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Volumetric intracoronary ultrasound: A new maximum confidence approach for the quantitative assessment of progression-regression of atherosclerosis?

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Abstract

Quantitative assessment of atherosclerosis during its natural history and following therapeutic interventions is important, as cardiovascular disease remains the most significant cause of morbidity and mortality in industrial societies. While coronary angiography delineates the vessel lumen, permitting only the indirect determination of atherosclerotic wall changes encroaching upon the lumen, intracoronary ultrasound permits direct plaque assessment and quantification. The angiographic percent diameter stenosis, previously suggested as measure of a maximum confidence approach, is still commonly used to quantify stenosis severity, but the reference segments which are required for angiographic interpolation of the normal vessel dimensions are frequently involved in the general process of atherosclerosis, including progression or regression. Considering also the variability of vascular remodeling during the evolution of atherosclerosis, including compensatory enlargement and paradoxical arterial shrinkage, intracoronary ultrasound appears currently to be the only reliable technique to measure plaque burden and progression or regression of atherosclerosis. However, correct matching of the site of measurement at follow-up with the site of the initial ultrasound study is often difficult to achieve, but is significantly facilitated by the use of volumetric intracoronary ultrasound. This approach permits not only area measurement, but also measurement of plaque volume, which appears to be the ideal measure for quantifying the atherosclerotic plaque, as it is highly reproducible and directly reflects the changes of an entire arterial segment.

Keywords: Coronary artery disease; Progression-regression; Vascular remodeling; Intravascular ultrasound; Volumetric quantification; Plaque volume; Atherosclerosis; Three-dimensional reconstruction

1. Introduction

Coronary artery disease (CAD) remains the cause of death and disability in the industrialized countries, despite our increased knowledge about

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the pathogenetic mechanisms of atherosclerosis [1–5] and our subsequently increased awareness and management of unfavourable risk factors including hypercholesterolemia hypertension, obesitas, smoking and psychological stress. The search for effective interventions remains and the reliable quantitative assessment of atherosclerosis during its natural history and various therapeutical interventions is thus of paramount importance and required in order to define the efficacy of these therapeutical measures [6].

During the last two decades, coronary angiography has been considered the standard method to evaluate the coronary anatomy. The development of semi-automated quantitative angiography in the late 1970s [7] and its clinical application to interventional cardiology in the early 1980s [8] allowed the replacement of visual assessment by a semi-automated approach [9–11], providing objective and reproducible measurements of luminal dimensions. However, coronary angiography delineates only the vessel lumen as a silhouette, a perspective that is incapable of reflecting the irregular nature of the atherosclerotic vessel wall changes. Thus, plaques may be present in angiographically normal segments.

A prognostic value of angiographic endpoints has been demonstrated for both visual assessment and semi-automated coronary angiography [12,13], but the limitations of angiography may explain the minimal changes in luminal dimensions observed in large angiographic studies, aimed at the assessment of progression or regression of coronary atherosclerosis during pharmacologic or dietary interventions [14]. Particularly the use of the relative percent diameter stenosis, recently suggested as the angiographic measure of a maximum confidence approach to quantify stenosis severity [15], nowadays appears to be doubtful, as the angiographic reference segments themselves are frequently involved in the general process of atherosclerosis, including progression or regression. Accordingly, new quantitative coronary imaging techniques such as intracoronary ultrasound, which permits the direct qualitative and quantitative assessment of the coronary plaque, may provide an important addition to the understanding of the natural history and prognosis of coronary atherosclerosis as well as the potential of pharmacological interventions [11,16,17]

2. Current angiographic measures and their limitations

The distribution of atherosclerosis can be either focal or diffuse [18]. If the process of atherosclerosis is predominantly diffuse, relative measurements are unable to quantify plaque severity, explaining the findings of several pathologic studies which indicate that angiography may underestimate the extent and severity of the atherosclerotic changes [19–22]. The angiographic percent diameter stenosis [15] is commonly used to quantify stenosis severity, but the 'normal' reference segments which are required for the calculation of the relative lumen diameter stenosis are frequently involved in a general process of atherosclerosis including progression or regression, thus suggesting pseudo-progression or pseudo-regression [11,23–25]. Furthermore, a relative parameter does not accurately reflect the functional significance of the lesion [26], since lesion length and absolute luminal dimensions are not taken into account. Indeed, such an approach to quantify progression or regression of atherosclerosis appears to be far away from 'a maximal confidence'.

