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How to assess regression of the atherosclerotic plaque

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Introduction

During recent years a large body of evidence has emerged that clearly demonstrates a link between cholesterol reduction, reduction in the frequency of clinical events and the arrest or even regression in angiographic coronary-artery-disease severity [1–3]. Currently, pharmacotherapeutic modification of atherogenesis has become a reality, and its effects on coronary atherosclerosis can be assessed by serial coronary angiography or by newer techniques such as intracoronary ultrasound or intracoronary Doppler [4].

Coronary angiographic intracoronary ultrasound and Doppler endpoints are considered as surrogate endpoints that represent one aspect of a continuum of clinical and pathophysiological manifestations of disease. The continuum encompasses abnormalities of lipid metabolism detected in serum samples, early 'pre-stenotic' sub-intimal thickening detected by intracoronary ultrasound, and advanced coronary arterosclerosis detected by coronary angiography and by intracoronary ultrasound, or functionally assessed by intracoronary Doppler and by the clinical manifestations of angina pectoris, myocardial infarction and coronary death.

In this review we will focus on the value and limitations of coronary angiography, intracoronary ultrasound and intracoronary Doppler to assess progression/regression of coronary atherosclerosis.

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Quantitative coronary angiography

Recently published serial angiographic studies to assess the retardation of progression or the regression of coronary-artery disease have only focused on changes of pre-existing lesions or on the development of new lesions [1–3]. The observed changes have been expressed in terms of changes of the percentage diameter of stenosis or in absolute measurements of the minimal luminal diameter (mm) of a stenosis. However, progression, and possibly regression, of coronary atherosclerosis is a complex process that is not limited to focal areas of the coronary-artery tree but that frequently involves the entire arterial wall [5–7]. Therefore, to assess the effect of an intervention on coronary atherosclerosis, both focal and diffuse changes of progression and regression should be measured [4].

Visual interpretation of coronary angiograms has its acknowledged limitations, because assessment of stenosis severity is associated with: (1) a large intra- and inter-observer variability (8–37%), (2) the provision of only relative stenosis measurements, and (3) difficulty in estimation by eye of the severity of diffuse atherosclerosis [4]. Quantitative coronary angiography, however, allows the assessment of focal and of diffuse atherosclerosis and provides us both with relative measurement (diameter stenosis, area stenosis) and with absolute measurements, both from the lesion and from segments of the coronary tree [minimal luminal diameter stenosis (mm) and mean luminal-diameter segment (mm)]. Coronary angiography is an 'in-

direct, luminographic' technique and coronary atherosclerosis is detected only after luminal encroachment.

Conceptually angiographical assessment of progression or regression should be viewed as an increment or decrement of the volume that intrudes on the arterial lumen of the entire coronary tree. Progression is defined as the occurrence of (1) an increase of degree and extent of focal atherosclerosis, (2) the development of a new lesion, (3) an increase in the degree and in the extent of diffuse atherosclerosis, and (4) the combination of (1), (2) and (3). This implies that we should measure changes in the luminal volume of the opacified coronary-artery tree. However, due to the complex coronary anatomy, the varying course of the arteries in a three-dimensional plane and the cyclically changing calibre of the coronary arteries, complicated by the beating heart, it is impossible to measure the 'volume' of the coronary tree in man with current angiographic techniques. A simplified two-dimensional approach must be employed. The surface area of a coronary segment can be calculated in a two-dimensional plane (Figure 1). The surface area is derived from the mean of the individual luminal diameters determined at many sampling points along the entire segment from the proximal end to the distal end of the segment, multiplied by the length of the entire segment. The length of the entire segment can be kept equal in a baseline and follow-up serial angiogram, and thus can be discarded from the equation. Progression/regression of focal or diffuse coronary atherosclerosis will result in a change in the individual luminal diameters at the site of disease, and this will be reflected in a change of the mean-luminal diameter. Therefore, the derived mean-luminal diameter (the average of all individual luminal diameters) can be considered as a measure that does assess, in a two-dimensional plane, either focal or diffuse coronary-atherosclerotic processes. In addition, this method also identifies the minimal luminal diameter (focal atherosclerosis) of a coronary segment.

