Intravascular Ultrasound Volumetric Quantification: the Current "Gold Standard" for Characterization of Coronary Artery Disease

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Ultrasound examination of coronary artery disease became possible after the development of miniaturized transducers. After 2 decades,[1] intravascular ultrasound (IVUS) has evolved into a mature technology. In spite of multiple failures to demonstrate the utility of IVUS to improve clinical outcomes after percutaneous intervention, IVUS remains an integral part of interventional cardiology because of its ability to provide information on the lumen, vessel wall morphology, and atherosclerotic plaque characteristics. Beyond technological advances, which included development of catheters with lower profile and higher frequencies, development and improvement in quantification techniques have played a major role in the integration of IVUS into routine clinical practice and research protocols.

The growing interest in plaque characterization as a mean to predict arterial thrombosis may be unrealistic. However, this has triggered the development of novel imaging modalities, including non-invasive methods such as multi-slice computer tomography, and a revisit to the core concepts of IVUS technology. IVUS images are captured during withdrawal of a miniaturized ultrasound probe mounted on an intravascular catheter (typically <3F in diameter) through a vessel segment during continuous imaging. This results in a series of cross sectional images which are continuously acquired in a rate of 20-30 images per second—near real time. IVUS imaging only provides a 360 degree axial or tomographic image of the vessel. Assuming a constant speed (0.5 or 1 mm per second) and straight pullback trajectory, volumetric quantification of vascular structures have been performed based on the sum of IVUS cross-sectional areas (Simpson's rule).[2] This can be performed manually, which is extremely time consuming or via semi automated contour detection algorithms, as proposed in the the study of Sanz et al in this issue of Revista Española de Cardiología.[3] Images are displayed in only 2 dimensions (cross-section or longitudinal views), but volumetric quantification has been referred to as three-dimensional IVUS imaging. Notably, three-dimensional IVUS techniques have been extremely important to document the effects of coronary therapies.[4-6]

IVUS has several limitations which are inherent to the technology and should not be forgotten. At typical frequencies of 30 to 40 MHz, axial resolutions of 200 μm are achieved, which limits its ability to define the atheroma cap thickness. A spatial resolution lower than 70 μm is required to properly evaluate the fibrous cap. Nevertheless, among the clinically approved technologies, IVUS has the highest resolution, which compares quite favorably with non-invasive methods. Magnetic resonance imaging and remains with resolutions above the "millimeter," which is certainly inadequate not only for cap thickness evaluation, but for plaque characterization as well. The assumption of a steady and stable pullback of the catheter is also part of the basics of volumetric quantification. However, such assumption is far from reality as one can observe as much as 5-mm longitudinal displacement of the IVUS catheter because of cardiac cycle and vessel movement.[7] One way to overcome such hurdle is to integrate an ECG-gated pullback system[7] as opposed to the commercially available time-based pullback devices, or retrospectively trigger the IVUS image based on ECG.[8] One should realize that the speed of the signal between IVUS image and ECG is different, thus retrospective ECG gating should be done on raw ultrasound signals rather than using the ECG tracings displayed on the IVUS images. Finally, the visual display of a straight coronary vessel does not correspond with the true spatial configuration of the coronary artery, but this should not affect the volumetric quantification because it is based on individual cross-sectional images.

