Intravascular ultrasound tissue characterization.
I like the rainbow but... what’s behind the colours?

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Online publish-ahead-of-print 16 June 2008

This editorial refers to ‘The correlation between lipid volume in the target lesion, measured by integrated backscatter intravascular ultrasound, and post-procedural myocardial infarction in patients with elective stent implantation’† by T. Uetani et al., on page 1714

Intravascular ultrasound (IVUS) remains the gold standard for, precise, high-quality visualization of atherosclerotic plaque on the vessel wall. Conventional grey-scale IVUS provides unique insights into the underlying substrate of atherosclerotic disease, and classical studies have demonstrated that plaque echogenicity correlated with its histological composition. However, despite its ability to provide direct insight on plaque composition, grey-scale IVUS has been unable to identify vulnerable plaques. The reason for this appears to be multifaceted. First, the current resolution of the technique is unable to define some subtle characteristics of these plaques, including the thickness of the fibrous cap. Secondly, ‘thrombotic-prone’ plaques have several pathological substrates apart from the classical ‘vulnerable plaque’ (i.e. thin cap fibroatheroma) and, phenotypically, constitute a moving target. Thirdly, further accuracy to identify better the distinct histological components of atherosclerotic plaques with IVUS is clearly required.

What have we learnt from IVUS tissue characterization?

Some technological developments have attempted to overcome the limitations of conventional IVUS to elucidate plaque components. All of them rely on sophisticated mathematical analyses of the raw radiofrequency signal, aim to obtain real-time clinically meaningful tissue characterization, and provide a ‘rainbow’ of appealing colours encoding different plaque components. Direct use of radiofrequency data avoids signal alterations induced by automated processing and gain adjustments.

Integrated backscatter IVUS (IB-IVUS) uses the fast Fourier transformation to analyse frequencies within the signal and provides colour-coded tissue maps of plaque components (lipid, fibrous, and calcified) enabling tissue characterization with a good correlation with histological and angioscopic findings. Some provocative preliminary studies have even suggested that IB-IVUS may allow the detection of changes in plaque characteristics induced by lipid-lowering drugs and could also help to predict future coronary events. Alternative modalities of tissue characterization, namely wavelet analysis of radiofrequency signals, have also been validated to identify lipid-laden plaques.

Virtual histology (VH) uses autoregressive spectral analysis of radiofrequency ultrasound backscatter signals to assess plaque composition (fibrotic, fibrolipidic, necrotic core, and dense calcium). VH data generated from mechanical transducers were validated in human coronary arteries, initially ex vivo and more recently also in vivo using atherectomy specimens, with very good predictive accuracies. However, recent data from a porcine model have suggested that VH may have a limited accuracy to assess plaque components in complex lesions. In contradistinction to IB-IVUS and wavelet analysis, VH has been commercially available (phased-array transducers) for several years and has been widely used around the world, yet good-quality studies supporting its clinical role are surprisingly scarce. Most clinical studies have demonstrated that the amount of ‘necrotic core’ on VH is significantly larger in patients with acute coronary syndromes who also more frequently present thin-cap fibroatheromas as compared with stable angina patients, a notion that is expected according to the dominant pathophysiological paradigms. Necrotic core appears to be more prevalent in proximal vessels and lesions with outward remodelling, high strain, or ruptures. Notably, however, other studies have failed to find these—theoretically appealing—relationships.

Some limitations of IVUS tissue characterization should be acknowledged: first the plaque components identified by each

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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† doi:10.1093/eurheartj/ehn248

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system vary and a uniform colour codification is lacking. Secondly, only some plaque components are identified. Thrombus, for instance, is not recognized by the encoding algorithms and currently there is no information regarding which colour will eventually be given to thrombus-laden lesions (the software is forced to assign colour to every pixel). Thirdly, in contradistinction to grey-scale IVUS, calcium does not prevent the assessment of distal structures, yet the accuracy of the radiofrequency recognition algorithm in this scenario remains to be demonstrated. Indeed, very recent studies suggest that the necrotic core seen surrounding areas of dense calcium may actually be an artefact. This is relevant because VH images often depict relatively large areas of calcium closely surrounded by necrotic core in a typical ‘patchy’ configuration, which is qualitatively different from the classic histological pattern of small, speckled, microcalcifications within relatively large areas of confluent necrotic core. Furthermore, lumen and external elastic lamina boundaries may be difficult to delineate due to signal attenuation, and this could affect measurements of relative plaque components. Finally, in the clinical setting, the accuracy of the pullback system may be suboptimal, especially when the device pulls from the entire catheter shaft, inducing significant friction against the vessel wall, rendering some volumetric data unreliable.

**Can tissue characterization predict the risk of myocardial injury?**

Distal embolization has been widely associated with adverse clinical and angiographic outcomes. Ruptured plaque debris and fragmentation of thrombotic material appear to be responsible for downstream embolization in acute coronary syndromes and also during coronary interventions. Distal embolization has been associated with an IVUS-detected reduction in plaque volume. Conventional IVUS studies have shown that plaque burden, vessel size, lesion length, and images of lipid pools, ruptured plaques, or mural thrombus are associated with the no-reflow phenomenon and myonecrosis. However, some of these features, particularly lining thrombus, are difficult to diagnose with grey-scale IVUS.

Identification of the high-risk plaque for distal embolization remains a challenge during coronary interventions, and tissue characterization might give unique information in this scenario. Furthermore, tissue characterization of plaque components causing embolization or myonecrosis would be perceived as a validation of the clinical utility of this technology, while the diagnosis of vulnerable plaques remains elusive. Accordingly, several studies have focused on the identification of markers of distal embolization in patients with acute myocardial infarction, unstable angina, or stable angina.

