Intravascular ultrasound: defining plaque regression

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Intravascular ultrasound allows accurate assessment of the arterial vessel, including vessel luminal diameter and assessment of vessel disease in terms of plaque morphology, plaque volume and extent of calcification. Recently published trials highlight the role of intravascular ultrasound in monitoring disease progression in a clinical setting.

Intravascular ultrasound (IVUS) has been a major development in the imaging of coronary arteries that allows the operator to view both the lumen and the wall of an artery under investigation in sequential tomographic slices. It has an integral role in the detailed evaluation of coronary disease in both diagnostic and interventional settings. Clinical studies in IVUS began in 1989 with the development of catheters initially in the 5 French (F) size range with the current catheter size miniaturized to 2.6 F (Yock et al, 1995). IVUS has permitted not only a greater understanding of plaque morphology and its response to interventional procedures but has provided accurate online quantitative information regarding lumen size and residual plaque load, an important predictor of restenosis. The presence of disease not only at the site of focal stenosis but also in reference segments believed by angiography to be free of disease has modified interventional practice significantly.

An IVUS catheter is a monorail device that is introduced into a coronary artery on a regular 0.014" guide wire. The catheters exist in two basic forms:

1. A mechanical device comprising a rotating mirror reflecting ultrasound energy at 1800 revolutions per minute (rpm) in a circumferential manner (*Figure 1a*)
2. A solid state device which generates ultrasound energy by an electronically trigger from an array of 64 piezo-electric crystals (*Figure 1b*).

The radiofrequency backscatter is analysed and digitally converted into a visible image on the ultrasound console. Where the intimal thickness is greater than 150 μm, a three-layer appearance may be seen of intima, a thin echolucent media and an echoreflective adventitia (Fitzgerald et al, 1992). It is possible to measure lumen and vessel area by planimetry and calculate the intimal or plaque area from the equation:

intimal area = vessel area – lumen area

A more accurate representation of plaque load in a given coronary artery segment may be achieved by using software to reconstruct a three-dimensional image using an automated pullback device to achieve a standard length of

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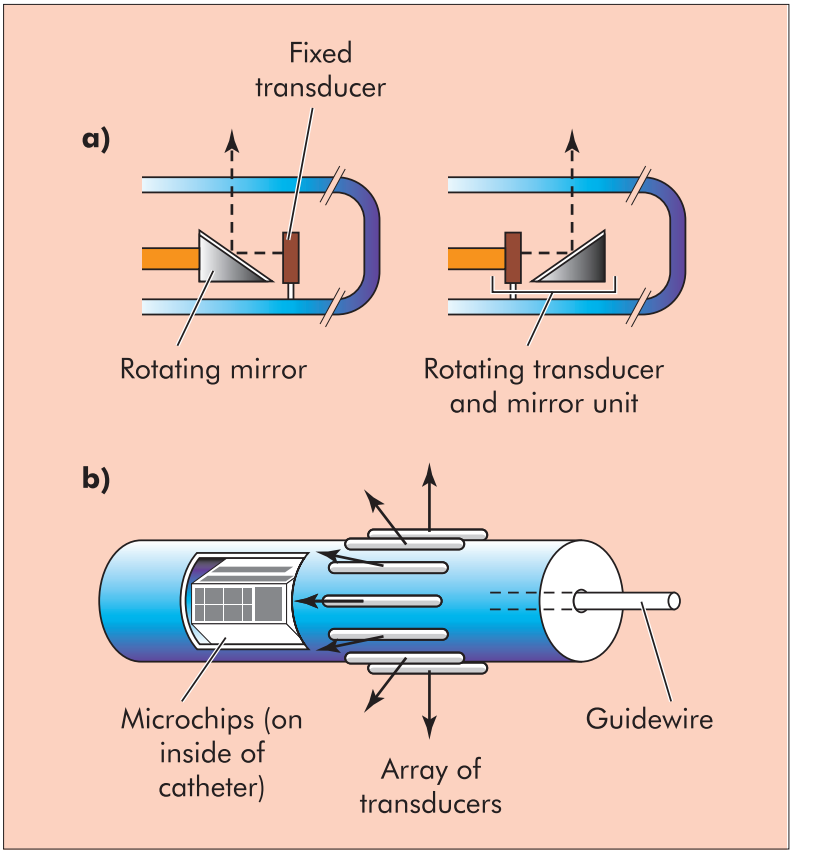
Figure 1. a. Rotating mirror device. b. Multiple array design.



segment for analysis. This pullback may be electrocardiogram-gated to reduce motion artefact and improve image quality.