Absolute measurements such as minimal or mean luminal diameter generally appear to be superior indicators of stenosis severity [27–29] or progression of atherosclerosis [30]. However, the minimal luminal diameter which is the most important determinant of the functional significance of coronary stenoses [26,27] is also crucial, since an increase of the lumen diameter at the site of the minimal luminal cross-section can be associated with an overall reduction of the mean lumen diameter. Nevertheless, the mean lumen diameter is the best angiographic measure to determine progression or regression of diffuse atherosclerosis of entire coronary segments [23].

3. Potential and limitations of two-dimensional intracoronary ultrasound

Intracoronary ultrasound is a relatively new method which provides cross-sectional images of both the vessel lumen and wall. The size of the ultrasound transducers had gradually been reduced so that recently introduced ultrasound catheters have a distal tip diameter of even less than 1 mm.

The sensitivity of intracoronary ultrasound in detecting minimal atherosclerosis is superior to angiography [31–35] and additional qualitative information on the plaque composition [31,36–40] is provided. Plaque thickness can be directly quantified by ultrasound [41], a feature which was first utilized during epicardial high-frequency ultrasound imaging [42], a forerunner of intracoronary ultrasound. Direct measurement of the vascular dimensions by intracoronary ultrasound can nowadays be performed with high accuracy [31]. Finally, the safety of the invasive intracoronary ultrasound examination, particularly if performed during diagnostic catheterization [43], should be emphasized.

Many problems of the first generation intracoronary ultrasound catheters have been solved or minimized and the image quality has been significantly improved, but the angle of incidence of the ultrasonic beam is still important, since a non-coaxial position of the transducer may result in a distortion of the ultrasound image [44]. Plaque compression by the ultrasound catheter at vessel curvatures and the lateral or out-of-plane resolution of current ultrasound transducers remain fields of future improvement [45].

4. Insights gained from studies of vascular remodeling

Coronary angiography detects atherosclerotic changes in the vessel wall only if the plaque encroaches the lumen. This does not occur during the early stage of plaque expansion as demonstrated by Armstrong et al., who detected in monkeys during an atherogenic diet an enlargement of the coronary artery in response to luminal encroachment by the coronary plaque [46–48]. These experimental findings were confirmed by Glagov et al. [46] in human coronary arteries, demonstrating in histological sections of the arteries an enlargement of the total vessel area as plaque area increases. This mechanism appears to be capable of compensating for an increase of plaque burden until the plaque occupies 40 percent of the internal elastic membrane area.

As a consequence of the compensatory enlargement of the vessel, luminal area may be preserved, as seen angiographically despite extensive CAD. Stiel et al. confirmed in a study comparing post-mortem quantitative angiography with morphometric analysis on histologic sections of the coronary arteries that compensatory enlargement of diseased coronary segments results in a significant angiographic underestimation of coronary atherosclerosis during the early stage of the disease [49].

The compensatory enlargement of the coronary arteries during the early progression of atherosclerosis does not represent any problem for the quantitative assessment by intracoronary ultrasound. The method itself can even be used to study the mechanism of the arterial remodeling [50]. Ultrasonic confirmation of the compensatory enlargement during evolving atherosclerosis was first performed non-invasively, using epicardial high-frequency echocardiography [51] and carotid duplex scanners [52], and was subsequently demonstrated by intravascular ultrasound in coronary [53–55] and femoral arteries [56].

Thus, coronary angiography is unable to detect and quantify the early stage of evolving atherosclerosis, while intracoronary ultrasound permits direct inspection and measurement of the plaque burden without need for interpolation or reference segments, clearly demonstrating its superiority in assessing the early phase of atherosclerosis.

In order to correct the angiographic measurement of the percent diameter stenosis during later stages of atherosclerosis, a correction for the compensatory enlargement of the artery could theoretically be performed, if coronary remodeling occurs in all arteries in the same way. However there is evidence that some arteries show remodeling while others do not enlarge and even seem to show a reverse modeling. Such a 'paradoxical arterial wall shrinkage' has been described by Pasterkamp et al. in human atherosclerotic femoral arteries [57]. It remains unclear in how many cases this 'reverse Glagovian modeling' accounts for or contributes to the luminal narrowing. Current concepts of vascular remodeling are based on a complex interaction between growth factors, vasoactive substances, pressure, flow, and shear stress, while the endothelium plays an important role as the sensor and transducer of signals [50,58–60]. Disturbance of this balance or the enlargement of the distal post-stenotic reference segment may result in 'arterial shrinkage'.

