
- BMS
- In-stent restenosis
- Brachytherapy
- DES

Prior to the seminal serial IVUS studies, it was believed that intimal hyperplasia was the cause of restenosis in non-stented lesions and that chronic stent recoil was the cause of restenosis in stented lesions.
Mechanisms of Restenosis - I

• (Except, perhaps, in diabetic patients, who have more intimal hyperplasia than non-diabetics) late arterial responses to nonstent coronary interventions are determined less by tissue growth than by the direction and magnitude of arterial remodeling (increase or decrease in EEM).
• Early (w/i 1 month) positive remodeling prevents lumen loss.
• Early positive remodeling is followed by late negative remodeling (vessel contraction) that is distinct from passive elastic recoil and that is responsible for 70% of late lumen loss in non-stented lesions.
• The residual plaque burden is the strongest predictor of restenosis in non-stented lesions.

Kimura et al Circulation 1997;96:475-83
Mintz et al J Am Coll Cardiol 1996;27:1678-87
Editorial

Vascular Remodeling

Honey, I Think I Shrunk the Artery

Jeffrey M. Isner, MD

The mechanisms responsible for both favorable and unfavorable outcomes of balloon angioplasty continue to provoke controversy. Nowhere is this more profound than in the case of restenosis, clearly the most frequent complication of percutaneous transluminal coronary angioplasty. Despite the fact that 385 patients describing treatment strategies designed to limit restenosis have been issued during the past decade, until recently successful clinical application of derivative therapies has been virtually without success. There can be little doubt that our lack of understanding regarding the mechanisms responsible for restenosis has prevented the underpinnings of our inability to successfully prevent its recurrence.

See p 2816

The vast majority of medical therapies designed to prevent restenosis have been predicated on the assumption that smooth muscle cell (SMC) proliferation constitutes the principal pathogenetic basis for restenosis. This concept has its origins in the fundamental studies of human atherosclerotic arteries that identified SMC accumulation within the intima of (primary) lesions obtained at autopsy and in supportive experimental observations in a variety of animal models. Subsequently, beginning with the report of Austin et al., necropsy examination of sporadic patients dying at various intervals after percutaneous transluminal coronary angioplasty (PTCA) disclosed foci of hypercellularity, including cells with phenotypic characteristics of vascular SMCs, at the original site of balloon angioplasty.

These reports were subsequently amplified by systematic study of vascular SMCs, and the matrix surrounding these cells typically had a distinctly lighter hue and less-compact appearance than the matrix of primary or adjacent plaque. These contrasting findings regarding primary and restenotic lesions were perhaps best illustrated in a group of 15 patients studied in our laboratory in whom directional atherectomy had been performed both as the primary intervention and again when the lesion returned with restenosis. These patients thus offered a unique opportunity to study the same lesion site in the same artery of the same patient at two different points in time. Light microscopic examination documented distinctive features, including hypercellular focus consisting of proliferative vascular SMCs surrounded by a loose neomatrix in 13 of 15 cases (86%). In 5 important exceptions, however, neither the primary nor the restenotic specimen demonstrated such a “restenotic focus.” Of 23 restenosis specimens (85%) retrieved by directional atherectomy and studied in our laboratory, a similar restenotic focus was identified in 16 (65%); among the remaining 8 specimens (35%), however, no distinctive histological features were observed.

Additional evidence supporting the proliferative nature of restenosis versus primary lesions is derived from in vitro studies of SMCs cultured directly from explanted fragments of human atherectomy specimens. These studies documented that the outgrowth kinetics of SMCs cultured in this manner were indeed a reflection of the lesion type. Among 41 lesions retrieved by directional atherectomy and used in our laboratory to initiate cell growth, the vast majority of explants...
Post DCA+PTCA

EEM = 14.7mm²
Lumen = 10.2mm²
P&M = 4.6mm²

7 month F/U

EEM = 5.5mm²
Lumen = 1.0mm²
P&M = 4.5mm²
SURE Trial: Restenosis in non-stented lesions

Average of the two image slices with the smallest pre-intervention and follow-up lumen CSA

61 native vessel lesions (26 DCA, 35 PTCA) with complete serial IVUS studies (out of 79 lesions enrolled in the study)

Kimura et al. Circulation 1997;96:475-83
Mechanisms of Restenosis - II

• Stents reduce restenosis by achieving a better post-procedural result and by eliminating remodeling. This offsets a stent-related increase in tissue growth.

• In-stent restenosis is solely the result of tissue growth. However, stent edge restenosis is a combination of negative remodeling and intimal hyperplasia and is determined, in part, by the plaque burden at the edge at the time of implantation.

• Mechanical problems - that occurred at the time of stent implantation - are present in a significant percentage of in-stent restenosis lesions.