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Highly automated techniques, as proposed in the accompanying article (3), which do not require significant user interface for border detection are extremely important. It reduces inter-observer variability and decreased the operators' bias, providing a true independent and non subjective evaluation of the vessel wall. However, a fully automated interpretation of IVUS image has yet to be developed. There are currently 3 main companies that commercialize quantitative IVUS systems which are used by most core laboratories worldwide: INDEC Imaging Systems, Inc based in the United States, Pie Medical Imaging BV (Maastricht) and Medis Medical Imaging Systems BV(Leiden) in The Netherlands. Longitudinal reconstructed (L-mode) views at 5° increments are displayed. The Medis and INDEC systems use minimal cost algorithm and segmentation similar to the original platform from Tomtec Imaging Systems GmbH (Germany),[4] in which contours are made primarily in individual cross-sectional images. The system commercialized by Pie Medical applies the concept of Bezier splines. The resulting cross-sectional Bezier contours can be visualized immediately superimposed on a running video loop and may be edited manually. The mathematical description consists of a connected series of Bezier curves, which allows contours to be drawn automatically in the longitudinal images. This allows for a much faster quantification process. The report of Sanz et al[3] applies a similar concept of transposing the quantitative measures to the adjacent segments and allows the correction when images are not well aligned. This algorithm appears to add speed to the process, although such statement would require proper comparison between methods. The validation of these systems have been limited to small sample size studies, such as the current report, which is somewhat inadequate for the wide spectrums of variability in coronary anatomy. Moreover, it is difficult to define the gold standard to validate a new 3-D border-detection methods Image quality and vessel movement, as discussed by the authors, are common limitations which impacts any contour detection algorithms and usually requires more operator interference. Unfortunately, image artifacts are more common than expected.[9] Typically 10%-20% of images can be lost because of poor imaging acquisition in clinical studies. Nevertheless, 3D-IVUS has become an integral part of clinical research and improvement in current algorithms is always welcome.

Many recent brachytherapy and drug-eluting stent trials benefited from 3D-IVUS measurements. Such therapies often require a more refined method of evaluation to provide subtle distinctions between therapies or evaluate for potential new pathological side effects which cannot be appreciated by angiographic methods.[10-12] 3D-IVUS also plays an important role to evaluate the heterogeneity pattern of the atherosclerotic and restenotic processes.[4,5,13,14] Mechanistic interpretation of vascular effects of new therapies can only be made by the use of IVUS as pathological changes in the vessel wall, such as excessive remodeling, stent malapposition or dissections can only be determined by quantitative 3D-IVUS.[15,16]

More recently, a series of atherosclerosis progression or regression trials were launched and gained the spotlight based on quantitative IVUS measurements. The ASTEROID trial suggested that very high-dose statin therapy reducing an average LDL-cholesterol to approximately 60 mg/dL resulted in regression of atherosclerosis by means of IVUS volumetric measurements[17]. This study did not use semi-automated quantitative algorithms, but the robustness of using IVUS volumetric measurements as primary end points in mega pharmacological therapy trials is illustrated. However, one should interpret such results with caution. Although properly designed and applied statistics may discriminate differences in plaque volume over time, small differences of less than 5% may be due to the intrinsic variability of the repeated measurements, as illustrated by the accompanying article (Tables 1 and 2).[3] Thus, one needs to account for the method variability beyond a pure statistical interpretation of IVUS results to really differentiate between plaque progression, regression or no change in plaque volume. We should also remind ourselves that prevention of plaque development and clinical events caused by either plaque rupture or erosion remains the ultimate goal. Given that plaque composition becomes more stable and less prone to thrombosis, one may be allowed to even experience a small progression of plaque volume, but such hypothesis remains to be tested. Likely, volumetric quantification of different plaque components represents the next step in 3D-IVUS methodology, although such goal appears more challenging because of the properties of ultrasound imaging. Above all, a systematic approach to image quantification using proper methodology and interpretation of the results is as important as the quantitative algorithm itself.

Although IVUS technology has been around for many years, our understanding of the atherosclerotic process remains in its infancy. The knowledge and experience accumulated with IVUS-based imaging represents the foundation for the future of cardiovascular imaging. Integrative efforts combining engineering and medical expertise as proposed by Sanz and co-workers[3] and continuous development of new quantitative algorithms and analysis techniques remains of paramount importance for scientific progress in our field. Application of such quantitative algorithms in upcoming imaging modalities appears as a natural transition. It is nevertheless important to

notice that IVUS still remains the only "high" resolution, approved and widely available technology, which will certainly play a major role for in vivo validation of the new upcoming technologies for atherosclerosis evaluation.

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