Our experience with three-dimensional intracoronary ultrasound (Fig. 1) demonstrates that a reverse vascular modeling also occurs in coronary arteries. In this light, a correction of the percent diameter stenosis, measured by quantitative coronary angiography, appears to be highly questionable. If there is such a variability of vascular remodeling and if the plaque may grow inside or outside of the coronary lumen, intracoronary ultrasound appears to be currently the only reliable technique which permits a direct measurement of plaque burden and progression or regression of atherosclerosis.

5. The benefit of the third dimension in intracoronary ultrasound

After the introduction of intracoronary ultrasound in research and clinical use, a substantial role of this technique in the assessment of progression or regression of coronary atherosclerosis will be expected. Indeed, the accuracy [61] and in vivo feasibility [62,63] of intracoronary ultrasound has been well demonstrated in experimental stud-

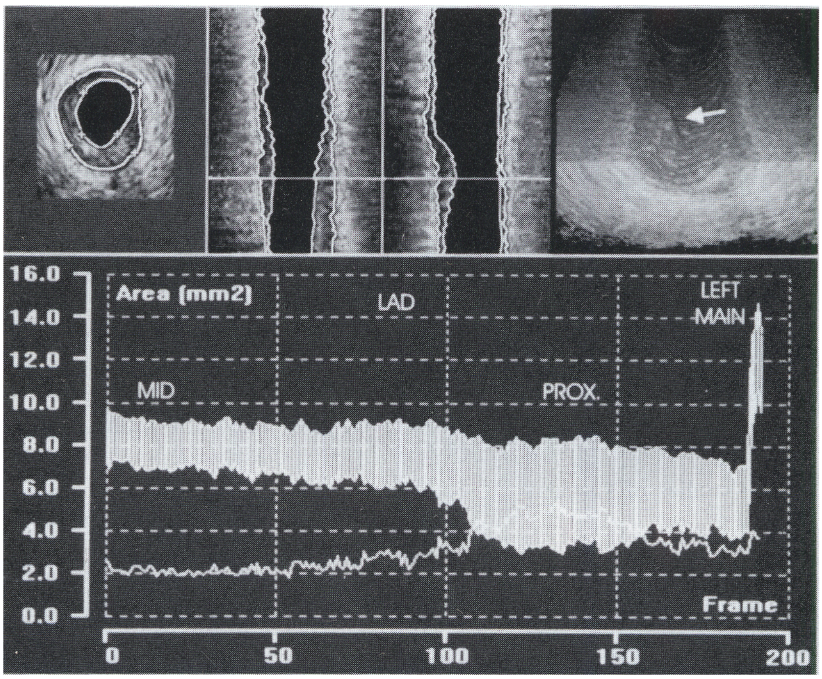

Fig. 1. Primary lesion in the proximal segment of the left anterior descending coronary artery (LAD), assessed by a new system for quantitative analysis of three-dimensional intracoronary ultrasound images. The cross-sectional ultrasound images, representing a segment of round 10 mm length, were reconstructed in two perpendicular longitudinal sections (mid panels). A computerized contour detection was performed providing a three-dimensional view (right upper panel; arrowhead indicates target stenosis) and area measurements (mm^2) of the lumen, plaque, and total vessel on 200 consecutive ultrasound frames (lower panel). The values of the plaque area are shown as a white field between two lines, representing the absolute values of the total vessel and lumen areas. The absolute value of the plaque area can be derived from this white field, but is also displayed as a single white line. The area stenosis at the site of the mid segment of the LAD was round 20%. According to the mechanism described by Glagov, an enlargement of the total vessel area, partly compensating the plaque burden, may be expected at the site of a relatively focal plaque. In the measurement display of this case, however, a paradoxical reduction of the total vessel area from the distal reference in the early mid LAD (MID) to the target stenosis in the proximal segment (PROX) was observed. Plaque volume of the entire arterial segment was 32 mm^3.