THE VALIDATION OF IVUS

IVUS is the current imaging technology of choice for studying the morphology of atherosclerotic plaques in vivo. Early studies used a large 8F catheter to correlate ultrasound appearances with histological findings in arteries collected at the time of autopsy (Nishimura et al, 1990; Maheswaran et al, 1995). The arteries studied were combinations of elastic, transitional (musculo-elastic) and muscular types with respect to media and adventitia appearance. The results confirmed that a highly accurate measurement of luminal area was achieved comparing ultrasound to direct measurement of perfused isolated arteries. A distinct interface between media and adventitia was obtained only where there was a significant difference in the acoustic qualities of the two layers (namely, loose collagen in the adventitia of elastic arteries or where there was a minimal smooth muscle cell component in the adventitia of transitional or muscular arteries). The interface between plaque and media was only apparent where there was a dense internal elastic lamina or a significant amount of necrotic material in the plaque.

The earliest accumulations of atherosclerotic plaque consist of crescentic intimal thickening of an intermediate echointensity. A common site for initial and increased plaque accumulation occurs at branch points and bifurcations because of the shear stress effect of blood flow. Transplant vasculopathy is a good model for the early development of coronary artery disease as these patients undergo ultrasound studies at angiographic follow up early after transplantation.

In one study, IVUS was used to study epicardial arteries in 25 recently transplanted hearts from young donors (mean age 28 years) (St Goar et al, 1992a). In this unique study group, all donors aged under 25 years had a homogeneous non-layered vessel wall. Another group of donors of mean age 32 years manifested a three-layered appearance. In five hearts, significant eccentric intimal thickening >500 μm was shown in donors with risk factors for coronary disease, implying early coronary disease in the presence of angiographically normal arteries. Subsequent work by the same group in a larger group of transplant recipients over a period of long-term follow up has shown that all 60 hearts had variable degrees of concentric intimal thickening after 1 year, 42 of whom had normal coronary arteries at angiography (St Goar et al, 1992b).

With a greater accumulation of plaque, there is a greater complexity to the plaque that may be differentiated by broad ultrasound criteria. A fibrous plaque has an echodensity intermediate between less echodense media or lipid and more echodense calcification. Thus by comparing the brightness of the tissue in question to that of the adventitia, a relative grading of the plaque may be obtained. Such fibrous plaques with similar brightness to adventitia may then be described as hard or soft (with respect to the grey scale) depending on the presence or absence of shadowing behind the plaque. Fatty plaques are significantly more echolucent and when large may be appreciated as lipid pools. However, because shadowing in relation to a fibrous plaque may be misinterpreted as a lipid collection, there is a tendency to broadly classify plaques containing lipid as fibro-fatty in nature (*Figure 2*).

Calcification is commonly seen on IVUS as a bright echo with shadowing behind often associated with reverberation artefact in the area of the shadow as a result of oscillation of the ultrasound beam between calcium and transducer (*Figure 3*). Calcium may be seen in relatively small plaque accumulations indicating the age of the plaque or the site of previous plaque rupture and repair. In one series of patients undergoing balloon angioplasty, 82% of arterial segments exhibited small areas of calcium that were visible in only 8% of angiograms at the lesion site

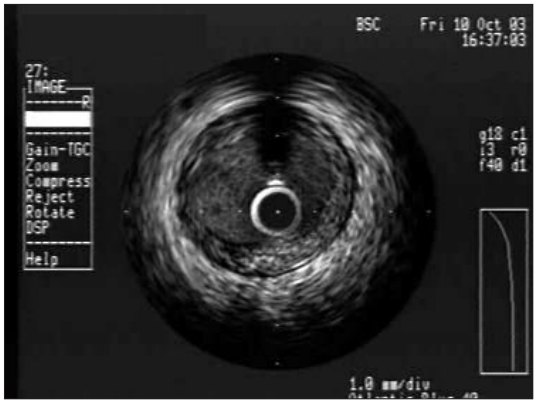


Figure 2. Fibrofatty plaque.

