Chapter 11: Value of Preintervention Imaging Before Interventions Balloon Coronary Angioplasty

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Intravascular ultrasound (IVUS) is a relatively new imaging technique with the unique ability to study vessel wall morphology in vivo (1-5). In vitro and in vivo studies have demonstrated the accuracy and reproducibility of the method to measure vessel lumen dimensions and delineate wall morphology (5-7). Intracoronary ultrasonic imaging is increasingly recognized for its ability to accurately display the details of vessel structure (8), but quantitative angiography is still used as the gold standard to assess coronary artery disease. The coronary angiogram represents only a projectional image of the vessel lumen. Several comparative studies of angiography and pathology have demonstrated the shortcomings of angiography for estimation of atheromatous plaque (9-10). One of the major weaknesses of angiography is that selective contrast injections provide only longitudinal silhouette images of the vessel surface lining the lumen and present no information concerning vascular wall architecture. Ultrasonic imaging can potentially provide information about tissue characteristics and atheroma area. This may be particularly relevant in the setting of coronary interventions, since the amount of wall “destruction” induced by the different devices has been shown on several pathology studies where the limitations of angiography to recognize these changes have been demonstrated (11).

Several studies have shown the ability of intravascular imaging to assess vascular responses to pharmacological stimuli (12) and evaluate the acute success of mechanical interventions such as balloon angioplasty, stent placement and atherectomy (11,13-16). IVUS detects measurable intimal proliferation and atheroma formation before angiographic evidence of coronary artery disease (17). Therefore it offers a unique potential to study atheromatous coronary artery disease at different stages, including following progression and regression of plaque atheroma (18). IVUS has also been shown to be a safe and feasible imaging technique for the study of coronary artery disease, including during coronary interventions (19,20).

The use of IVUS during coronary interventions has been the subject of several recent publications, some with contradictory results, but all together with enough data for us to draw some conclusions. Two important documents developed within the

European Society of Cardiology and the American College of Cardiology have been published, where some of the issues regarding the clinical use of IVUS were approached (21,22). In this chapter we will approach the use and advantages of IVUS pre and during balloon angioplasty.

Lesion assessment before coronary balloon angioplasty:

IVUS has been shown to be useful in the identification of certain lesion characteristics that may be helpful in the selection of device and also to predict intervention results. There are, however, some limitations in the use of IVUS pre intervention, mostly related to the relation between luminal size and catheter size. In addition, the introduction of an imaging catheter inside a vessel with a tight lesion may result in flow occlusion and acute myocardial ischemia. Even if there is no flow occlusion the catheter is usually stuffed inside the lesion (particularly in tight lesions), which is a limiting factor in luminal and plaque visualization and image interpretation. Alfonso et al (23) showed that unsuccessful IVUS studies prior to intervention occur more frequently in vessels with proximal tortuosities or severe luminal narrowing, in calcified lesions and when large imaging catheters are used. Despite these limitations there are very important pieces of information provided by IVUS. These include lesion composition, eccentricity and length that may be responsible for treatment strategy modifications in approximately 20% of the cases in some high volume institutions (24,25).

Sizing. Sizing the vessel at the lesion site and perform other simple measurements can be done by IVUS. All measurements should be performed under close to optimal conditions, therefore avoided if artifacts such as Non Uniform Rotational Distortion (NURD) are present or if the IVUS catheter is not parallel to the vessel long axis. Area measurements can also be added to calculate volumes.

Border identification. Measurements should be performed at the leading edge of boundaries, never the trailing edge as shown in Fig 11-1. With few exceptions, the location of the leading edge is accurate and reproducible regardless of system settings or image-processing characteristics of different ultrasound scanners (26).

Measurements at the trailing edge are inconsistent and frequently yield erroneous results.