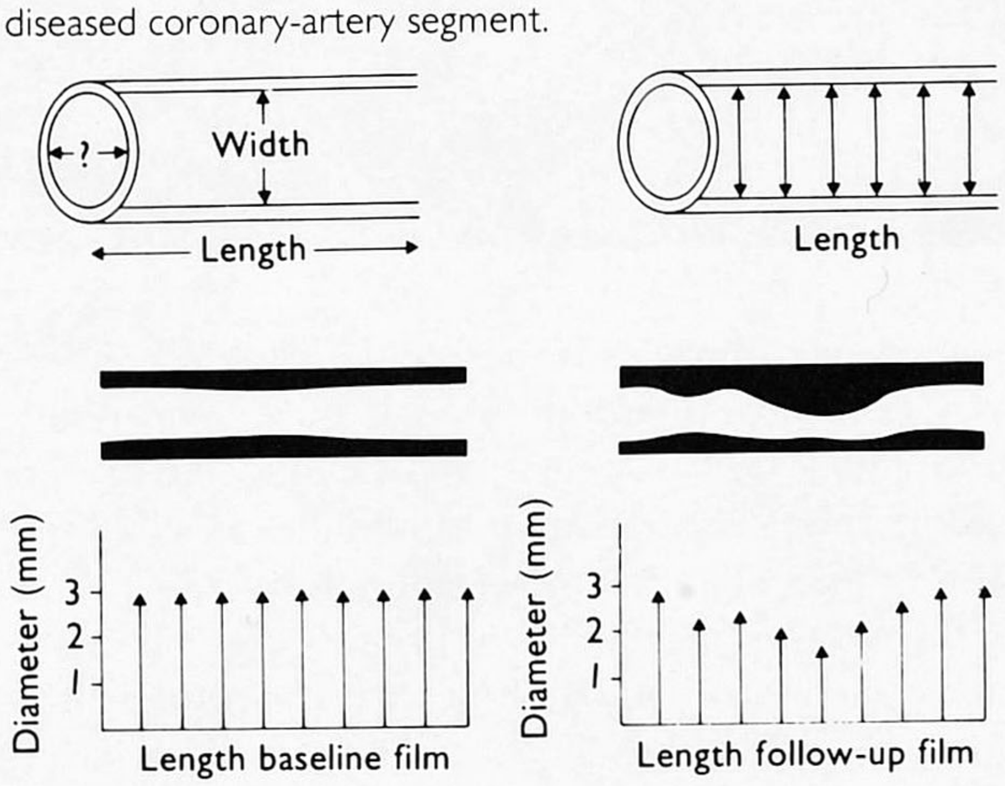
Another approach would be to assess the actual vessel area by the summation of all pixels between the contours; this has been implemented in the newest generation of systems for quantitative angiography.

A set of measurements derived from quantitative coronary angiography is proposed that could be used to assess the progression or regression of coronary atherosclerosis (Table 1). The mean-luminal diameter (mm) is the most important measurement, because it is able to assess the progression/regression of diffuse atherosclerotic disease and of focal atherosclerotic disease. The absolute measurement (minimal luminal diameter in mm) of lesions is extremely valuable to assess changes of focal atherosclerosis. Although relative measurements are subject to many drawbacks, it may be useful to present these to meet the traditional clinical practice of grading stenoses as percentage stenosis.

Figure 1

Two-dimensional coronary angiography

(*a*) Surface area = length × mean-luminal diameters (width). (*b*) Determination of individual luminal diameters at different sample points to derive the surface area. The average of all individual luminal diameters is the mean-luminal diameter. (*c*) Determination of the mean-luminal diameter in a baseline film. (*d*) Effect of the progression of the disease on the change in individual luminal diameters and thus on minimal-luminal diameter (decreased) in a follow-up film. In addition, this method also determines the minimal luminal diameter of a diseased coronary-artery segment.



Limitations of coronary angiography

Angiographic assessment of progression/regression is limited, because it assesses only the contour of the arterial lumen, and thus the underlying pathologic process can be identified only by interference. This often causes underestimation of the severity and of the extent of coronary atherosclerosis, when compared with post-mortem pathological studies [8–16].