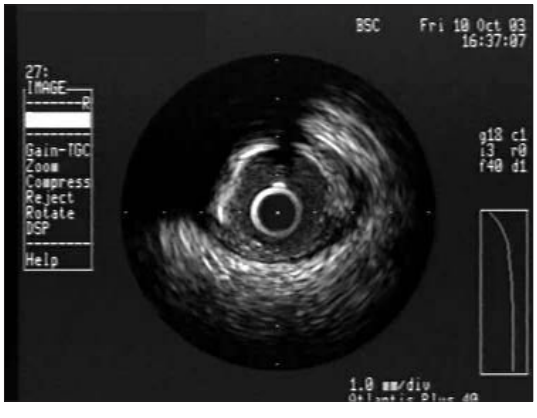


Figure 3. Calcified plaque.

(Tobis et al, 1991). In the GUIDE (Guidance by Ultrasound Imaging for Decision Endpoints) trial (phase I), 70% of target lesions had areas of calcium by ultrasound, compared to 40% of angiograms (GUIDE Trial Investigators, 1996). Calcification may be graded from absent (0) to severe (3+) by the extent of the arc subtended by a fibrocalcific matrix (Farb et al, 1990). In general, at least 180° of calcium is required to achieve a mass of calcium identifiable by angiography (74% identification by fluoroscopy) increasing to 86% of cases identified if more than two quadrants or calcium length ≥6 mm is present (Mintz et al, 1992).

By definition, plaque calcification results in shadowing of deeper structures, obscuring evaluation of underlying arterial wall components. Furthermore, shadowing may occur without any obvious calcification as the calcium may be out of plane and not visualized unless hit by the ultrasound beam in a perpendicular fashion. The calcium may be distributed in the plaque in several ways: as a deep deposit in an arc at the intima–media border, in a superficial rim at the luminal surface, or as a concretion within a fibrous plaque. In one study of 110 patients, superficial calcium was present in 50%, deep calcium in 15% and both in 35% (Mintz et al, 1992). On occasion, the fibrous cap may be intensely echoreflective with shadowing extending to and around the periphery of the artery, suggesting a more uniform distribution of calcium throughout the wall. Dense fibrotic plaques may be sufficiently underpenetrated by the ultrasound beam to cause significant shadowing, and such plaques are usually referred to as fibrocalcific.

CLINICAL INDICATIONS FOR IVUS

IVUS is used as a diagnostic modality and can be used in the setting of routine coronary angiography and also as an adjunct to percutaneous coronary intervention. IVUS allows the accurate assessment of disease at the site of a coronary lesion with accurate lumen measurement and provides additional information on reference segment disease adjacent to the stenosis under investigation. This is particularly useful where angiographic assessment is sub-optimal such as in ostial disease and where there is foreshortening or branch overlap. An ambiguous angiographic appearance may also be better defined by IVUS where the plaque load is uncertain by angiography.

In an interventional context, the morphology of plaque may be defined and the extent and severity of calcification demonstrated by IVUS may lead the operator to an alternative interventional strategy such as rotablation.

Stent placement

Another important indication for IVUS is in the optimal deployment of stents. The first trial to suggest benefit was the MUSIC (Multicentre Ultrasound guidance of Stents In Coronaries) trial which was a prospective non-randomized observational study designed to examine the additional value of IVUS in determining optimal stent deployment in vessels with a reference segment larger than 3.0 mm, with the intention of reducing the need for antithrombotic medication (de Jaegere et al, 1998). A stent thrombosis rate of only 1.3% was reported after a mean follow up of 198 days in 155 patients treated with aspirin alone. Emergency bypass surgery was required in 0.6% of patients with an overall target lesion revascularization (TLR) of 4.5%, suggesting clinical benefit from the adjunctive use of IVUS to guide stent expansion.