In muscular arteries such as the coronary arteries, there are frequently three layers (7,27,28). The innermost layer consists of a complex of three elements: intima, atheroma (in diseased arteries), and internal elastic membrane. This innermost layer is relatively echogenic compared with the lumen and media. The trailing edge of the intima (which would correspond to the internal elastic membrane) cannot always be distinguished clearly. Moving outward from the lumen, the second layer is the media, which is usually less echogenic than the intima. In some cases the media may appear artifactually thin because of blooming, an intense reflection from the intima or external elastic membrane (EEM). In other cases the media can appear artifactually thick because of signal attenuation and the weak reflectivity of the internal elastic membrane. In elastic arteries such as the carotid artery, the media is more echo reflective because of the higher elastin content. The third and outer layer consists of the adventitia and periadventitial tissues

Lumen measurements. Lumen measurements are performed using the interface between the lumen and the leading edge of the intima. In normal segments, the intimal leading edge is easily resolved because the intima has thickened enough to be resolved as a separate layer and has sufficiently different acoustic impedance from the lumen. Under such circumstances, the leading edge of the innermost echogenic layer should be used as the lumen boundary. Occasionally, particularly in younger normal subjects (e.g., post-transplantation), the vessel wall will have a single-layer appearance because the intima cannot be resolved as a discrete layer. In such cases, a thin, inner echo lucent band corresponding to the intima and media is usually present and it is this boundary that should be measured. While lumen boundaries defined in this manner may include the intima, the thickness of this layer will be <160 μm and will add negligible error to the lumen measurement.

Once the lumen border has been determined, the following lumen measurements can be derived:

Lumen Cross Sectional Area (CSA): The area bounded by the luminal border; Minimum lumen diameter (MLD): The shortest diameter through the center point of the lumen; Maximum lumen diameter: The longest diameter through the center point of the lumen.

Lumen Eccentricity: 1 [(maximum lumen diameter minus minimum lumen diameter) divided by maximum lumen diameter.]

Lumen area stenosis: (Reference lumen CSA minus minimum lumen CSA)/reference lumen CSA. The reference segment used should be specified (proximal, distal, largest, or average—see above).

Post-intervention (if dissection is present), it is important to state whether the lumen area is the true lumen or a combination of the true and false lumens.

EEM measurements. A discrete interface at the border between the media and the adventitia is almost invariably present within IVUS images and corresponds closely to the location of the EEM. The recommended term for this measurement is *EEM CSA*, rather than alternative terms such as vessel area or total vessel area.

External elastic membrane circumference and area cannot be measured reliably at sites where large side branches originate or in the setting of extensive calcification because of acoustic shadowing. If acoustic shadowing involves a relatively small arc (<90°), planimetry of the circumference can be performed by extrapolation from the closest identifiable EEM borders, although measurement accuracy and reproducibility will be reduced. If calcification is more extensive than 90° of arc, EEM measurements should not be reported. In addition, some stent designs may obscure the EEM border and render measurements unreliable.

Disease-free coronary arteries are circular, but atherosclerotic arteries may remodel into a non-circular configuration. If maximum and minimum EEM diameters are reported, measurements should bisect the geometric center of the vessel rather than the center of the IVUS catheter.

Atheroma measurements. Because the leading edge of the media (the internal elastic membrane) is not well delineated, IVUS measurements cannot determine true histological atheroma area (the area bounded by the internal elastic membrane) (26). Accordingly, IVUS studies use the EEM and lumen CSA measurements to calculate a surrogate for true atheroma area, the plaque plus media area. In practice, the inclusion of the media into the atheroma area does not constitute a major limitation of IVUS, because the media represents only a very small fraction of the atheroma CSA. The term plaque plus media (or atheroma) has been suggested to be used and the following measurements be performed:

Plaque plus media (or atheroma) CSA: The EEM CSA minus the lumen CSA.

Maximum plaque plus media (or atheroma) thickness: The largest distance from the intimal leading edge to the EEM along any line passing through the center of the lumen.

Minimum plaque plus media (or atheroma) thickness: The shortest distance from intimal leading edge to the EEM along any line passing through the luminal center of mass.

Plaque plus media (or atheroma) eccentricity: (Maximum plaque plus media thickness minus minimum plaque plus media thickness) divided by maximum plaque plus media thickness.