Kawaguchi et al. recently demonstrated the value of VH to predict distal embolization in patients undergoing primary stenting for ST-segment elevation myocardial infarction. VH-derived necrotic core volume predicted ST-segment re-elevation, used as a surrogate marker of distal embolization. However, a strong positive correlation was also found between necrotic core and dense calcium volumes, leading to the suggestion that calcium could also be implicated in the aetiology of distal embolization. Nakamura et al. used VH to study 50 patients with ST-segment elevation myocardial infarction treated by primary stenting. The no-reflow phenomenon was more frequently seen in patients with larger plaques and also in patients with ‘marble-like plaques’ (mainly fibro-fatty and fibrous components). However, in this study, the appearance of no-reflow was not correlated to the volume of necrotic core. Finally, in patients electively treated for stable or unstable angina, Kawamoto et al. investigated the relationship between VH findings and high-intensity transient signals by intracoronary Doppler, used as a surrogate for small particle embolization. Notably, plaque components were similar in patients with stable and unstable angina. Vessel size, plaque burden, dense calcium, and necrotic core area, however, were significantly larger in patients with the higher number of embolized particles. Only necrotic core area emerged as an independent predictor of Doppler-detected distal embolization. Interestingly enough, there was a negative correlation between distal embolization and coronary flow reserve after stenting.

Uetani et al. present in an elegant study their results in 114 relatively stable patients undergoing elective coronary stenting; IB-IVUS findings were correlated to the occurrence of myonecrosis (assessed by creatine kinase-MB and troponin-T in single blood samples at 18 h). This is the largest series using tissue characterization to assess implications of plaque components during interventions, and the only series directly assessing myonecrosis and not surrogate markers. Myocardial injury was associated with larger plaque volumes and larger volumes of each component. Myocardial necrosis was directly related to the relative lipid volume and inversely related to the relative fibrous volume. Although significant, the correlation between the lipid fraction \( r = -0.183, P = 0.044 \) and fibrous fraction \( r = -0.185, P = 0.049 \) with post-procedural creatine-MB was rather weak. However, both total lipid volume and lipid fraction were independent predictors of myocardial injury on multivariable analyses. These findings are of special interest considering that, due to the stable patient presentation, the amount of associated thrombotic material would appear to be very limited.

To place all this novel information into perspective, some common methodological issues must be considered. First of all, tissue characterization is currently unable to identify coronary thrombus, a key factor explaining distal embolization according to clinical experience. While it is as yet unclear how VH codifies residual thrombus (fibrous plaque?), thrombus and lipid-rich tissues are difficult to differentiate on IB-IVUS, and this problem may profoundly affect the results of plaque assessment. Secondly, all these studies were single-centre experiences including a small number of patients, thus selection biases cannot be disregarded. Thirdly, the bulk of the friable material near to the lumen may be disrupted with the simple passage of the IVUS catheter (Dotter effect). Therefore, tissue characterization will only be able to analyse the residual material left on the vessel wall. Fourthly, in all these studies, only patients who achieved adequate coronary perfusion before imaging were included. Likewise, thrombectomy devices were recommended in unstable patients and, by protocol, cases with angiographically visible large thrombus and those eventually requiring embolic protection devices were excluded. Finally, neither clopidogrel nor glycoprotein IIb/IIIa inhibitors were administered to unstable patients because all these studies come from Japan where these drugs are not
approved for routine use during coronary interventions. Therefore, all the above results only apply to highly selected patients where the problem of distal embolization was specifically analysed focusing on the risk associated with the final stenting procedure.

**Potential clinical implications**

In aggregate, the information provided by these studies, and in particular by the study of Uetani et al., supports the rationale behind the hypothesis of using tissue characterization to identify patients at higher risk of distal embolization and myonecrosis after stenting. Another interesting challenge for this exciting technology would be the identification of plaques with a higher restenotic risk which, theoretically, could optimize the selection of patients requiring drug-eluting stents. All of these, together with the invasive identification of ‘evasive’ vulnerable plaques, will undoubtedly open up new research venues for IVUS tissue characterization.

Nevertheless, whether this novel information on plaque composition will affect clinical practice remains uncertain. Several randomized trials failed to demonstrate the clinical benefit of distal protection devices in patients with acute coronary syndromes. Therefore, currently, the systematic use of mechanical thrombectomy or distal protection devices cannot be advocated in this setting, although these attractive tools could be of potential clinical benefit in carefully selected patients. Likewise, selected high-risk patients might potentially benefit from more aggressive antithrombotic strategies, including higher doses of clopidogrel, prasugrel, or glycoprotein IIb/IIIa inhibitors, although further studies are still warranted.

Rainbows are beautiful on the skyline and even emotionally appealing but, from a pragmatic standpoint, the best aspect of them comes from their ability to anticipate a change in the weather conditions. Until further validation and additional clinical data are compiled from large-scale, prospective, longitudinal trials (the results of PROSPECT, SPECIAL, and IBIS II are eagerly awaited), we should keep challenging the information provided by tissue characterization, while maintaining our scientific enthusiasm and research efforts to unravel the potential clinical role of this exciting new technology. Ultimately, only a definitive change in the weather forecast—provided by definitive studies with robust clinical end-points—will allow the routine implementation of these persuasive, rainbow-like colours, for clinical decision making, either during diagnostic procedures or during coronary interventions.

**Conflict of interest:** none declared.

**References**