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In-Vivo Imaging of Acute Coronary Syndromes

P. J. de Feyter

Imaging of a vulnerable plaque, underlying the occurrence of acute coronary syndromes, would be an important step to a better understanding of the progression and regression of coronary atherosclerosis. *In-vivo* imaging with coronary angiography, intravascular ultrasound and coronary angioscopy is possible but each imaging modality has its own value and limitation. Angioscopy can reliably distinguish between a stable and unstable coronary plaque, while intracoronary ultrasound and coronary angiography are less reliable. However, angioscopy and ultrasound should be regarded as "research" tools and today no reliable routine imaging modality exists to image the vulnerable plaque. *J Clin Basic Cardiol 2000; 3: 95–7.*

Key words: angioscopy, coronary angiography, ultrasound

Acute coronary syndromes – unstable angina, acute myocardial infarction or sudden death – are associated with rupture of a coronary plaque with superimposed thrombosis which transiently or permanently may partially or totally occlude the coronary vessel [1]. *In-viv*o imaging of acute coronary syndromes can be achieved by routine diagnostic coronary angiography, intracoronary ultrasound and intracoronary angioscopy. Each image modality has its own particular value and limitation, which will be addressed in this review.

Coronary angiography

Until now coronary angiography has been the gold standard in assessing coronary artery disease *in vivo*. Coronary angiography is a powerful, clinically extremely useful, worldwide available technique considered to be the diagnostic mainstay of patient management. Its major strengths are: a) it provides a 3-dimensional high resolution image of the lumen of the entire coronary tree and hence b) provides a comprehensive evaluation of the extent and severity of coronary obstructions, and c) is the only technique capable of demonstration of the collateral circulation.

Computer-assisted automated contour detection using sophisticated algorithms allow for accurate quantification of the severity of lumen obstructions and, more crudely, about the length of various obstructions [2].

Patients presenting with unstable angina have significant coronary obstructions in 80–90 % of the cases. It appears that the extent of coronary artery disease and the degree of coronary arterial narrowing does not differ between patients with stable angina and those with unstable syndromes (except for patients with an acute transmural myocardial infarction who often present with a thrombotic occlusion of the infarct-related vessel [3]. The sensitivity of coronary angiography to identify angiographic characteristics that distinguish an acute coronary syndrome from stable angina is rather low.

Angiographic features of an unstable plaque have been extensively described by Ambrose et al. [4] and include a) stenosis with irregularity, scalloping, or clefts indicative of surface ulceration and b) the presence of a stenosis related intracoronary thrombus represented by a filling defect, sometimes with associated staining of contrast medium or occlusions with a convex border often in case of acute myocardial infarction. Commonly the filling defects are seen just distal to the area of severe narrowing, but they may also be seen proximal to the stenosis and occasionally even in the absence of a significant lumenal obstruction. Coronary artery obstructions with such characteristics are often described as "complex lesions". The complex lesion has been reported to occur in approximately 60 % of patients with unstable angina, but also in 14 % of patients with stable angina (Table 1) [4–9]. The presence of an intracoronary thrombus varies greatly, but appears to be highest immediately after an ischaemic episode and diminishes in frequency if there is a longer duration of time between the last ischaemic attack and angiography (Table 2) [7, 9–16].

Since the inception of coronary angiography it has been acknowledged that angiography has its inherent limitations. The most important being that angiography is a three dimensional silhouette image of the lumen of the coronary artery. This is the main cause of underestimation of the presence and extent of coronary artery disease. Firstly, the earlier manifestations of coronary atherosclerosis are wall thickening without encroachment upon the lumen due to re-

Table 1. Angiography in stable and unstable angina

Author	Stable % (n. pt)	Unstable % (n. pt)
Ambrose [4]	16 (29)	71 (41)
Bresnahan [5]	2.5 (201)	35 (67)
Haft [6]	47 (36)	73 (73)
Rehr [7]	21 (42)	70 (50)
de Feyter [8]	39 (23)	55 (44)
Ahmed [9]	14 (50)	48 (238)
Overall	52/381 14 %	310/513 60 %