Another problem is that the early stages of coronary atherosclerosis are associated with remodelling of the coronary artery. Remodelling of the coronary artery, due to compensatory wall enlargement and medial thinning underneath the plaque, results in the preservation of the normal lumen cross-sectional area, so that early-stage coronary atherosclerosis is angiographically undetectable [17–21]. Also gradually proceeding diffuse atherosclerotic disease, causing a smooth

Table 1

Significance of measurements used to assess the progression or regression of coronary atherosclerosis

Measurement	Significance in assessment of progression/regression		
	Diffuse athero-sclerosis	Focal athero-sclerosis	Combination of diffuse and focal atherosclerosis
Mean width per vessel segment (mm)	+ +	+	+ +
Absolute measurements			
Minimal luminal diameter (mm)	±	+ +	+
Relative stenosis measurements			
Diameter stenosis (%)	—	+	±

narrowing of an entire vessel often develops unnoticed and is only suspected in severely end-stage disease. Misinterpretation of regression is likely in cases of (1) lysis of a mural or an occlusive thrombus, (2) relaxation of vasospasm (catheter-induced; related to endothelial dysfunction), and (3) age-related vasodilatation. Intravascular ultrasound imaging has the potential to overcome the problems encountered by coronary angiography.

Intracoronary ultrasound imaging

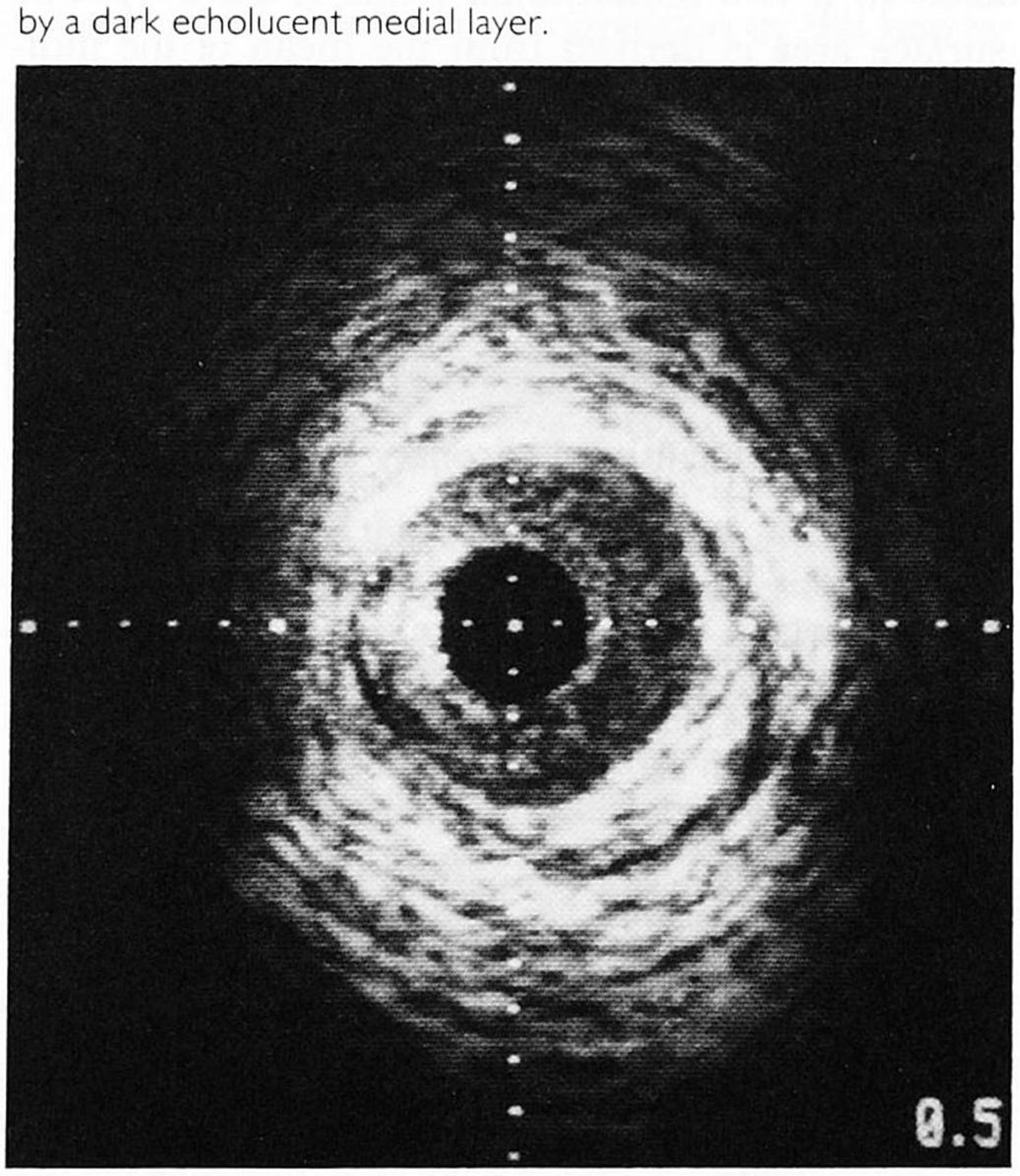
Unlike coronary angiography, intracoronary ultrasound imaging has the potential to image the coronary-artery wall beyond the lumen. This ability permits *in vivo* inspection of the vessel wall and the atherosclerotic plaque in the early pre-stenotic phase of atherosclerosis as well as in the more advanced stages of disease. The normal coronary vessel wall generally shows a three-layered appearance [22–27]. The bright inner layer represents a combination of the intima and the internal elastic lamina. The media is poorly reflective of ultrasound and appears as a characteristic dark band. The adventitia is bright, forming an outer layer that is usually indistinguishable from the surrounding peri-adventitial tissue (Figure 2).