Plaque (or atheroma) burden: Plaque plus media CSA divided by the EEM CSA. The atheroma burden is distinct from the luminal area stenosis. The former represents the area within the EEM occupied by atheroma regardless of lumen compromise. The latter is a measure of luminal compromise relative to a reference lumen analogous to the angiographic diameter stenosis.

Calcium detection. IVUS has a much higher sensitivity than coronary angiography for detection of calcifications (29,30). The presence, depth and circumferential distribution of calcification are very important factors for selecting the type of

interventional device and for estimating the risk of complications (31,32). For instance, the presence of an area of superficial calcium greater than 180 degrees is considered as an indication to use rotational atherectomy (33). This will create more easily a smooth channel, which can be further enlarged with balloon angioplasty, directional atherectomy or stent implantation with a lower risk than using directly any of these techniques instead of rotational atherectomy (34). In addition, the presence of calcium is a major determinant of dissections post-PTCA, which most likely occurs at the border between calcium and soft tissue (35,36).

Calcific deposits appear as bright echoes that obstruct the penetration of ultrasound, a phenomenon known as acoustic shadowing. Because high frequency ultrasound does not penetrate the calcium, IVUS can detect only the leading edge and cannot determine the thickness of the calcium. Calcium can also produce reverberations or multiple reflections that result from the oscillation of ultrasound between transducer and calcium and cause concentric arcs in the image at reproducible distances.

Calcium deposits should be described qualitatively according to their location (e.g., lesion vs. reference) and distribution:

Superficial: The leading edge of the acoustic shadowing appears within the most shallow 50% of the plaque plus media thickness.

Deep: The leading edge of the acoustic shadowing appears within the deepest 50% of the plaque plus media thickness.

The arc of calcium can be measured (in degrees) by using an electronic protractor centered on the lumen. Because of beam-spread variability at given depths within the transmitted beam, this measurement is usually valid only to ±15°. Semi-quantitative grading has also been described, which classifies calcium as absent or subtending 1, 2, 3, or 4 quadrants. The length of the calcific deposit can be measured using motorized transducer pullback.

Plaque thickness and eccentricity. These are other elements of great importance to guide interventions where IVUS has shown to be more sensitive than angiography. The presence of highly eccentric plaques, without significant sub endothelial calcification, may be an indication to use directional atherectomy. The origin of side branches from the diseased part of the vessel wall with an eccentric plaque is a predictor of occlusion after PTCA or stent deployment. IVUS can also clarify unusual lesion morphologies, such as aneurysm versus pseudoaneurysm. The ability to assess longitudinal vessel involvement and the degree of diffuse disease is particularly important in saphenous vein grafts, where IVUS can help in defining the extension and characteristics of wall morphology (37) and guide the type of intervention (38). It is noticeable the fact that only 9% of the stents are optimally expanded with angiography matching the reference cross-sectional area in vein grafts (39).

The ability to serially assess interventioned lesions and, therefore, determine the mechanism of vessel remodeling (restenosis) is an important advantage of IVUS (40). It can basically distinguish between the two main types of vessel remodeling: negative remodeling, where expansion of total vessel area using a stent to avoid chronic vessel recoil may be the best therapeutic strategy; or positive remodeling, with plaque accumulation and a large plaque burden, where plaque debulking with adjunctive balloon angioplasty or stent implantation may be the best option. Dangas et al. (41) have shown in a total of 777 lesions in 715 patients treated with nonstent techniques that positive lesion-site remodeling is associated with a higher long term Target Lesion Revascularization (TLR). In their study, lesions with positive remodeling had more revascularization events (31.2% vs. 20.2% for the negative/intermediate-remodeling group, p=0.0001), despite a larger final IVUS lumen CSA after the interventional procedure. This adds to the evidence that long-term clinical outcome appears to be determined in part by preintervention lesion characteristics. These findings also suggest that positive-remodeling lesions should be targeted for treatment with interventions that have been shown to reduce

restenosis, such as stents. Conversely, negative-remodeling lesions may be suitable for a provisional stent-implantation strategy.

