For years, patients have been under the misconception that a coronary intervention of a coronary stenosis was “preventing an impending heart attack.” As cardiologists, we know better. In stable coronary artery disease, when we perform a coronary intervention, we do not know if the target site is going to evolve into a ruptured plaque and result in acute coronary syndrome. Prediction and prevention of an acute coronary syndrome is what the patient wants and what we have been striving for years but with much frustration. We know the characteristics of a vulnerable plaque (a large plaque burden with positive remodeling, a large lipid core with a thin fibrous cap, and evidence of macrophage infiltration, to name a few) but remain handicapped in our ability to find an imaging modality that can reliably identify which plaques will indeed rupture and which will not. Inability to foresee which one of the multiple ruptured plaques would cause an acute coronary syndrome further complicates the task of prediction.

Virtual histology (VH) intravascular ultrasound (IVUS) has been an exciting step forward for intracoronary ultrasound. The technology uses a proprietary algorithm that assesses the returning ultrasound signal to seek information about plaque morphology. Conventional gray-scale ultrasound relies on the amplitude (or strength) of the returning radiofrequency signal to provide gross classification of morphology (hard, soft, and calcified). Simply stated, a hard or calcified surface will reflect more ultrasound back to the transducer so it will appear brighter (or whiter) on the screen. More advanced quantification of the radiofrequency signal, before postprocessing (used to form a better image), is the basis for integrated backscatter–IVUS. Integrated backscatter–IVUS has been used primarily by investigators in Japan to successfully study several aspects of plaque characterization.1,2 VH-IVUS also uses the amplitude information but adds to this information an assessment of the radiofrequency signal. The concept is that different tissue types will alter the radiofrequency signal in different ways, and, by developing an algorithm with known plaque types, unknown components of a human atheroma can be identified.3 A similar method that also uses the radiofrequency signal from known morphologies to classify new signals has recently been introduced by Boston Scientific Corporation (Maple Grove, Minn) and is called iMap technology.4

All 3 IVUS plaque characterization techniques (integrated backscatter–IVUS, VH-IVUS, and iMap) have undergone pathological validation, and all have now been applied clinically. Although all 3 are commercially available somewhere in the world, only VH-IVUS is broadly distributed across many countries. Because of the widespread experience with VH-IVUS, it has become the source of critical review. The concerns raised are, for the most part, reasonable and based on historic perspective and personal experience. Skepticism about ultrasonic tissue characterization is longstanding. For more than 4 decades, scientists have been trying to perfect echocardiographic tissue characterization of the myocardium, with very limited success. Many factors can alter the radiofrequency signal reflected from the tissue (plaque) besides the tissue characteristics, and these alternations have become fatal flaws with most tissue characterization techniques. Many had renewed optimism with IVUS. IVUS is thought to be the ideal candidate in which to apply tissue characterization, given its high frequency, close proximity to the region of interest, and lack of structural barriers between the transducer and plaque. However, despite the high hopes, skepticism has quickly risen about the accuracy of VH-IVUS shortly after it was introduced. Many with practical experience with this technology in the catheterization laboratory have noted that small movements of the catheter can produce large changes in the plaque classification. Although this can be due to true changes in morphology millimeter by millimeter, it also may be due to artifacts created during signal processing. An example of this is a new “necrotic core” that appears immediately on placement of a stent. Obviously, necrotic core cannot appear within a few minutes of stent placement, but rather VH IVUS misinterprets the tissue around a stent strut as necrotic core because of the influence of the highly reflective strut.5

Given these concerns, Thim et al6 at Aarhus University in Denmark and the Cardiovascular Research Foundation in New York performed an independent validation study of VH-IVUS, using a swine model. They chose to concentrate on validation of the necrotic core size, a reasonable approach given the importance of the necrotic core in determining if a plaque is vulnerable, with the markings of a thin-capped fibroatheroma (TCFA). In 18 advanced lesions in the adult atherosclerotic-prone minipig model, there was no correlation between the VH-identified necrotic core and the true “gold
standard” necrotic core size by histology. Most of the VH necrotic cores were not determined to be necrotic cores on histology, and most of the true necrotic cores were not recognized as such by VH-IVUS. In fact, the disparities were not subtle. The figures from this article are remarkable for the gross misclassification of plaque morphology by VH-IVUS.

