In search of vulnerable features of coronary plaques with optical coherence tomography: is it time to rethink the current methodological concepts?

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This editorial refers to ‘Thin-cap fibroatheroma and microchannel findings in optical coherence tomography correlate with subsequent progression of coronary atheromatous plaques’, by S. Uemura et al., on page 78

Intravascular optical coherence tomography (OCT) is increasingly being used to assess coronary vessel pathology in vivo due to its unrivalled high resolution of 10–20 μm. Previous reports have shown that OCT is capable of visualizing thin-cap fibroatheromas (TCFAs),1 which are thought to be the precursor lesions of ruptured plaques responsible for the majority of thrombosis-mediated sudden death.2 In addition, OCT is able to identify features that have been related to the advancement of atherosclerotic lesions, including neovascularization3,4 and macrophage infiltration.5,6 It is against this background that Uemura and colleagues describe the baseline OCT morphological characteristics of angiographically non-significant, non-culprit coronary lesions exhibiting rapid progression over a period of 6–9 months.7 At a median follow-up of 7 months, 13 (19%) of the 69 studied lesions showed angiographic progression from a mean diameter stenosis of 28.8–61.4%, compared with 28.9–29.3% in the remaining lesions. Progression was clinically silent in all but three patients. OCT at baseline suggested a higher incidence of TCFAs, intraplaque microchannels, lipid pools, macrophages, intimal lacerations, and intraluminal thrombi in the progressed lesions, thus being in line with pathology-driven hypotheses of the role of these features in the progression of coronary atherosclerosis.7

The study is intriguing in that it reports for the first time the innovative concept of using OCT to evaluate potential markers of rapid plaque progression. Nevertheless, the results should be interpreted with caution: first due to the small size and possible selection bias in the evaluated cohort; and secondly, in view of the current methodological concepts. Concerning the former, lesions were selected from the angiogram by the identification of a focal discrete non-significant stenosis (<50% diameter stenosis), thus disregarding important information about the plaque (total burden) at baseline, as this can be visualized neither by the angiographic lumenogram nor by OCT in view of its limited tissue penetration. By the selection of only a very short segment (10 mm of length), other non-significant regions were excluded, thus making it somewhat difficult to generalize the results. In relation to the latter, the study indirectly draws attention to the challenges of developing a methodological approach that accounts for the limitations of present OCT embodiments in characterizing plaque-related features—in particular those of TCFAs. These challenges merit further consideration and will be the focus of this editorial.

Pitfalls in the OCT interpretation of TCFAs

Given the assumed importance of TCFAs in causing clinical events, there is a strong desire in the interventional community to identify and treat these lesions before they cause harm. TCFAs, with their lipid-rich/necrotic cores and thin fibrous caps,8 visualized by OCT as diffusely demarcated signal-poor regions with overlying thin signal-rich layers (Figure 1A and C),1 are often diagnosed with confidence, although there is emerging evidence of several factors that may obscure a correct diagnosis.

First is the intrinsic capability of OCT to distinguish lipid from non-lipid plaques. This capability was shown to be very high in the landmark validation study from 2002 where Yabushita et al. observed an excellent sensitivity and specificity (90–94% and 90–92%, respectively) of OCT for detecting lipid plaques.1 However, subsequent reports have shown conflicting results, which can in part be attributed to the heterogeneity between studies in terms of vessel types (coronary vs. carotid vs. aortic),

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sample sizes, previous experience of OCT observers, and plaque dimensions (small vs. large; superficial vs. deep).\textsuperscript{9–11} Nevertheless, most studies showed a varying degree of misclassification of fibrous plaques into lipid-rich as well as fibrocalcific plaques. Recent data have proposed that the accuracy of plaque characterization with OCT, and then in particular the detection of lipid pools and necrotic cores, may be increased by combining OCT with other intracoronary modalities, such as intravascular ultrasound-virtual histology (IVUS-VH).\textsuperscript{11} Additional improvement in tissue characterization by OCT may also be expected from the application of quantitative analysis techniques involving the measurement of signal attenuation and backscatter intensity.\textsuperscript{12}

A second factor to be considered as differential diagnosis of the TCFA is the presence of macrophages. OCT displays macrophages as punctate, highly backscattering (i.e. signal-rich) structures with significant signal attenuation.\textsuperscript{6} Given the similarities in optical properties, thin bands of accumulated macrophages close to the luminal surface can mimic the appearance of TCFAs (Figure 1D–F).\textsuperscript{13} Recent studies, including the one by Uemura et al.\textsuperscript{7}, point to the fact that macrophage infiltrations are becoming a target of interest in the search for markers of vulnerability. For the time being, the incidence of macrophage accumulations, and to what extent they affect the TCFA diagnosis, remains unknown. However, considering that they are being assessed in parallel with TCFAs, it is highly desirable to identify means that can aid in the differentiation of the two, as well as to assess the reproducibility. The latter would in particular have been interesting to know in the study by Uemura and colleagues.\textsuperscript{7}

 Artefacts represent a third issue that may complicate the correct diagnosis of a TCFA. The most relevant artefacts include those related to the luminal marginalization of the imaging light source, namely ‘attenuation in the line-of-sight’ and tangential signal drop-out, which typically occur when the light beam travels more or less parallel to the vessel wall.\textsuperscript{11} Insights into the technical background of OCT image display is crucial for identifying these features. Their occurrence and, more importantly, how often they cause misinterpretation are presently unknown but certainly deserve further investigation.