• The strongest predictor of in-stent restenosis is the final minimum stent CSA.

Hoffmann et al. Circulation 1996;94:1247-54
Hoffmann et al Am J Cardiol 1997;79:951-3
Mintz et al. AM J Cardiol 1996;78:18-22
Castagna et al. Am Heart J 2001;142:970-2
De Feyter et al. Circulation 1999;100:1777-83
Restenosis in Stented Lesions

- IH or P&M CSA (mm²)
- Stent or EEM CSA (mm²)
- Lumen CSA (mm²)

Hoffmann et al. Circulation 1996;94:1247-54
Therefore, in-stent restenosis is all intimal hyperplasia

\[
\begin{align*}
\Delta \text{lumen CSA (mm}^2\text{)} & \quad \Delta \text{lumen CSA (mm}^2\text{)} \\
\Delta \text{Stent CSA (mm}^2\text{)} & \quad \Delta \text{IH CSA (mm}^2\text{)} \\
\end{align*}
\]

\[r=0.212 \quad r=0.967\]

Hoffmann et al. Circulation 1996;94:1247-54
Proximal
Impact of lesion length and final minimum stent area (MSA) on restenosis

*No actual observations in this range

* de Feyter et al. Circulation 1999;100:1777-83
IVUS Predictors of Stent Thrombosis (27/7484=0.4%)
Crushed stent leading to subacute thrombosis

Pre-intervention | s/p JJIS+PTCA | 2 week follow-up

Crushed stent leading to subacute thrombosis
Clinical Utility

- Assess lesion severity
- Assess LM disease severity
- Whenever the angiogram, non-invasive tests, and clinical symptoms do not agree or whenever the angiogram is difficult to interpret
  - Hazy lesions
  - Aneurysms
  - Filling defects
  - ACS patients
- Select device and size
- Optimize procedural results
  - Maximize stent and lumen dimensions
  - Detect and treat complications
Stent sizing using IVUS

Max LD = 3.3 mm

Max LD = 3.5 mm
Iterative IVUS can be used to ‘fine-tune’ the final MSA during stent implantation - Angio cannot

**QCA MLD (mm)**

- 8ATM: 2.5
- 12ATM: 3.0
- 15ATM: 3.1
- 18ATM: 3.1

**IVUS Stent CSA (mm²)**

- 8ATM: 7.7
- 12ATM: 9.2
- 15ATM: 10.1
- 18ATM: 10.9

*ANOVA P<0.0001*
<table>
<thead>
<tr>
<th>Study</th>
<th>Angio Better</th>
<th>IVUS Better</th>
<th>IVUS Also Cheaper</th>
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<tr>
<td>Choi et al (AHJ 2001;142:112-8)</td>
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<td>Gaster et al (Scan Cardiovasc J 2001;35:80-5 &amp; Heart 2003;89:1043-9)</td>
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<td>TULIP (Circulation 2003;107:62-7)</td>
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<td>BEST (Circulation 2003;107:545-551)</td>
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<td>OPTICUS (Circulation. 2001;104:1343-9)</td>
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<td>DIPOL (Am Heart J. 2007;154:669-75)</td>
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## Safety of Intracoronary Ultrasound

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<th>Certain</th>
<th>Uncertain</th>
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<tr>
<td><strong>n = 2207</strong></td>
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<tr>
<td>Spasm</td>
<td>63 (2.9%)</td>
<td>0</td>
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<td>Acute complications</td>
<td>6 (0.3%)</td>
<td>9 (0.4%)</td>
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<td>Major complications*</td>
<td>3 (0.1%)</td>
<td>5 (0.2%)</td>
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*MI, CABG, or death

Hausmann et al., Circulation 1995;91:623-30
Safety

- **Gorge et al., J Am Coll Cardiol 1996;27:155A.**
  - 7085 IVUS studies at 51 centers
  - 10 (0.1%) major complications other than spasm (7 dissection, 1 thrombus, 1 VF, 1 severe unresponsive spasm)

- **Batkoff et al., Cath Cardiovasc Diagn 1996;38:238-41**
  - 718 IVUS studies at 12 centers
  - 8 (1.1%) major complications (4 spasm, 2 dissection, 2 guidewire entrapment)
Essentials of an IVUS Program

- Director
- Dedicated Technicians, Nurses, and/or Fellows
- Procedure standards
- Image acquisition protocol(s)
- Identify ways to make imaging more efficient and effective*
- Reports
- Housekeeping issues

* will vary from laboratory to laboratory
Director

- Overall responsibility for the clinical IVUS service* including selection of equipment, staff, standards, protocols, and education.