IVUS during balloon angioplasty.

IVUS has helped to understand the mechanism of balloon angioplasty (11,13). It can detect plaque fractures or dissections at risk, which require immediate further treatment. In the setting of acute coronary syndromes it showed that plaque area reduction is the major cause of luminal gain, suggesting that compression, redistribution or dislodgement of mural thrombus occurs in these syndromes (42,43).

The use of stents has increased dramatically over the last few years. Interestingly, stent availability has also improved the efficacy of stand-alone balloon angioplasty. With stents as a safety net, the operators can be more aggressive optimizing the results of balloon angioplasty. IVUS guided balloon angioplasty has gained a new breathe with the results from CLOUT (44). In its pilot phase it reported that IVUS reference segment mid-wall dimensions could be used to safely upsize PTCA balloons (44). In CLOUT, PTCA was first performed using conventional angiographic balloon sizing; then PTCA was repeated using IVUS balloon sizing. This study showed that on the basis of the vessel size and extent of plaque burden in the reference segment evaluated with IVUS, 73% of the lesions needed balloons of a larger size even after achieving an optimal angiographic result [Nominal balloon/artery ratios increased from 1.12±0.15 to 1.30±0.17 ($p<0.0001$); and Quantitative Coronary Angiography (QCA) measured balloon/artery ratios increased from 1.00±0.12 to 1.12±0.13 ($p<0.0001$)]. The success rate of IVUS-guided PTCA was 99.0%. These angiographic oversized balloon angioplasty IVUS-guided resulted in a greater final minimal lumen diameter (2.21±0.47 mm) and a QCA DS decrease from 28±15% to 18±14%, without increased rates of dissections or ischemic complications.

The Washington group has published a study that extended the findings of CLOUT in three important areas: balloon sizing, acute endpoint determination, and long-term follow-up (45). In CLOUT the proximal and distal reference segment mid-wall

dimensions were measured after angiographic-guided PTCA, and the smaller of the proximal and distal reference segment mid-wall dimensions was used for balloon sizing. The distal vessel is often small and underperfused pre-intervention, especially when the IVUS catheter is placed across the lesion. In their report, the pre-intervention lesion site EEM diameter was used to select the PTCA balloon size. They enrolled 284 consecutive patients with 438 native coronary artery stenosis in a study of IVUS-guided provisional stenting. The axial center of the target lesion was identified. Maximum and minimum EEM diameters were measured; and the two were averaged to select the balloon size. Any semi-compliant, or non-compliant balloon was used; the manufacturer-supplied "in-air" nominal inflated balloon diameter had to match the lesion site EEM diameter at the maximum inflated pressure during the PTCA. If necessary, quarter-sized balloons were used for more exact size matching. When the operator felt that the best angiographic result had been achieved, IVUS was repeated. Patients were crossed-over to stent implantation if angiography showed less than TIMI-3 flow or an NHLBI grade C or greater dissection or if post-PTCA IVUS did not show an optimal result. An optimal IVUS result was defined as 1. a minimum lumen CSA 65% of the average of the proximal and distal reference lumen areas or a minimum lumen CSA 6.0mm2 and 2. no major dissection. A major dissection was defined as 1. a mobile flap, 2. a dissection involving >90% of the vessel circumference, or 3. a dissection causing a sub-optimal true lumen CSA (excluding the area subtended by the dissection plane) as defined above. When necessary, stents were implanted using conventional techniques, followed by high-pressure adjunct PTCA. The IVUS criteria for optimum stent implantation were a minimum stent CSA >80% of the average reference lumen CSA (or an absolute minimum stent CSA $\geq$7.5mm2) and complete stent-vessel wall apposition. Overall, 206 lesions in 134 patients were treated with PTCA alone. Conversely, 232 lesions in 150 patients crossed over to stent implantation; this included 2 lesions (2 patients) that developed out-of-laboratory abrupt closure post-PTCA. Reasons for crossover were angiographic or IVUS flow-limiting or lumen compromising dissections in 65 (27.9%) or a sub-optimal IVUS minimum lumen CSA (as defined above) in 167 (72.1%). Sixty-three lesions (27.2%) were treated with Gianturco-Roubin stents and