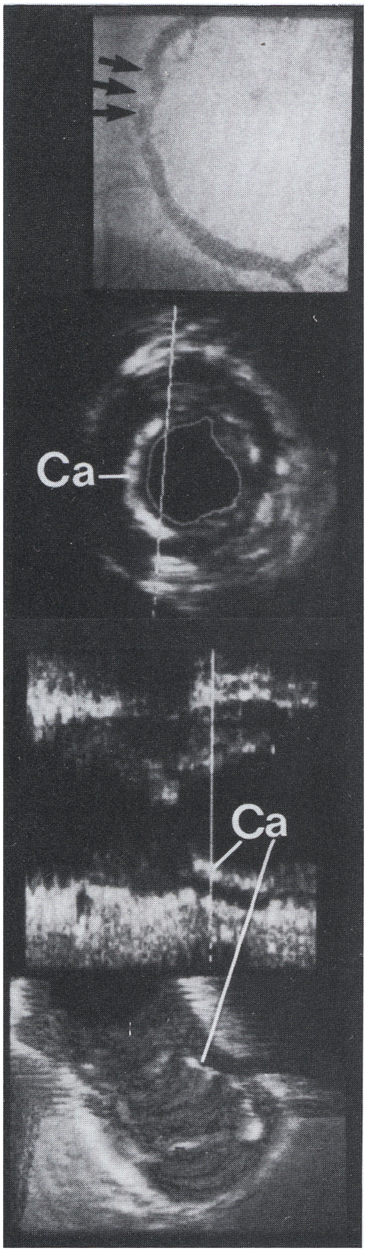

Fig. 2. Calcified lesion in a mid right coronary artery. Arrowheads in the angiogram indicate the segment which was reconstructed. The superficial calcification is visible in the cross-sectional, longitudinal, and three-dimensional cylindrical view (upper mid, lower mid, and low panel respectively). The longitudinal and cylindrical displays permit a much more comprehensive insight into the complex spatial distribution of the plaque.

ies of progression or regression of atherosclerosis. The principal reason why this technique has not yet been introduced to major human progression-regression trials are the difficulties with correctly matching the sites of measurement in serial ultrasonic studies [62–70], but a reliable serial evaluation of progression or regression of atherosclerosis depends critically on the correct matching of the images. This limitation results from the lack of the third dimension in conventional two-dimensional ultrasound [67]. This procedure can be significantly facilitated by the use of three-dimensional reconstruction of intracoronary ultrasound images, permitting in serial ultrasound studies the assessment of the same site of the artery.

6. Volumetric intracoronary ultrasound

Three-dimensional reconstruction of intracoronary ultrasound images was first used [71] to visually assess the spatial configuration of atherosclerotic plaques (Fig. 2). Examination of dissections and stents by this technique has provided valuable clinical information [72–76].

The basic cross-sectional intracoronary ultrasound images are acquired while the ultrasound catheter is pulled back through the coronary artery segment of interest. A continuous pull-back at a uniform speed resulting in an equidistant spacing of adjacent images [77] is still the most common approach. A stepping motor, developed at the Thoraxcenter, performs an electrocardiogram (ECG)-gated withdrawal of the ultrasound catheter and can also be used to perform an ECG-gated image acquisition [78]. This approach allows to minimize artifacts induced by the cyclic movement of the ultrasound catheter in the lumen and the systolic-diastolic pulsation of the vessel wall.

Subsequently, the stack of cross-sectional images is reconstructed. The reconstruction systems differ mainly in the image segmentation, a processing step which performs a distinction between vessel wall structures and the blood-pool. The semi-automated detection facilities of commercial analysis systems are limited to the distinction between the blood-pool in the lumen and the vessel wall [71,79–83]. They are based on the definition of grey-level thresholds or acoustic quantification (Fig. 3).

