To date, cardiologists have alleviated the symptoms of patients with significant lesions in the coronary angiography by stenting or coronary artery bypass grafting. While normal-looking coronary segments in angiography have been regarded as ‘disease-free’ and mild/moderate stenoses as ‘non-treatable’, today that we know that from these non-significantly diseased areas may potentially arise acute coronary events if no further action is taken other than standard care for cardiovascular risk factors. Indeed, despite intensive management, many patients continue to experience recurrent coronary events. In response to this, many researchers have recently turned their eyes towards the study of areas with mild to moderate atherosclerotic disease. Some researchers have even tried to focally modify the natural course of the non-significant stenoses by applying local therapies.

This article describes the relationship between histopathological assessment and in vivo investigations in patients with vulnerable plaques. Thin-capped fibroatheroma (TCFA) is the morphology that most resembles plaque rupture. Detection of these vulnerable plaques in vivo is essential in order to be able to study their natural history and to evaluate potential treatment modalities that may ultimately have an important impact on the prevention of acute myocardial infarction (AMI) and death.

New Pathological Findings on Vulnerable Plaques

The current pathological definition of a vulnerable plaque is an inflamed thin fibrous cap overlying a necrotic-rich core. However, it is difficult to translate post mortem findings into a prospective, prognostically relevant concept for patients. The reported mean thickness of the fibrous cap of vulnerable plaques as assessed by pathologists differs as follows: Mann and Davies reported a mean cap thickness of 250µm (range 20–1,140µm) in type IV and V plaques, while Burke et al. reported a mean fibrous cap thickness of 23±19µm in ruptured plaques, and in 95% of these plaques cap thickness was <65µm. This cap thickness value for ruptured plaques has recently been widely used for the definition of non-ruptured TCFA. As atherosclerosis is a systemic disease, plaque rupture is considered a ubiquitous process that may be clinically silent or symptomatic in different regions of the vascular system. Chevuru et al. recently reported that the prevalence of TCFAs and ruptured plaques is low (0.46±0.95 and 0.38±0.70 per heart, respectively), focal and located in the proximal segments of the coronaries. The majority of TCFAs and ruptured plaques localised in the proximal third of the major coronary arteries, and in 92% of cases these lesions clustered within two or fewer non-overlapping 20mm segments. Necrotic core size was 1.6±1.8mm² and 2.7±2.0mm long in TCFAs, while in ruptured plaques these measurements were 2.2±1.9mm² and 1.9±3.6mm.

Update on Imaging of Vulnerable Plaques

Although coronary angiography represents the standard modality for visualisation of coronary artery disease, there is a clear discrepancy between the appearance of the opacified vascular lumen and the actual extent of atherosclerosis. Therefore, a number of intravascular imaging techniques have recently been developed in order to study the vessel wall in more detail. Lately, a number of manuscripts addressing a combined approach for vulnerable plaque characterisation have been published. These studies, which have been mainly performed in Eastern countries (Eastern approach), required the use of multiple devices and sometimes multiple coronary occlusions.

We are convinced that today there is no single imaging technique that can provide information on the various characteristics of the vulnerable plaque and that a combination of techniques potentially improves complete characterisation of the plaque. However, in applying these techniques a balance between risks and benefits for the patient should be considered. In contrast, the Western approach would require the use of a single catheter and no occlusions from which three different types of information can be derived.

Eastern Approach

This multimodality imaging approach for the coronary arteries consists of using coronary angiography (CAS), intravascular ultrasound (IVUS) – some studies use virtual histology (VH) – and optical coherence tomography (OCT) in order to image the same coronary region (see Figure 1).

Intracoronary Angioscopy

Angioscopy allows direct visualisation of the plaque surface and intraluminal structures. Angioscopically, normal artery segments appear

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as glistening white, whereas atherosclerotic plaques can be categorised
based on their angioscopic colour as yellow or white. Platelet-rich
thrombus at the site of plaque rupture is characterised as white granular
material, and fibrin/erythrocyte-rich thrombus as an irregular red
structure protruding into the lumen. Yellow plaques are associated with
acute coronary syndromes (ACS)\(^2\) and thrombosis.\(^6\) The major limitations
of angiography are:

- it requires a blood-free field during image acquisition, which can be
  obtained either by complete vessel occlusion or by continuous saline
  flushing in front of the angioscope;
- only a limited part of the coronary tree can be investigated (i.e. vessels
  >2mm diameter); and
- assessment of stenotic lesions may prove difficult.

