Virtual histology and the hunt for the vulnerable plaque

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This editorial refers to ‘Coronary plaque composition of culprit/target lesions according to the clinical presentation: a virtual histology intravascular ultrasound analysis’ by J.F. Surmely et al., on page 2939

It is a generally accepted concept that acute thrombotic coronary artery occlusion occurs at the site of a vulnerable plaque (VP). Three different types of histopathological entities have been described in coronary arteries from victims of sudden death related to coronary artery disease: (i) plaque rupture, (ii) plaque erosion, and (iii) calcified nodule. A ruptured plaque consists of a necrotic core (NC) with ruptured overlying thin fibrous cap. In plaque erosion, there is a luminal thrombus with proteoglycans and smooth muscle cells and minimal inflammation in the vessel wall. NC is absent or covered with a thick fibrous cap. The calcified nodule consists of deposits of calcifications with discontinuation of the fibrous cap and the absence of endothelium. In autopsy studies on cases of sudden death, thrombi related to the above changes have been seen in 60, 30–35, and 2–7% of the cases. The pathological studies indicate that prior to plaque rupture with thrombosis, the plaque was an inflamed, thin cap fibroatheroma (TCFA) or a VP resembling a ruptured plaque without the rupture itself.

It would be highly desirable to be able to detect a suspected VP before it causes thrombosis and acute myocardial infarction (AMI). The latest technology developed for this purpose is spectral analysis of intravascular ultrasound (IVUS) radio frequency data. This technique has improved the tissue characterization in coronary artery disease to a degree that it is called virtual histology (VH), as it has been found to have a very close correlation with histopathological findings from cadaver arteries. In the VH analysis, four histological tissue components (fibrous, fibro/fatty, NC, and calcium) are correlated with the radio frequency data and given a colour code (green, greenish-yellow, red, and white, respectively). VH analyses have been found acceptably reproducible.

It can thus be hypothesized that (i) the underlying cause of coronary artery occlusion is the development of atheroma with necrotic lipid core (VP) that ruptures and leads to coronary thrombosis; (ii) VP can be detected by VH; and (iii) PCI on VP stabilizes the lesion and improves prognosis.

Testing of hypothesis includes establishing a connection between VH-defined VP and (i) acute coronary syndromes (ACSs); (ii) clinical outcome; and (iii) treatment of VP with improved prognosis.

VH studies on coronary patients have been very few. Rodriguez-Granillo et al. investigated 55 non-significant, non-culprit lesions in 23 patients with ACS and in 32 patients with stable angina pectoris (SAP). Zero per cent of the patients had at least one TCFA, which were more frequent in ACS than in SAP (TCFA was defined as >40% plaque burden and >10 NC). The amount of NC and total plaque burden were the same in both the groups. However, in a later publication on the same patient population, the authors describe more NC but less fibrous atheroma in ACS than that in SAP.

The same group has also reported a three-vessel VH study on 40 patients (13 SAP and 27 ACS). Plaque rupture was seen in 31% in SAP and 59% in ACS. There were no differences with respect to VH analysis between the two clinical groups. Comparison between culprit/target and non-culprit/target lesions showed highest plaque burden in the former. The area (mm2) of NC and calcium was larger in ruptured plaques than that in the non-ruptured plaques, although the per cent area was the same. Body mass index was positively related to the plaque rupture.

Surmely et al. further contribute to our knowledge on VH. They report a study on target lesions in 85 patients (28 ACS and 57 SAP). Grey-scale IVUS showed more positive remodelling, more echoluent area, and more frequent intraluminal thrombus in ACS than in SAP. At the site of the minimal luminal diameter, the per cent amount of fibrous atheroma was larger, and NC and calcium contents were smaller in ACS than in SAP. There was no significant difference when the area was measured in mm2. Volume measurements over the entire lesion length showed more fibrous atheroma in ACS than in SAP (both pct. and mm3), whereas there was no significant difference in the volume of NC. The occurrence of TCFA was not different between the clinical groups. TCFA was defined as plaque burden of >40% and amount of NC >20%.

At this moment, we are just on the first step of the above hypothesis testing. We have data indicating that there are more NC and calcium in ruptured than in non-ruptured plaques, but there is, as a whole, no difference in VH data between ACS and SAP patients when all vessels are
studied; there are conflicting reports regarding the amount NC in non-culprit lesions in ACS compared with SAP, and there is less NC in ACS than in SAP in culprit/target lesions.

An interesting new picture seems to emerge from the present VH data indicating that in living ACS patients, the culprit lesion and basis for thrombus often is an erosion and not a ‘classic’ TCFA.

It can be hypothesized that when a classic TCFA ruptures, it is prone to give rise to a massive thrombus with ST-elevation AMI, compared with possibly more fleeting thrombi over an erosion causing non-ST-elevation AMI and unstable angina. It remains to be clarified to what degree it is VH-defined TCFA that ruptures.

The VH tissue characterization has its limitations. Intraluminal thrombus must be excluded visually/manualy as it would be given the same colour as fibrous tissue. Calcification and NC are partly combined in the same red colour (necrotic calcification). TCFA cannot be identified on the basis of cap thickness, which is <65 μm (VH resolution 100 μm). Furthermore, it has not yet been established which VH criteria are the most adequate to define a VP: the quantity of plaque burden; amount of NC and its distance from the luminal surface; plaque content quantification in pct., mm², or mm³; and analysis of single slices or plaque volume measurements.

There is solid evidence for improved prognosis when angiographic culprit lesions are treated with PCI in ACS patients, whereas the existing evidence is against PCI of non-significant lesions (‘plaque sealing’).

The present VH experience is not very supportive of the idea that the classic VP is the dominant culprit around even in ACS patients. Probably, any plaque can be eroded and be substrate for thrombus development, making the VH picture too unspecific for reliable identification of future culprit plaques.

However, at present, it is probably justified to conclude that a plaque with only fibrous content by VH can be considered as stable with minimal risk of causing thrombosis. Identification of low risk plaques at crucial locations can thus already be of some clinical value.

It is probable that in the future, VPs have to be identified together with patients at increased risk of thrombotic cardiovascular events incorporated in a multivariate score including history, clinical data, coronary risk factors, coronary angiography, data from grey scale IVUS, VH, lipid profile, inflammatory markers, and coagulation data. There has never been a simple answer to a complex diagnostic problem.

The ongoing PROSPECT study will provide important information on the clinical significance of VH analysis. The study has included 700 patients who have been treated with PCI for ACS. Non-culprit, non-flow limiting lesions have been studied by VH and the outcome of the patients will be related to VH findings. The clinical follow-up is in progress.

The VP seems to be an evasive animal with different disguises, but we hunters are closing in.

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References