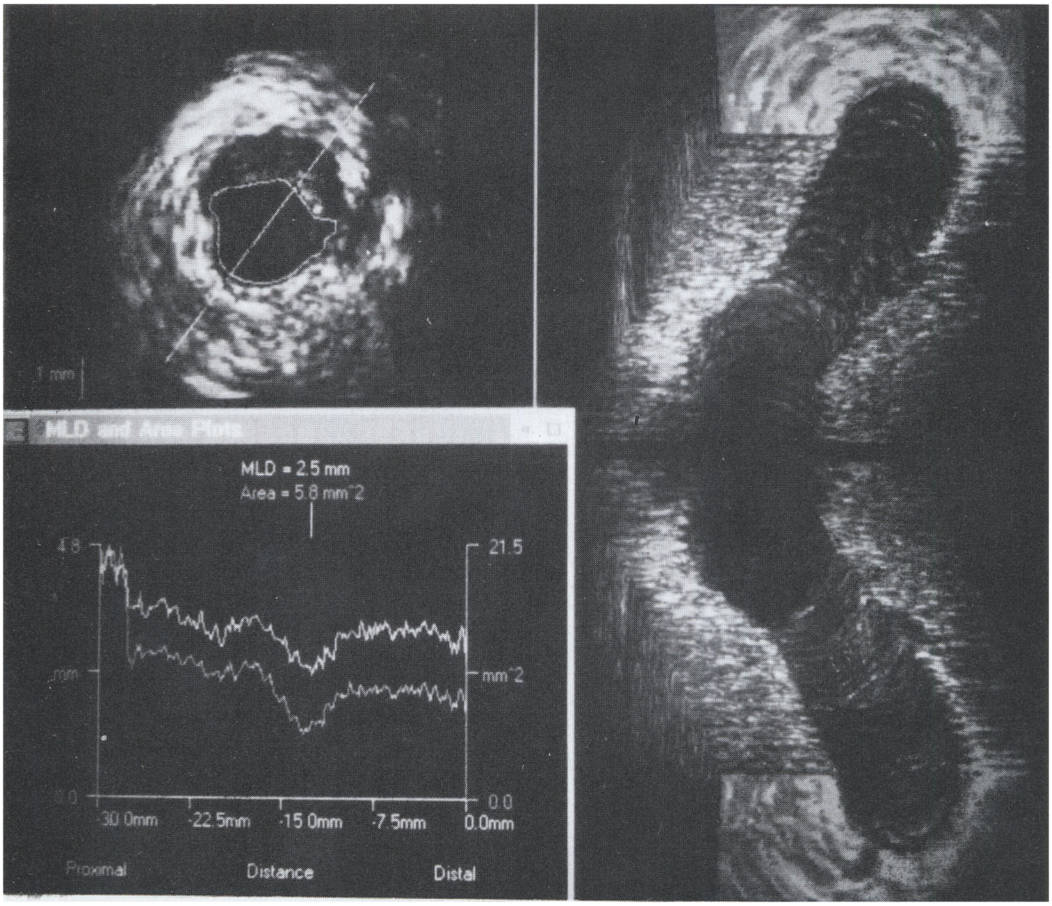

Fig. 3. Three-dimensional reconstruction of a short eccentric atherosclerotic plaque of relatively low echogenicy in the proximal segment of a coronary artery. A semi-automated distinction between the blood-pool and the vessel wall was performed by an acoustic quantification method, based on the recognition of the blood speckle, which shows a quite uniform pattern in the vessel wall and a varying pattern in flowing blood. Measurement of the lumen area and the mean luminal diameter are displayed in the left lower panel. Currently, no automated measurements of plaque area or volume can be performed by this approach.

At the Thoraxcenter, a computerized analysis system has been developed which performs a contour detection, based on the application of a minimum cost algorithm, and permits the identification of both the boundaries between the lumen and plaque as well as the plaque-media complex and adventitia (Fig. 1) using the complete volumetric information of the stack of intracoronary ultrasound images [68,84]. During the interactive contour detection on the longitudinal images, dynamic programming techniques are used to permit frequent up-dates of the displays including a cross-sectional plus two longitudinal views (Fig. 4). The visual information from both the cross-sectional and the longitudinal views facilitates the detection of the external boundary of the vessel wall. The advantage of this approach is particularly evident if calcium or stent struts obscure parts of the underlying vessel wall, rendering the morphometric measurement on sole cross-sectional images impossible. Even with short circumferential calcifications of the plaque, a reliable interpolation of the external vessel contour can be performed. The longitudinal contours guide the otherwise automated contour detection on the cross-sectional images, which is finally checked and may be manually corrected. Using the whole set of volumetric information, the analysis system performs a semi-

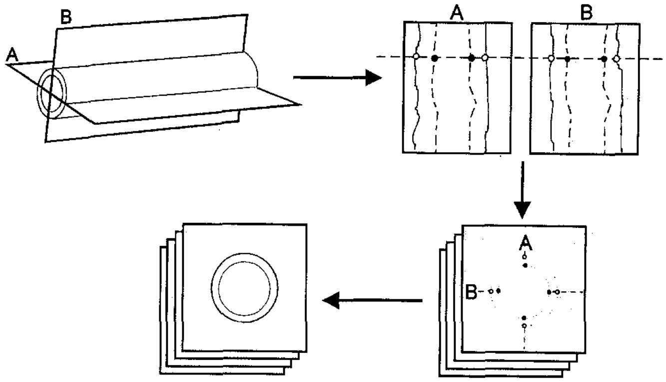

Fig. 4. Principle of the contour detection method, developed at the Thoraxcenter [68,84,85]. The intracoronary ultrasound images, obtained during a motorized pull-back of the ultrasound catheter, are used to reconstruct two longitudinal sections from the voxel space (voxel = volume unit). An automated contour detection of the intimal leading edge and the external boundary of the vessel is performed, based on the application of a minimum-cost algorithm, dynamic programming techniques, and user interaction. The longitudinal contours are represented as individual edge points in the whole stack of cross-sectional images. These points define center and range of the final contour detection process on the cross-sectional ultrasound images. Finally, the contours are checked and may be corrected. The analysis system provides information about areas, mean diameters and volumes of the lumen, total vessel and plaque (Fig. 1).