Imaging of the plaque permits quantitative analysis of the cross-sectional area of the plaque and gives information about the plaque composition, because the variations in the ultrasound backscatter permit, to some extent, the various tissue components to be discriminated [23–31]. In general the plaques can be classified as soft, hard or calcified. The images obtained from fibro-muscular tissue generally have a soft appearance compared

Figure 2

Cross-sectional ultrasound image

The image demonstrates the preserved lumen, an eccentric plaque between 2 and 6 o'clock, separated from the adventitia by a dark echolucent medial layer.



with dense fibrous plaques, which produce bright echoes. Calcium produces an intense echo reflection and a lack of penetration beyond the area of calcification ('shadowing'). Lipid-lakes in atheroma appear as echolucent areas within the plaque [32].

Intravascular ultrasound imaging has some apparent limitations. The precise measurement of the plaque may be difficult if there is (1) a strong

reflection from a prominent internal elastic lamina causing 'blooming' of the interface echo, so that the plaque size is overestimated [33], (2) a thinning of the media underneath the plaque, which makes the precise definition of the border of plaque/media more difficult [34], and (3) calcium with shadowing behind the calcific deposits, which precludes identification of the exact depth of the plaque.

Until now the majority of ultrasound systems provide only two-dimensional cross-sectional images at regions of interest. However, successful attempts have been made to reconstruct serially recorded two-dimensional images into a three-dimensional display [35–37]. The serial cross-sections are digitized and reconstructed in a stacked format along the length of the artery, to yield saggital and cylindrical formats. The three-dimensional representation of the coronary artery lumen and of the atherosclerotic plaque provides very useful information to understand plaque morphology better.

It appears that intracoronary ultrasound imaging is a very promising new diagnostic tool. Intracoronary ultrasound imaging offers the opportunity to acquire information above the vessel wall, the atherosclerotic plaque and the vessel-wall motions under the physiologic conditions in living patients. It can differentiate between lipid plaques, which are potentially amenable to regression with lipid-lowering intervention, from fibro-calcific plaques that are less likely to regress. It allows the 'monitoring' of progression/regression interventions and may provide information about the pathophysiological processes that underlie regression.