**Challenge in the quantification of the fibrous cap**

An additional concern related to the diagnosis of a TCFA is the partly quantitative aspect of the assessment. On the one hand...
there is the cut-off value of the thin fibrous cap, which continues to be a matter of dispute; and on the other hand there is the subjective, manual delineation of this layer. The often used cut-off to indicate a thin cap and thus vulnerability is based on autopsy reports and is 65 µm, as 95% of ruptured fibrous caps causing sudden coronary death were below this threshold. It could be argued that this value may be inappropriate for non-ruptured TCFA s considering that they have less necrotic core, cholesterol clefts, and macrophage infiltration than ruptured plaques, but also because histological processing techniques may cause up to 20% tissue shrinkage. Recent in vivo OCT data from Yonetsu and colleagues support the latter, as they found that 95% of ruptured fibrous caps (visualized as thin signal-rich flaps in relation to cavities) had a minimum thickness of 80 µm, suggesting that this may be a more appropriate value for ruptured plaques. However, a suitable cut-off for non-ruptured plaques still needs to be defined. In this regard, we need first to scrutinize the methods for quantifying the thickness of intact caps.

The current approach is to measure the distance from the arterial lumen to the inner border of the lipid pool at the point where the fibrous cap thickness is considered minimal. To the best of our knowledge, the only available validation study of cap thickness measurement is the one from 2006 by Kume et al. who found a good agreement (mean difference −24 ± 44 µm) between OCT and histology in 35 lipid-rich plaques with histology-derived cap thicknesses between 10 and 450 µm (mean: 138 µm), out of which ~7–8 were histology-defined TCFA s according to the correlation plot. The interobserver variability was low, with a mean difference of 20 ± 59 µm. However low, this difference may be of crucial importance for classifying a lesion as a TCFA or not, in particular for cap thicknesses in the range 45–100 µm, depending on the cut-off value used (65 vs. 80 µm). Further, the process of delineating the cap also deserves some attention: This involves initially the identification by eye-ball ing of the ‘thinnest point’ selected from ‘TCFA-looking’ areas within the longitudinal and circumferential direction, followed by the manual measurement, where a line is traced from the relatively well demarcated lumen contour to the lipid border, which by definition is diffuse. The subjectivity of both steps suggests that this may not be as straightforward as previously anticipated—something that is illustrated in Figure 1C. The additional challenge to assess the same location in a blinded fashion at a later time point, in order to assess progression or regression of the cap thickness, needs no further mention. Bearing in mind that Uemura et al. found TCFA s to be highly correlated with subsequent disease progression, it would have been interesting to know the reproducibility and distribution of cap thickness measurements in the two assessed groups, as well as to what extent a consideration of different cut-off values would have influenced the results.

Rethinking the current methodological concepts

With the above in mind, we can conclude that the issues complicating the TCFA diagnosis require attention; both because prior studies need to be interpreted with caution, and because a number of OCT studies involving the assessment of TCFA s are under way. Considering the mentioned points, the diagnosis of TCFA s could possibly be made more reliable by implementing a phenomenological approach consisting of a number of inclusion as well as exclusion criteria. These could be complemented by semi-automatic techniques to measure cap thicknesses in order to, on the one hand, increase the reproducibility, and, on the other hand, to take full advantage of the large amount of data provided by OCT. For the latter, this could involve the extension of cap thickness measurement to larger areas of the lesion rather than only one specific point, which would provide interesting information about the lesion in general. This information may, together with other assessed features, help us to better understand why some TCFA s cause events while others do not. Moreover, validation of the specific entity of OCT-defined TCFA as well as that of the necrotic core needs to be considered, as this has not yet been performed.

Additional refinements of our methodological concepts should suggestively involve a revision of the manner in which the qualitative findings are reported. In this regard, it may be argued that a semi-quantitative expression of the data may reflect the effect of a certain feature more accurately than a mere binary approach—something that may be important for the further interpretation of the results, as well as for the comparison with other studies. Accordingly, it would have been interesting to know the percentage of frames with TCFA in the two groups studied by Uemura et al., and whether a semi-quantitative rather than a binary reporting of the data could have influenced the final results.

Taken together, an awareness of the limitations of current methodological concepts will allow us to develop ways to circumvent these in order to be able to use the large amount of information provided by OCT more accurately. This may eventually allow us to take full advantage of what OCT can offer in order to better understand the diagnostic benefits of this wonderful high-resolution modality.

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References