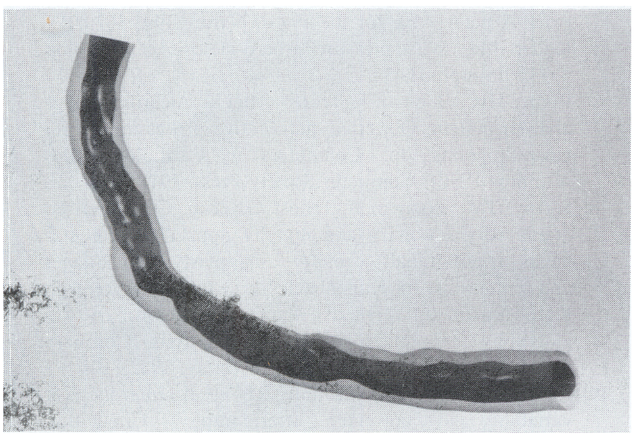

Fig. 5. Combined use of biplane angiography and three-dimensional intracoronary ultrasound by ANGUS, a new method which allows the analysis of the true geometry of the vessel lumen and plaque, taking vessel curvatures and catheter bends into account [88]. A reconstruction of a diseased right coronary artery is displayed in a frontal projection. Ultrasound data provided by the contour detection method were spatially arranged and interpolated, using biplane data on both the pull-back trajectory and the angiogram.

automated measurement of plaque volume. It reflects a function of the plaque area over the length of the reconstructed segment and can be calculated as the mean plaque area times the length of the reconstructed segment. Minimal differences in the start and end in repeated studies are unlikely to impair the accuracy of the changes in plaque volume measurements, assessed for an entire coronary arterial segment.

Volumetric measurements by the Thoraxcenter analysis system have been studied in a phantom in vitro showing a high accuracy [68]. The volumetric measurement has a lower intraobserver and interobserver variability than the measurement of areas on individual cross-sectional images [85], reflecting an averaging of the differences of the area measurement. Measurement of plaque volume [68–70,86] is particularly promising to quantify atherosclerotic plaques in progression-regression trials since it directly reflects changes of the plaque burden of an entire arterial segment with a high reproducibility.

7. Perspective of volumetric intracoronary ultrasound

Some limitations of three-dimensional reconstruction remain [67], but artifacts resulting from the movement of the ultrasound catheter during the cardiac cycle and systolic-diastolic changes in vessel dimensions can be minimized by the use of an ECG-gated pull-back system [67,87].

Combined use of biplane angiography and three-dimensional intracoronary ultrasound by a new method (ANGUS) may in the future help to analyze the true geometry of the vessel lumen and plaque, taking vessel curvatures and catheter bends into account [88]. In Fig. 5, a clinical example of a spatial reconstruction by ANGUS is given, showing a diseased right coronary artery in frontal projection. Ultrasound data on the intimal leading edge and the external boundary of the total vessel, provided by the contour detection method, were spatially arranged and interpolated, using biplane data on the pull-back trajectory and on the contrast angiogram. The example demonstrates that the external contour of the vessel provides additional information which cannot be obtained from a silhouette of the lumen which is normally provided by the angiogram [89]. This approach may permit a more distinct assessment of the progression or regression of atherosclerosis, an issue which is interesting as plaque progression or regression of the outer and inner curve of a bended coronary segment may differ significantly.

8. Conclusions

Coronary angiography depicts the silhouette of the vessel lumen permitting only an indirect analysis of the 'footprints' induced by the atherosclerosis of the coronary wall, not reflecting the early stage and the complex nature of the disease. Intracoronary ultrasound directly assesses and quantifies atherosclerotic plaques and is currenly the only reliable technique to measure progression or regression of atherosclerosis in the cardiac catheterization laboratory. The reliability of serial ultrasound studies can be further improved by using volumetric intracoronary ultrasound, which allows reliable and highly reproducible quantification of the plaque volume of entire arterial segments.

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