Table 2. Frequeney of angiographically detected i.c. thrombosis

Author	N	Time from ischaemia to angiography	With i.c. thrombus
Gotoh [10]	37	immediately	56
TIMI IIIA [11]	306	11.5 h	35
Capone [12]	44	< 24h	55
Ahmed [9]	139	< 48 h	17
Capone [12]	75	1–14 days	28
Rehr [7]	50	1.1 days	32
Ahmed [9]	163	> 2 days	13
Freeman [13]	54	< 4 days	50
Bugiardini [14]	116	4–7 days	22
Vetrovec [15]	129	< 1 month	6.2
Holmes [16]	16	1 month	1.3

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modelling of the coronary vessel. Secondly, the necessity to compare diseased vessel segments with a reference vessel segment which is assumed to be normal but which is often diseased.

Intracoronary angioscopy

Coronary angioscopy permits direct inspection of the surface of the vessel wall and coronary lesion and therefore has a great potential to differentiate between a stable and a complex coronary plaque. A stable plaque is defined as a plaque with a smooth surface and no signs of thrombus. The plaque may be yellow or white. A complex plaque is defined as a plaque with a disrupted surface and an attached red thrombus. The thrombus may be mural, protruding or occlusive.

From a pooled analysis it appeared that in patients with unstable angina angioscopy identified in 74 % of these patients a complex lesion whereas angiography detected only 28 % complex lesions in the same population (Table 3) [8, 17–21]. An interesting notion is the fact that angioscopy was unable to detect signs of rupture and thrombosis in approximately 25 % of the patients. Several reasons for "angioscopically silent" unstable angina can be proposed: a) technical failure of angioscopy to detect unstable plaque, b) other mechanisms of instability such as vasoconstriction [22] or a recently suggested possibility of excessive smooth muscle cell proliferation [21]. An extremely interesting finding was the overall 11 % occurrence of a complex lesion in patients with stable angina (Table 4) [8, 17–21]. This confirms the predominantly pathological observations that plaque rupture and thrombosis is a rather frequent occurrence *in vivo*, which may take place unnoticed or without increase in symptoms. Thieme et al. [24] correlated the angioscopic findings with histomorphologic findings obtained with directional coronary atherectomy. They found that grey-white coloured lesions represented a fibrous plaque (with or without necrosis); grey-yellow coloured lesions represented a necrotic plaque and yellow-red lesions represented either lipid or necrosis.

Uchida et al. [25] studied the prognostic value of angioscopy in 157 patients with stable angina who were followed for 12 months. Yellow plaques were strong predictors of future acute coronary syndromes; in particular glistening yellow plaque (suggestive of thin fibrous cap) (Table 5).

The main limitations of angioscopy are: 1) inability to assess consistently the entire coronary plaque, 2) inability to assess very proximal lesions, 3) not always possible to cross severe lesions, 4) the need to occlude the vessel during imaging while irrigating the vessel segments with a transparent solution and 5) unfortunately it is not possible to reliably quantify the angioscopic images *in vivo*.

Table 3. Unstable angina pectoris: angioscopy versus angiography detection of unstable plaque

Author	No. pts	Angioscopy (%)	Angiography (%)
Sherman [17]	10	70	10
Mizuno [18]	10	90	10
Ramee [19]	16	50	13
de Feyter [8]	44	68	55
Tabata [20] (Post MI)	17	100	36
White [21]	95	74	21
Overall	141/192 74 %	54/92 28 %	

Table 4. Unstable plaque: angioscopy in stable angina

Author	No. pts	Unstable plaque (%)
Sherman [17]	10	0
Mizuno [18]	20	5
Ramee [19]	4	0
de Feyter [8]	23	17
White [21]	27	15
Overall		9/84 11 %

Intracoronary ultrasound imaging

Intracoronary ultrasound imaging is able to provide real-time high resolution cross-sectional images of the coronary wall and coronary plaque. This allows *in vivo* examination of the tissue components of the coronary plaque and, because the total vessel (lumen and wall) are studied, allows monitoring of processes such as compensatory enlargement or paradoxical shrinkage of the vessel [26–31]. It has been shown that ultrasound is able to classify plaques on the basis of the tissue composition into 3 groups: a) a poorly-echoreflective intimal thickening corresponding to loose fibrous tissue, lipid, thrombus or necrosis, b) a highly-echoreflective intimal thickening without shadowing corresponding to dense fibrous tissue and c) a highly-echoreflective intimal thickening with shadowing corresponding to a calcified plaque [30].