In the first randomized trial of ultrasound-guided stenting, CRUISE (Can Routine Ultrasound Influence Stent Expansion) included nine centres in which stents were deployed using IVUS guidance and compared with patients in seven centres in which stenting was guided by angiography alone followed by blinded IVUS assessment (IVUS-documentary) (Fitzgerald et al, 2000). A total of 499 patients were followed up with larger balloon sizing (3.88±0.51 *vs* 3.69±0.59 mm, $P<0.001$) and greater dilatation pressure (18.0±2.6 *vs* 16.6±3.0 atm, $P<0.001$) used in the IVUS-guided and IVUS-documentary groups respectively. At 9-month follow up, a 44% reduction in the clinical end-point of target vessel revascularization (TVR) was demonstrated (8.5% *vs* 15.3%, $P<0.05$) (Fitzgerald et al, 2000).

In the AVID (Angiography Versus Intravascular Ultrasound Directed stent placement) trial of ultrasound- and angiography-guided stent deployment (Russo et al, 1999), 759 patients undergoing elective single or multiple stent placement in native vessels >2.5 mm or saphenous vein grafts were included. Patients were randomized after optimal angiography-guided stent deployment (<10% residual stenosis). After 12 months' follow up, the primary clinical endpoint of TLR was 8.4% in the IVUS-guided group *vs* 12.4% in the angiography-guided group ($P=0.08$). When protocol violations such as the inclusion of vessels smaller than 2.5 mm were excluded, the difference achieved statistical significance (4.9% *vs* 10.8%, $P=0.02$). The benefit of IVUS guidance

was particularly evident in three subgroups: saphenous vein grafts (TLR 5.7% *vs* 20.4%, *P*=0.05), vessels with a diameter stenosis greater than 70% (TLR 3.5% *vs* 14.9%, *P*=0.003), and vessels with a distal reference diameter less than 3.25 mm (TLR 7.9% *vs* 14.6%, *P*=0.04).

Ultrasound-guided stenting leads to balloon upsizing in up to 40% of patients, which results in a greater initial minimum stent area with no increase in acute complications. Despite encouraging results from uncontrolled studies, the randomized trials have shown no difference in angiographic restenosis rate, although there appears to be a reduction in clinical restenosis, particularly in specific subgroups. This has resulted in a selective use for IVUS in clinical practice. However, it remains the diagnostic modality of choice for the assessment of atherosclerotic plaque.

PLAQUE REGRESSION AND THE REVERSAL TRIAL

IVUS produces high-resolution cross-sectional tomographic images of coronary arteries and may be used sequentially to assess the effect of drug therapy on coronary plaque load. The first randomized clinical trial to investigate the effect of statin therapy on coronary plaque load compared 10 mg pravastatin with diet *vs* diet alone over 3 years' follow up in 36 Japanese patients (Takagi et al, 1997). Plaque load was calculated from 10 consecutive end-diastolic images in arteries with less than a 25% diameter stenosis.

In the statin group, the total cholesterol level fell by 16% (from 6.05±0.35 mmol/litre) with a low-density lipoprotein (LDL) cholesterol reduction of 26% (from 4.4±0.49 mmol/litre). Follow up was achieved in 25 patients. Plaque index (plaque area/vessel area) decreased by 7±16% in the pravastatin group compared to an increase of 27±17% (*P*<0.001) in the control group. As a confounding variable, 84% of patients smoked at baseline with all stopping during the trial. Nonetheless, this study suggested that the atherosclerotic process could be modified by statin therapy.

TABLE 1.
Endpoints in REVERSAL

End points (95% CI)	Pravastatin 40 mg (*n*=249)	Atorvastatin 80 mg (*n*=253)	*P* value
% change in atheroma volume	2.7 (0.2–4.7)	-0.4 (-2.4–1.5)	0.02
Change in total atheroma volume (mm^3)	4.4 (0.1–6.0)	-0.9 (-3.5–1.6)	0.02
Median % change in atheroma volume	1.6 (1.2–2.2)	0.2 (-0.3–0.5)	0.0002

CI = confidence interval; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering. From Nissen et al (2004)

There is some evidence to show that unstable coronary plaques are more likely to remodel positively, i.e. to undergo compensatory enlargement, compared to stable plaques (Jeremias et al, 2000). It is therefore possible that if a drug therapy can prevent the positive remodelling process, it may also reduce plaque vulnerability.