Intracoronary Doppler

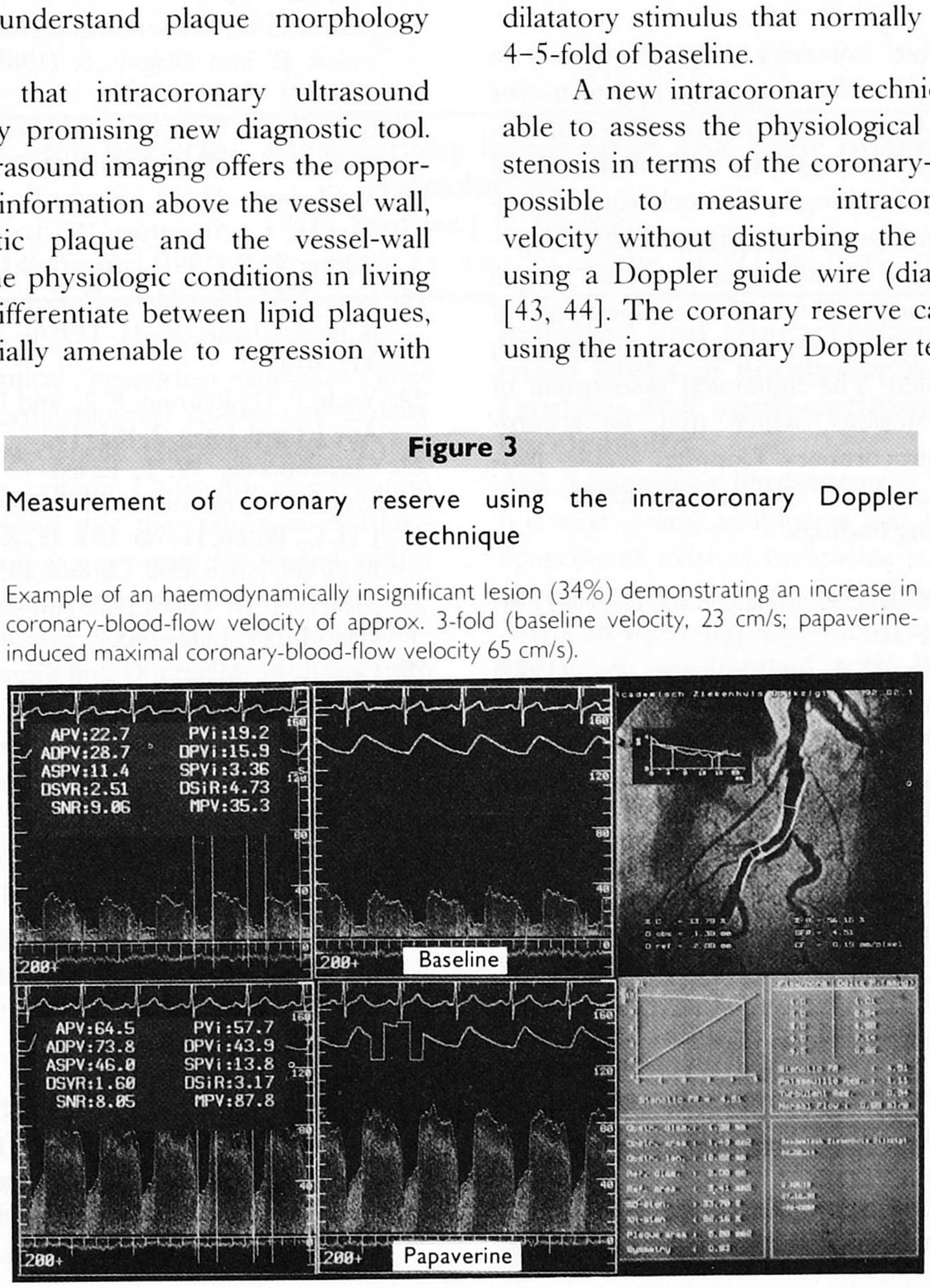
The physiological significance of a coronary stenosis can be assessed by its effect on the coronary-blood-flow reserve capacity, since physiologically significant obstructive lesions should decrease the vasodilatator reserve [38–42]. Coronary-blood-flow reserve is the ratio between the maximal coronary blood flow and the resting coronary blood flow. Maximal coronary blood flow can be obtained, for instance, by the intracoronary injection of papaverine, inducing maximal distal myocardial vasodilatation (Figure 3). Coronary-flow reserve begins to decrease at 40%–50% diameter stenosis for a vasodilatatory stimulus that normally increases flow to 4–5-fold of baseline.