169 (72.8 %) with Palmaz-Schatz stents with an average of 1.2±0.6 stents/lesion. Long-term follow-up was available in 96% of patients. There were no deaths and one MI. The 1-year TLR rate was 8.2% for the PTCA group and 15.5% for the stent crossover group (p=0.016). Using multivariate logistic regression analysis, the only predictor of TLR was use of the Gianturco-Roubin stent (odds ratio=4.7, 95% confidence interval of 2.1 to 10.5, p=0.0103). The TLR rate was 32.2% in the Gianturco-Roubin stent group (p=0.001 vs. both PTCA and Palmaz-Schatz stents) and 10.4% in the Palmaz-Schatz group (p=0.37 vs. PTCA).

A similar study was performed at Tubingen, Germany (46). The authors reported 252 patients who had 271 lesions treated with IVUS-guided balloon angioplasty. IVUS was performed before and after intervention to determine the EEM diameter at the lesion site. The balloon catheter was sized according to the EEM diameter measured by IVUS. The mean balloon diameter was 4.1±0.5 mm, the dilation time 130±60 seconds with a balloon pressure of 7.0±2.0 atm. Clinical acute and 1-year long-term follow-up were obtained for all patients and follow-up angiography in 71% of patients. Acute events occurred post-interventionally in 5 patients (2%). The cumulative event rate during long-term follow-up was 14%. The angiographic restenosis rate (DS >50%) after 1 year was 19%.

Haase et al (47) whom using a similar approach to CLOUT confirmed the ability to reach a larger final minimal lumen diameter (2.23±0.58 mm) without an increase in in-hospital complications and a 12% incidence of clinical events and a 21% restenosis rate at one year follow-up. The extension of this approach to more complex lesions and to diffuse disease still has to be proven, but may well be a good strategy to further decrease clinical events and restenosis in some problematic lesions.

Predictors of restenosis

IVUS has also been used to define predictors of lesion restenosis. In the early 1990s, studies were initiated to determine whether intravascular imaging could predict clinical and angiographic outcome after intervention. The goal of these

investigations was to determine whether some morphological features, such as the presence or extent of dissection, or morphometric features (e.g., lumen size or plaque burden) were related to restenosis. The first multicenter trial, Post-IntraCoronary Treatment Ultrasound Result Evaluation (PICTURE), showed no statistically significant predictors of outcome in a relatively small cohort (250 patients) using early generation equipment (48). Single-center studies, however, identified residual plaque burden as an independent predictor of outcome in multivariable analysis (50). To examine this issue more completely, phase II of the Guidance by Ultrasound Imaging for Decision Endpoints (GUIDE) trial enrolled 524 patients undergoing angioplasty and/or atherectomy. Among the angiographic and ultrasound variables, ultrasound-derived residual percent plaque burden was the most powerful predictor of clinical outcome, with a risk ratio of 1.7 (50,51). However, the long-term clinical impact of differences in angiographic result has not been well established.

Despite some contradictory results there is currently some evidence that residual plaque burden is an important predictor of restenosis. In GUIDE II trial in addition to residual plaque burden, minimal luminal diameter measured by IVUS was also a predictor of restenosis (51). Other studies have confirmed these results not only in balloon angioplasty but also in atherectomy, such as OARS (51) and ABACAS (52), although in PICTURE, a study that enrolled 200 patients, no correlation was found (48).

For the first 15 years of interventional cardiology, investigators believed that the predominant mechanism of restenosis after angioplasty and atherectomy was intimal proliferation. Ultrasound studies in the peripheral vessels by Pasterkamp and colleagues (54) presented the first indication that negative remodeling, or localized shrinkage of the vessel, was a major mechanism of late lumen loss. Mintz et al (55) studied 212 native coronary arteries in patients undergoing repeat catheterization for recurrent symptoms or research protocols after coronary interventions. At follow-up, there was a decrease in EEM area and an increase in plaque area at the target lesion. Interestingly, >70% of lumen loss was attributable to the decrease in EEM area, whereas the neointimal area accounted for only 23% of the loss. Moreover, the

change in lumen area correlated more strongly with the change in EEM area than with the change in plaque area. For lesions with an increase in EEM area at follow-up (47% of segments studied), there was no change or an actual gain in lumen area and a reduction in angiographic restenosis (26% versus 62%; $P<0.0001$) (55).