Although this study does raise further concern about the accuracy of VH-IVUS, it is important to also review the details of the study before drawing definitive conclusions. Thim et al used a swine atherosclerotic model. Although this is used for many interventional studies, its utility for plaque characterization must be carefully considered. As the authors note, swine atherosclerosis lacks cholesterol crystals and is different from human necrotic cores. VH-IVUS was developed and validated on human plaque (and necrotic core) anatomy; therefore, expecting it to perform well on an animal model may not be reasonable or fair. Ultrasonic reflection from a lipid pool (with very few interfaces) is expected to be markedly different from an area with “cellular debris” with several interfaces on which to reflect ultrasound. Even if we use simple, gray-scale IVUS, a human (lipid-filled) necrotic core would have a low-amplitude signal (appearing dark), and a swine (cellular debris-filled) necrotic core would have a higher amplitude (appearing whiter). It is counterintuitive to expect the ultrasonic signal that is characterizing the plaque to be the same if the characteristics of the plaques are different.

Another limitation identified by the authors is the difficulty encountered in aligning IVUS images with histology images. In this study, histology was obtained every 4 mm and registration with the IVUS images was performed using fiduciary landmarks. This is the standard method to perform IVUS histology validation, and it is clear that the authors paid particular attention to this issue. Nonetheless, when plaque characteristics can change so dramatically over the course of the plaque length, accuracy to within 4 mm may not be good enough. This is another source error that will appear as a mismatch of VH-IVUS and histology, despite the most meticulous care by the investigators. Finally, it should be noted that there are several routine practices in an animal laboratory that could also affect the quality of the VH-IVUS data. VH is only as good as the radiofrequency signal available from the IVUS transducer and the signal processing available. In an animal laboratory, catheters are often reused, and other equipment that emits radiofrequency signals are often in use. Both of these things, if relevant in this study, could have altered the results.

Although it is intellectually interesting to debate the technical advantages and limitation of ultrasonic vulnerable plaque imaging and whether this study discredits VH-IVUS, the real question is: Does any of this matter for the patient? The PROSPECT study was recently presented, which addresses this question directly by prospectively evaluating patients with VH-IVUS and following them for clinical events. Although the preliminary results of the yet to be published PROSPECT study showed that, across the population studied (700 patients with acute coronary syndromes), there was a statistically significant relationship between VH-IVUS findings and clinical events \( (P=0.0002) \). Many of the events were worsening angina requiring coronary interventions rather than development of acute coronary syndromes. Furthermore, the incremental value of VH-IVUS was relatively small. In fact, all coronary locations responsible for nonculprit major adverse coronary events had a plaque burden of \( \geq 40\% \) by gray-scale IVUS. No coronary segment with \( <40\% \) plaque burden resulted in a nonculprit event during the median of the 3.4-year follow-up period. This reinforces that plaque burden, as identified by conventional gray-scale IVUS, remains an important parameter for identification of areas of the coronary artery at risk and raises questions about the role of VH-IVUS to be helpful for individual patients and individual lesions. PROSPECT also provided important information about the natural history of VH-IVUS–identified TCFA. In this study, 75% of TCFAs heal spontaneously. If the vast majority of TCFAs heal spontaneously, then an invasive treatment strategy is not warranted. In fact, with the knowledge that most TCFAs will resolve, the use of an invasive imaging strategy (even if it were perfect at identifying a TCFA) would not justify the small but present risk of performing invasive imaging in the absence of clinical benefit. This finding also calls into question of whether a VH-IVUS identified–TCFA is indeed the vulnerable plaque, if we are to identify “vulnerable” by clinical standards. VH-TCFAs may be at higher risk of rupture, but the fact that the majority of these VH-TCFAs are clinically silent means that the clinical utility of identifying one in a single patient is minimal.

Why the disappointing results and continued inability to identify a plaque that causes a clinical event? Well, development of acute coronary syndrome is complicated. There is a high variability from patient to patient and plaque to plaque. The concept of “vulnerable plaque” waiting to rupture and cause myocardial infarction is an oversimplification of a very complex interaction of plaque–blood flow and hematologic characteristic resulting in a highly variable clinical course. The imaging is complicated as well, with its inherit variability. Whenever so many factors are involved and produce a dynamic interplay of events, accurate detection of a clinically relevant “vulnerable plaque” will remain extremely difficult. Much work remains ahead, but, in the meantime, we must decide where VH-IVUS fits within our armamentarium of clinical imaging modalities. The article by Thims et al adds to the questions and concerns about the accuracy of VH-IVUS. However, in perspective, this study probably just reinforces the fact that these imaging modalities (as well as all IVUS plaque characterization modalities) have a high degree of variability. They are almost certainly an improvement in plaque characterization over gray-scale IVUS and will continue to have a future in clinical trial assessments of plaque natural history and interventions (where the strength of large numbers will outweigh the variability in individual images to provide meaningful results). However, given the current limitations and variability in individual IVUS-derived plaque characterizations and limited clinically relevant incremental predictive value, VH-IVUS and all other IVUS plaque characterization modalities are probably best used across patients rather than for clinical decision-making based on a single image.
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References

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