* Not just a cath lab or an echo lab, but a combination both...
Dedicated Technicians*, Nurses, and/or Fellows

- Knowledge of imaging systems, catheters, and imaging protocol(s)
- Immediately available and patient care and flow of PCI procedure not interrupted
  - System and catheter preparation
  - System controls and image optimization
  - Annotation
  - *Make measurements, interpret images, and provide feedback to physician during procedure*
- Care of systems, catheters, video tapes, CDs, etc.
- Archive cases onto CDs
- Keep procedure logs
- Aware of research protocols
- Generate reports
- Teach residents, fellows, and attending physicians

* Technicians often “run” an echo lab, why not an IVUS service
Imaging Procedure

- Remember to give heparin prior to inserting guidewire and IVUS catheter – avoid thrombosis
- Remember to give intracoronary NTG prior to imaging (even if blood pressure is borderline) – avoid spasm
- Remember to disengage guiding catheter when imaging aorto-ostial lesions – avoid confusing the guiding catheter with the ostium
Image Acquisition Protocol(s)

- **Important for**
  - Viewing, understanding, and comparing studies at a later date
  - Serial IVUS analysis
  - Multicenter studies - often have their own protocols
- **Accurate voice annotation**
- **Label studies completely**
  - Vessel (e.g., LAD) and lesion location (e.g., proximal)
  - Device use (stent type, size, length, pressure)
  - Temporal relationship between imaging run and procedure (e.g., pre-intervention, post-stent #1, etc.)
- **Perform complete imaging runs back to aorto-ostial junction at least once during the procedure**
  - Free look at proximal vessel and at LMCA if imaging LAD or LCX
- **Motorized vs. Manual pullback**
Motorized Pullback

- 0.5mm/sec is recommended
- **Advantages**
  - Images acquired in a distal to proximal sequence – avoids “sightseeing” up and down the vessel
  - Steady, slow transducer pullback to avoid imaging any segment too quickly
  - Ability to concentrate on images without having to worry about catheter manipulation
  - Length and volume measurements
  - Mandatory for most multicenter and all serial studies
- **Disadvantages**
  - Inadequate examination of important regions of interest because transducer does not remain long at any one specific site in the vessel
Basic Report

- Patient demographics
- Indications
- Brief description of IVUS procedure
  - Equipment
  - Vessels(s) imaged
- Basic findings
  - Basic measurements (e.g., MLA, MSA, MSD, plaque burden, etc.)
  - Notable morphology (e.g., plaque rupture, thrombus, calcium, dissection, intramural hematoma, etc.)
- Changes in therapy because of IVUS imaging
- IVUS-related complications and consequent therapy
Comprehensive Report

- In addition to information contained in Basic Report.
- Pre-intervention and/or post-intervention quantitative analysis of three cardinal images slices: distal reference, lesion, proximal reference
  - EEM CSA
  - Lumen CSA
  - Plaque&media CSA and plaque burden
  - Area stenosis
  - Stent measurements
  - Lesion length
**Proximal Reference**

- EEM CSA = 20.4
- Lumen CSA = 9.7
- Max lumen diam = 3.7
- MLD = 3.1
- P+M CSA = 10.7
- Eccentricity = 1.0/0.3
- Plaque burden = 0.52
- Arc of Ca = 60

**Lesion Site**

- EEM CSA = 21.6
- Lumen CSA = 4.5
- Max lumen diam = 32.8
- MLD = 2.3
- P+M CSA = 17.1
- Eccentricity = 3.0/0.1
- Plaque burden = 0.79

**Distal Reference**

- EEM CSA = 13.3
- Lumen CSA = 8.9
- Max lumen diam = 3.6
- MLD = 3.0
- P+M CSA = 4.4
- Eccentricity = 0.6/0.2
- Plaque burden = 0.33

Average Reference EEM CSA = 16.9
Remodeling Index = 1.3
Average Reference Lumen CSA = 9.3
Area Stenosis = 52%
Imaging Efficiency and Effectiveness - I

- Perform imaging run(s), remove IVUS catheter, and make measurements from video tape or digital replay - NOT during live imaging
  - Less patient ischemia
  - More efficient use of cath lab time
  - Additional measurements can easily be made and additional questions easily answered
- Display images on angiographic monitors
  - Superior monitors
  - Easier to see
  - Get IVUS system away from table
  - Requires separate roadmap or reference monitors
- Full system integration
Full System Integration

- Easier for staff
  - Turn on system once a day
  - Eliminate looking for equipment and/or transporting equipment between rooms
  - Access is constant
  - No cables or wires between system and angiographic table

- Less hassle for physicians
  - Ready when they are
  - Minimize time added to procedure
  - Controls can be located within sterile field
  - Simply plug in the catheter and begin

- Customizable

- Cost

- (But not a new concept)
BSC iLab

Volcano V-Fusion

• Controls can be bedside or in the control room.