These observations have provided a key insight into the reduction of restenosis observed with stenting. Unlike the restenotic response to angioplasty or atherectomy, which is a mixture of arterial remodeling and neointimal growth, stent restenosis is primarily due to neointimal proliferation. In serial ultrasound studies, late lumen loss correlated strongly with the degree of in-stent neointimal growth ($r=0.98$) (55,56). The amount of intimal proliferation has been shown to correlate with the pre-stent plaque burden (58,59). In a serial study using IVUS of stented coronary segments, no significant change occurred in the area bound by stent struts, indicating that stents can resist the arterial remodeling process (56). This phenomenon, combined with the greater initial lumen expansion accomplished with stenting, results in a lower net restenosis rate than that with angioplasty or atherectomy.

Imaging Post-Intervention (Dissections and other complications after intervention)

Intravascular ultrasound is commonly employed to detect and direct the treatment of dissections and other complications after intervention (11,60-63). Dissections can be classified into five categories:

Intimal: Limited to the intima or atheroma not extending to the media.

Medial: Extending into the media.

Adventitial: Extending through the EEM.

Intramural hematoma: An accumulation of blood within the medial space, displacing the internal elastic membrane inward and EEM outward. Entry and/or exit points may or may not be observed.

Intra-stent: Separation of neointimal hyperplasia from stent struts, usually seen only after treatment of in-stent restenosis.

The severity of a dissection can be quantified according to: 1) depth (into plaque—useful only in describing intimal dissections that do not reach the media); 2) circumferential extent (in degrees of arc) using a protractor centered on the lumen; 3) length using motorized transducer pullback; 4) size of residual lumen (CSA); and 5) CSA of the luminal dissection. Additional descriptors of a dissection may include the presence of a false lumen, the identification of mobile flap(s), the presence of calcium at the dissection border, and dissections in close proximity to stent edges. In a minority of patients, the dissection may not be apparent by IVUS, because of the scaffolding by the imaging catheter or because the dissection is located behind calcium. Usually, ultrasound occult dissections can be demonstrated by angiography.

Conclusion

Intracoronary ultrasound has evolved over the last few years from its infancy to its early adulthood with some potential developments and applications still to be developed. After its reproducibility and safety was demonstrated it was fundamental in the understanding of the mechanism of action of some of the interventional devices, as well as in the restenosis mechanisms, introducing some new concepts such as the negative remodeling as one of the mechanisms of restenosis. It was also due to IVUS that a correct deployment of stents was developed and the burden of anticoagulation was taken away, improving the results and decreasing costs, the ultimate goal of any new technology. Several new developments in IVUS may be important, increasing the usefulness of IVUS pre and during balloon angioplasty. Finally we can easily admit that IVUS, although not needed all the time, can help, particularly in some unclear situations, that make more real the view that: coronary intervention can be done without IVUS, but it can be done better if you have IVUS available.

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Figures Legends

Figure 11-1. Example of commonly performed direct and derived IVUS measurements. **Panels A and B** illustrate the reference segment, whereas **panels C and D** represent the stenosis. In **Panel B**, the EEM and lumen areas are traced. In **panel D**, the minimum and maximum lumen diameters are illustrated using a double headed arrow (**open and solid arrowheads**, respectively). In **panel D**, the minimum and maximum atheroma thickness is also illustrated using **double headed arrows** (**white** for minimum and **black** for maximum). Also in **panel D**, the EEM and lumen areas are traced and the arc of calcification **(dotted line)** is shown. EEM = external elastic membrane (Reproduced from Ref 22).