Kubo et al.\(^9\) reported the ability of OCT to assess the culprit lesion (CL)
morphology in AMI in comparison with IVUS and CAS. The incidence
of plaque rupture observed by OCT was 73\%, by CAS 47\% (p=0.035)
and by IVUS 40\% (p=0.009). Furthermore, OCT (23\%) was superior to
CAS (3\%; p=0.022) and IVUS (0\%; p=0.005) in the detection of
fibrous cap erosion. The intracoronary thrombus was observed in all
cases by OCT and CAS, but it was identified in only 33\% by IVUS
(p<0.001 versus OCT). More recently, Kubo et al.\(^10\) assessed the
relationship between plaque colour evaluated by CAS and fibrous cap
thickness estimated by OCT in vivo. To this end, 77 coronary artery
plaques in patients with ACS were analysed. Plaque colour varied with
respect to the fibrous cap thickness: 389±74µm in white plaques,
228±51µm in light yellow plaques, 115±28µm in yellow plaques and
59±14µm in intensive yellow plaques (p<0.0001) (see Figure 1). In
Speakman rank-order correlation analysis, there was a significant
negative correlation between yellow colour intensity and fibrous cap
thickness (p=0.0001). Furthermore, 80\% of intensive yellow plaques
were TCFA with a cap thickness of 65µm.

Greyscale Intravascular Ultrasound

This is currently the gold standard for intracoronary imaging in
progression/regression plaque trials. In addition, visual assessment of
plaque echogenicity provides semi-quantitative tissue characterisation.
Calcification can be identified as bright echo signals with acoustic
shadowing, with a sensitivity and specificity of approximately 90\%. Lipid
deposits, visualised as echolucent zones, can be detected with high
sensitivity (78–95\%) but low specificity (30\%). Moreover, the axial
resolution of IVUS is in the range of 100–150µm, whereas the fibrous cap of
a TCFA is thinner than 65µm and therefore cannot be visualised by
IVUS. Despite these limitations, large eccentric plaques containing an
echolucent zone as assessed by IVUS were associated with the
development of ACS in a prospective study.\(^11\) Some of the limitations of
IVUS can be improved by analysing the echogenicity or backscattered
ultrasound signal, which are more sophisticated techniques for tissue
characterisation. Recently, an in vivo feasibility study showed that
automated 3D differential echogenicity analysis of IVUS images allowed
identification of different tissue types within atherosclerotic plaques.\(^12\)
Plaques were scored for echogenicity compared with adventitia as either
brighter (hyperchogenic) or less bright (hypochogenic). Areas of
hyperchogenicity correlated with the presence of smooth-muscle cells,
areas of hypochogenicity correlated with the presence of collagen and
areas of hyperchogenicity correlated with acoustic shadowing
correlated with calcium.

Optical Coherence Tomography

OCT is an optical analogue of ultrasound using light instead of sound
to create an image. The light waves are reflected by the internal
microstructures within biological tissues as a result of their differing
optical indices. This technique provides a resolution of 10–20µm in vivo,
which is comparable to that provided by IVUS (100–150µm). An
in vivo comparison of OCT, integrated backscatter IVUS – using a
similar methodology to IVUS: VH – and conventional IVUS found that
OCT had the best potential for tissue characterisation of coronary
plaques, with higher sensitivity and specificity compared with the
other imaging modalities.\(^13\) However, a recent study comparing OCT
with histopathology reported a lower sensitivity for plaque
components. Misclassification occurred in 41\% of lesions, predominantly
due to a combination of incomplete penetration depth into
the vessel wall and the inability to distinguish calcium deposits
from lipid pools.\(^14\)

As a result of its high axial resolution, there is no doubt that OCT is the
in vivo gold standard for identifying and measuring the thickness of
the fibrous cap; an in vivo study found a significant difference in
minimal cap thickness between AMI and stable angina patients, with
median (interquartile range) values of 47.0µm (25.3–184.3µm) and
102.6µm (22.0–291.1µm), respectively (p=0.02).\(^15\) In addition to its
reliability as a tool to measure the thickness of the cap in vivo, recent
post mortem and in vivo studies have shown that OCT is capable of
evaluating the macrophage content of infiltrated fibrous caps. Kubo et
al.\(^9\) evaluated the ability of intracoronary OCT to assess CLs during
primary percutaneous coronary intervention (PCI) in patients with AMI.
The thickness of the remnants of the fibrous cap after symptomatic
rupture measured in vivo was 49±1µm.