A new intracoronary technique is now available to assess the physiological significance of a stenosis in terms of the coronary-flow reserve. It is possible to measure intracoronary-blood-flow velocity without disturbing the flow pattern, by using a Doppler guide wire (diameter, 0.46 mm) [43, 44]. The coronary reserve can be determined using the intracoronary Doppler technique from the

Figure 3

Measurement of coronary reserve using the intracoronary Doppler technique

Example of an haemodynamically insignificant lesion (34%) demonstrating an increase in coronary-blood-flow velocity of approx. 3-fold (baseline velocity, 23 cm/s; papaverine-induced maximal coronary-blood-flow velocity 65 cm/s).



ratio between the maximal-flow velocity and the resting-flow velocity (Figure 3). The effects of progression or regression should be reflected in a change in the coronary reserve.

However, a major problem in assessing the effect of a coronary stenosis on coronary-blood flow is that myocardial perfusion is the integrated response of the entire coronary vascular system, which consists of many components including stenosis geometry and characteristics of the epicardial vessel, endothelial function, distal vascular bed, myocardium, collateral circulation, aortic pressure, coronary vascular tone as well as the effectiveness of the coronary vasodilatator stimulus. Hence the interpretation of changes in the coronary-flow reserve may not be exclusively related to changes in the severity of an epicardial coronary-artery stenosis.

Conclusion

Serial, quantitative coronary angiography is a widespread and powerful diagnostic tool to assess the progression/regression of coronary atherosclerosis. However, angiography is limited because it is an indirect, luminographic technique. Intravascular ultrasound provides a direct imaging technique and allows the actual regression of the plaque or the modification of specific components of plaque (lipids as against fibro-calcific components) to be demonstrated. The functional assessment of coronary artery lesions, which may be accomplished using intracoronary Doppler, would provide useful support for angiographic and ultrasound-imaging findings.

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Triglyceride-rich particles, high-density lipoprotein and their pharmacological modulation

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Lipoproteins are usually separated according to their physicochemical properties, such as their density. Most pharmacological studies use density classes, mainly low-density lipoproteins (LDL), as their main efficacy criteria. Using this classification system it was proved that the reduction of LDL-cholesterol by drug therapy was associated with a significant decrease in cardiovascular morbidity.

However, the use of physicochemical properties for lipoprotein identification does not take into account the protein component (apolipoproteins) of these entities, which plays a crucial role in lipoprotein metabolism.

The purpose of this paper is to illustrate how apolipoproteins may be used as specific markers of lipoproteins, and how this classification system may help to characterize lipoprotein metabolism and the effect of drugs on the plasma level of lipoproteins.

Abbreviations used: apo, apolipoprotein; HMG CoA, 3-hydroxy-3-methylglutaryl-CoA; LDL, low-density lipoprotein; Lp, lipoprotein.

Isolation and characterization of the main types of apolipoprotein A (apoA)- and apoB-containing lipoproteins

Apo A-containing lipoproteins

It is now clearly established that apoA-I-containing lipoproteins exist as two major species, those containing apoA-I and apoA-II [lipoprotein A-I and A-II (LpA-I/A-II)] and those containing apoA-I, but which are free of apoA-II (LpA-I) [1–4]. Besides lipids, both LpA-I and LpA-I/A-II contain apoCs and apoE as minor constituents [5]. Kinetic studies indicate that LpA-I and LpA-I/A-II behave as metabolically distinct entities [1]. *In vitro*, it was also suggested that LpA-I, but not LpA-I/A-II, may act as a promoter of cholesterol efflux from peripheral cells [6]. Therefore, although they are within the same density class, LpA-I and LpA-I/A-II apparently behave as distinct functional entities.

ApoB-containing lipoproteins

ApoB-containing lipoproteins may be divided into four major lipoprotein families, one containing only apoB (LpB), another containing apoB and apoC (LpB/C), another with apoB and apoE (LpB/E), and the last containing these three apolipoproteins