This early work lead to the rationale behind the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. This compared the effect of a standard lipid-lowering approach with an aggressive strategy on the progression of atheroma burden as measured by IVUS assessment of atheroma volume. REVERSAL was a multicentre double-blind trial that randomized 654 patients to either pravastatin 40 mg or atorvastatin 80 mg. IVUS was performed on a single vessel at baseline and after 18 months of treatment (Nissen et al, 2004). Patients were included in the study if they had symptomatic coronary disease, coronary stenosis of 20% or more, and an LDL cholesterol level of 3.0–5.4 mmol/litre after a 4–10-week washout period. The primary endpoint was the percentage change in atheroma volume. Secondary parameters included change in total atheroma volume (TAV) and change in per cent obstructive volume.

Patients were initially selected for the study based on angiographic evidence of >20% coronary stenosis. IVUS was then performed on the longest and least angulated vessel that displayed a >20% stenosis using a 30 MHz, 2.6 F mechanical transducer with automated pullback following intracoronary nitroglycerine. Repeat cardiac catheterization and IVUS was performed at 18 months' follow up. The same target vessel was imaged and identical conditions recreated by way of motorized pullback based on the original study. The primary end point was calculated as a percentage change in TAV.

TAV is the sum of the differences between external elastic membrane borders and lumen areas across all slices. Other secondary endpoints measured were change in percentage atheroma volume and nominal change in atheroma volume.

The study showed that intensive lipid lowering halted the progression of atheroma, whereas progression occurred in the moderate lipid-lowering arm (*Table 1*).

Statins have long been known to possess additional pleiotropic effects with demonstrable anti-inflammatory effects. Linear regression analysis showed a discrepancy between the pro-

gression rate at any level of LDL cholesterol reduction between the two drugs with the progression rate at any level of LDL cholesterol being lower with atorvastatin than pravastatin. An additional anti-inflammatory effect has been postulated, and is supported by a greater reduction in C-reactive protein (CRP) and atherogenic lipoproteins in the atorvastatin group (*Table 2*). It is further supported by the progression of atheroma in the pravastatin arm even in patients who achieved LDL cholesterol levels below the National Cholesterol Education Panel (NCEP) guideline level of 2.6 mmol/litre.

The REVERSAL trial has implications for the way we treat atherosclerosis. While it showed that aggressive lipid lowering with atorvastatin 80 mg halts the progression of atherosclerosis, it was not powered to examine clinical events. In the American College of Cardiology 2004 scientific sessions, however, the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial was presented, which showed that intensive lipid lowering with atorvastatin 80 mg reduced the cardiovascular clinical event rate in patients recently hospitalized with acute coronary syndrome when compared with standard lipid lowering with pravastatin 40 mg (Cannon et al, 2004). Although powered as a non-inferiority trial, it showed that intensive lipid lowering with high dose atorvastatin conferred a 16% relative risk reduction for all-cause mortality, a trend which was evident just 30 days into the trial and remained consistent throughout the 2 years of follow up.

These findings emphasize the role of aggressive lipid lowering in prevention of both disease progression and mortality. They also highlight the potential role of IVUS in the monitoring of disease progression and in defining further anti-atherogenic strategies in the management of coronary disease. **HM**

Figures 1a *and* b *are reproduced courtesy of www.images.md. Conflict of interest: none.*

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TABLE 2.
Lipid levels in REVERSAL

	Pravastatin 40 mg	Atorvastatin 80 mg	*P* value
LDL cholesterol (% change from baseline)	-25.2	-46.3	<0.001
Triglycerides (% change from baseline)	-6.8	-20.0	<0.001
Apolipoprotein (% change from baseline)	-22.0	-39.1	<0.001
CRP (% change from baseline)	-5.2	-36.4	<0.001

CRP = C-reactive protein; LDL = low-density lipoprotein; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering. From Nissen et al (2004)

KEY POINTS

- Intravascular ultrasound allows detailed imaging of atherosclerotic plaques.
- Intravascular ultrasound may be used sequentially to assess the effect of drug therapy on coronary plaque load.
- Detailed morphological assessment of intravascular ultrasound images can identify lipid-rich plaque which may be at risk of rupture.
- Aggressive lipid lowering has been shown to halt progression of atherosclerosis as assessed by intravascular ultrasound.