The main limitation of OCT is the shallow penetration depth (2mm) into
the tissue, which hampers imaging of the entire vessel wall in large
vessels and light absorbance by blood, which currently needs to be
overcome by saline infusion and balloon occlusion. This has recently
been partly addressed by the use of non-occlusive techniques whereby
contrast is flushed through the guiding catheter during simultaneous
image acquisition at 3.0mm/second (M3, LightLab Imaging Inc.,
Westford, MA, US). Furthermore, even more encouraging is the use of
optical-frequency domain imaging (OFDI), which enables even faster
pullback speeds without compromising image quality and resolution.
Recently, in 56 patients with angina (126 plaques), the combined use
of IVUS-VH and OCT for detecting TCFA in vivo has been reported.\(^16\)
IVUS-derived TCFA (IDTCFAs) were defined as >10% necrotic core of
the cross-sectional area (CSA) in contact with the lumen (NCCL) and
plaque burden >40%. OCT-derived TCFA were defined as a fibrous
cap thickness of <65µm overlying a low-intensity area with an unclear
border. Plaque meeting both TCFA criteria was defined as definite
TCFA. Sixty-one plaques were diagnosed as IDTCFAs and 36 plaques as
OCT-derived TCFA. However, only 28 plaques were diagnosed as
definite TCFAs; the remaining 33 IDTCFAs had a non-thin cap and eight
OCT-derived TCFAs had an NCCL (in discord with NCCL visualised by
IVUS-VH, mainly due to misreading caused by dense calcium). Based on
IVUS findings, definite TCFA showed a larger plaque and vessel volume,
larger plaque burden, higher vessel remodelling index (Ri) and greater
angle occupied by the NCCL in the lumen circumference than non-thin-
cap IVUS-derived TCFAs. The combined use of OCT and IVUS-VH
allowed a complete TCFA characterisation.
Our group evaluated the incidence of IDTCFA using IVUS-VH. ACS patients had a significantly higher incidence of IDTCFA than stable patients: 3.0 (interquartile range 0.0–5.0) IDTCFA/coronary versus 1.0 (interquartile range 0.0–2.8) IDTCFA/coronary (p=0.018). A clear clustering pattern was seen along the coronaries, with 66.7% of all IDTCFAs located in the first 20mm, whereas further along the vessels the incidence was significantly lower (33.3%; p=0.008). This distribution of IDTCFAs is consistent with results of previous ex vivo and clinical studies, with a clear clustering pattern from the ostium demonstrating a non-uniform distribution of vulnerable plaques along the coronary tree. Patients presenting with ACS had a significantly higher prevalence of IDTCFAs even in non-culprit vessels, supporting the concept of a multifocal process. Of note, the lesion percentage area stenosis and the mean necrotic core areas of the IDTCFAs detected by IVUS-VH were also similar to previously reported histopathological data (55.9 and 59.6% and 19 and 23%, respectively).

We have developed software to quantify the amount of necrotic core in contact with the lumen, enabling the refinement of our analysis. Our current definition of an IDTCFA is a lesion fulfilling the following two criteria in at least three consecutive CSAs: plaque burden ≥40%, and confluent necrotic core ≥10% in direct contact with the lumen (i.e. no visible overlying tissue) in the investigated CSA; all consecutive CSAs having the same morphological characteristics are considered as part of the same IDTCFA lesion (see Figure 2). Using this refined definition of TCFA as assessed by IVUS-VH, patients with ACS underwent IVUS of all three epicardial coronaries; on average, there were two IDTCFAs per patient, with half of them showing outward remodelling.18 Palpography was performed in the same population: only five IDTCFAs had also been detected by palpography, with the highest number of high-strain spots at baseline and the most marked relative decrease during follow-up compared with patients with stable angina (ROC III/IV) in the region of interest (p=0.009) and their density per centimetre (p=0.012) decreased significantly between baseline and follow-up. This decrease in the overall population was largely driven by changes in the subgroup of patients with ST-segment elevation myocardial infarction (STEMI): this group had both the highest number of high-strain spots at baseline and the most marked relative decrease during follow-up compared with patients with other clinical presentations.21
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Other Imaging Techniques

Thermography

Atherosclerosis is accompanied by inflammation, and vulnerable plaques have been associated with increased macrophage activity, metabolism and inflammation. In a prospective study, an association between temperature heterogeneity and the incidence of adverse events at follow-up was found in patients with coronary artery disease undergoing a successful percutaneous intervention. In addition, treatment with statins seems to affect the thermographic results: in non-CLs the temperature difference (ΔT) was lower in the group treated with statins compared with the untreated group (0.06±0.05 versus 0.11±0.10°C; p=0.05).

More recently, a correlation between the morphological and functional characteristics of CLs in patients with ACS and chronic stable angina has been reported. In 81 consecutive patients (48 with ACS and 33 with stable angina), Ri by IVUS and ΔT by thermography between the CL and the proximal vessel wall were measured. Patients with ACS had a higher Ri than patients with CSA (1.15±0.18 versus 0.90±0.12; p<0.01), as well as increased ΔT (0.08±0.03 versus 0.04±0.02°C; p<0.01). Patients with positive Ri had higher ΔT than patients with negative Ri (0.07±0.03 versus 0.04±0.02°C; p<0.001). Patients with rupture plaque had increased ΔT compared with patients without rupture plaque (0.09±0.03 versus 0.05±0.02°C; p<0.01). Multivariate analysis showed that ΔT was independently correlated with the presence of rupture plaque, positive Ri and ACS. However, there are several factors that deserve further investigation. The impact of different coronary flow conditions on plaque temperature ('cooling effect') is still not completely understood. Simulations have revealed that the correct interpretation of intravascular thermographic measurements requires data on the flow and the morphological characteristics of the atherosclerotic plaque.

There are a few limitations to the routine use of thermography in the catheterisation laboratory:

• most of the catheters used still comprise over-the-wire systems;
• accurate temperature assessment requires direct contact of the thermistors with the vessel wall, with the associated potential risk of endothelial damage; and
• because the temperature within the vessel changes rapidly with fluid application, any intracoronary injection of contrast dye, flush or medication has to be avoided before and during measurements.

Raman and Near-infrared Spectroscopy

A number of spectroscopic intravascular imaging techniques have been developed recently and are still under investigation. Spectroscopy can provide qualitative and quantitative information about chemical plaque composition. The Raman effect is created when incident laser light (typically 750–850nm wavelength) excites molecules in a tissue sample, which then scatter light at a different wavelength. This change in wavelength, known as the Raman effect, is dependent on the chemical components of the tissue sample and can therefore provide quantitative information about molecular composition. Raman spectroscopy has shown acceptable correlation compared with histology (r=0.68 for cholesterol and r=0.71 for calcification) and with IVUS in vivo. Raman spectroscopy technology collects scattered light with optical fibres and routes the collected signal to spectrometer systems for analysis. Previously, fibre optic probes utilised a region of the Raman spectrum called the ‘fingerprint’ (FP) region (−1,800cm⁻¹ shifted light) to conduct remote assays, but due to technical problems with this approach it has recently been replaced by using another region of the Raman spectrum, called high-wavenumber (HW) Raman shifted light (>2,500 cm⁻¹ shifted light). This allows us to collect Raman spectra via a single optical fibre, simplifying the size and complexity of the catheter and making this method clinically feasible. Thus, the optical catheter system (OCS) (vPredict™) has been introduced as a tool for measuring the chemical composition of coronary vessels in vivo using Raman spectroscopy and the subsequent mapping and quantification of the vessel and plaque components for evaluating plaque progression. In a xenograft model, lipid-laden plaques were identified with the collected Raman spectra by utilising the overall cholesterol content, i.e. the sum of the free cholesterol and cholesterol esters contents, and setting a decision threshold at 12%, as determined in previous studies. As expected, the lipid-laden plaques exhibit an increased free cholesterol and cholesterol ester content, while the non-atherosclerotic samples are mainly protein and triglycerides.

Alternatively, near-infrared (NIR) molecular vibrational transitions can be measured in the NIR region (750–2,500nm), and laser spectroscopy using wavelengths of 360–510nm has been evaluated in vitro. NIR spectroscopy observes how different substances absorb and scatter NIR light to different degrees at various wavelengths. An NIR spectrometer emits light into a sample and measures the proportion of light that is returned over a wide range of optical wavelengths. The return signal is then plotted as a graph of absorbance (y axis) at different wavelengths (x axis), called a spectrum. In aortic and coronary artery autopsy specimens, the ability of the technique to identify lipid-rich TCFA through blood has been confirmed. Initial clinical experience in six patients with stable angina demonstrates that high-quality NIR spectra can be safely obtained. Additional studies are planned to validate the ability of the technique to identify lipid-rich coronary artery plaques and ultimately link chemical characterisation with subsequent occurrence of an ACS.

Treatment

Treatment of asymptomatic, non-obstructive coronary lesions may be a desirable pursuit, but a pre-emptive strike may be a risky, time-consuming and expensive proposition. Assumptions include:

• accepting that the specific pathology can be defined in living subjects;
• presuming that this particular pathology is responsible for future clinical events; and
• presuming that the ‘fingerprint’ of this pathology can be reliably detected.

Based on these assumptions, initial risk stratification of asymptomatic patients drawn from the general population will be required, likely using an early screening method able to detect ‘non-obstructive high-risk lesions’.

Focal Therapy

Myocardial infarctions are typically the result of focal complex or vulnerable lesions, and it is quite reasonable that many interventionalists...
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have suggested treating non-flow-limiting high-risk plaques with the same tools currently employed for symptomatic lesions: bare-metal stents (BMS) or drug-eluting stents (DES). Balloon-expandable metallic scaffolds provide substantial radial forces for dilating hard, obstructive plaques, leading to the unavoidable and uncontrollable dissolution of the vascular structures intended to treat. Restenosis after treatment with a BMS has been curbed by slow-release antiproliferative drug coatings applied directly to the stent. Unfortunately, recent clinical evidence points to an apparent increased risk of late thrombosis as a result of the drug and its effect on endothelial cell functioning and vascular healing, especially in the setting of ACS. Based on these potential risks, these devices, in their current form, do not appear to be a proper approach to pre-emptive treatment of vulnerable or rupture-prone plaques.

It is clear that current practices and available technologies in focal treatment are primarily focused on improving luminal diameter in occlusive plaques and are not well suited to the treatment of vulnerable plaques. More focus is needed on achieving the main objectives of focal therapy: mechanical stabilisation, promotion of vascular healing and reduction of inflammation. If mechanical stabilisation is the objective, the proposed device must find a point of equilibrium between its intrinsic expansive force, radial force and ability to induce excessive vascular injury. Computational finite element and fluid structure interaction models are critical in the development of these devices. Recently, it has been shown that geometrical changes in the shape of the lumen may unfavourably or favourably affect the distribution of local stress, leading to either plaque rupture or reinforcing of the thin fibrous cap. Preliminary data using self-expandable Nitinol-based devices designed with the objective of inducing reinforcement of the cap and necrotic core compression but not cap rupture have been presented. Conceptually, these devices must reinforce the fibrous cap, ‘re-shape’ the necrotic core and mechanically stabilise the lesion at risk of disruption. Another important aspect of device development is the possibility of promoting tissue regeneration in situ. Specifically, the regeneration of the endothelium and recovery of its functionality by means of passive or active endothelial cell attraction is also under development. Ideally, drug elution specifically targeting the inflammatory components of the plaque are required to mitigate the use of these devices.

We are currently investigating whether pro-active treatment (‘shielding’) of a non-invasive imaging-derived rupture-prone plaque is safe. A pilot study designed to investigate intermediate lesions (quantitative coronary angiography [QCA] 40–50%) within the coronary tree remote from the CL is ongoing. The target plaque will be identified by established criteria for IDTCFAs and myocardial fractional flow reserve (FFRmyo) > 0.75. These lesions will be randomised to receive a dedicated vulnerable plaque stent, the VProtect Luminal Shield (Prescient Medical, Inc., Doylestown, PA, US) or standard of care. An angiographic follow-up will be performed at six months on all patients, during which protocol-mandated IVUS-VH, palmpography and OCT will be compared with those obtained in the control group at baseline and post-shield implantation. The study’s primary objective is to determine the feasibility and safety of stabilising a vulnerable plaque by shield implantation.

Conclusion
Several invasive imaging techniques are currently under development for the detection of vulnerable coronary plaques in human coronary arteries in vivo. To date, none of the techniques described above has been sufficiently validated and, most importantly, their predictive value for adverse cardiac events remains elusive. Intravascular palmpography and VH, based on conventional IVUS catheters, appear to be very promising and their predictive role is currently under investigation in a large international trial. Rigorous and well-designed studies are vital in order to define the role of each imaging modality. Non-invasive techniques and the assessment of humoral and genetic factors are complementary and important tools in this direction.

At present, the main purpose of all of these evolving techniques is to improve our understanding of atherosclerotic disease and to define its natural history. Ultimately, the aims are to identify patients at high risk of future cardiovascular events and to evaluate the benefit from either local or systemic therapeutic interventions.