Obviously, it would appear attractive to use ultrasound imaging to study whether there are differences in the tissue build-up of an unstable and stable plaque. Also it would be important to demonstrate that ultrasound can identify the presence of a thrombus and is able to measure the thickness of the fibrous cap.

Hodgson et al. [28] studied 65 patients: 22 patients had stable angina and 43 had unstable angina. They showed that, compared to stable angina, patients with unstable angina had more soft lesions (75 % vs 41 %) fewer calcified and mixed plaques (25 % vs 59 %) and fewer intraluminal calcium deposits (16 % vs 45 %). We have also compared the ultrasound characteristics of stable and unstable plaques [8]. However, we were unable to find significant differences in tissue components between the two groups (Table 6) even though the ultrasound system that we used had a higher dynamic range and resolution (30 MHz vs 20 MHz) than that used by Hodgson. Some investigators claim that it is possible to distinguish thrombus from soft plaque components. Lee et al. [32] suggest that thrombus presents as a fine homogeneous speckled pattern, or has a smooth pedunculated appearance, which is different from soft plaque. Kearney et al. [33] noted that unstable lesions had a demarcated inner layer, delimited by a fine circumferential line from the outer layer, a pattern which they could not discern in stable lesions. These features could represent thrombus attached to the lesion, but definitive proof (for instance with angioscopy) is lacking, to confirm the diagnosis. We were unable to identify i.c. thrombus with the current ultrasound

Table 5. Angioscopy to predict unstable angina (157 stable patients followed 12 months)

	Plaque		
	White (118)		Yellow (39)
Occurrence of acute coronary syndrome	4 (3.5 %)	p = 0.0002	11 (28 %) glistening (9 of 13) non glistening (2 of 26) p = 0.00026

Table 6. Intracoronary ultrasound characteristics of ischaemia-related lesions

	Unstable angina (n = 44)	Stable angina (n = 23)
Echo-reflectivity of plaque		
Homogeneous type, *n (%)	24 (55)	15 (65)
Poor	22	14
High without shadowing	1	0
High with shadowing	1	1
Mixed type, n (%)	20 (45)	8 (35)
Poor/high without shadowing	2	2
Poor/high with shadowing	18	6
Calcium present,** n (%)	20 (46)	7 (31)
Focal (30–90°)	5	1
Moderate (90–180°)	14	5
Diffuse (> 180°)	1	1
Eccentric plaque (index < 0.5)	27 (61)	13 (56)
Extent plaque, mm^2	15.2 ± 5	17.0 ± 5

* = homogeneous if plaque induces > 75 % of one type of echo-reflectivity. ** = Distribution of calcium was classified according to number of degrees of vessel circumference.

imaging technique. Echolucent zones sometimes noticed within a coronary plaque may represent a lipid pool. However, histologic evidence is lacking that these *in vivo* echolucent zones indeed represent lipid lakes.

So far, due to the limitations of resolution of current ultrasound imaging it is not possible to obtain reliable information about the thickness of a coronary plaque. Therefore we concluded that currently available ultrasound technology does not discriminate stable from unstable plaques.

Conclusion

Perhaps the ultimate way to assess clinically acute coronary syndromes is with the combined use of coronary angiography, intracoronary ultrasound and intracoronary angioscopy. Each diagnostic technique provides its own unique information which is complementary to the others. In particular, angioscopy does discriminate between stable and unstable plaque, whereas angiography and ultrasound are less reliable for distinguishing between stable and unstable plaques.

Currently, a lesion prone to rupture cannot be detected with either one of the three available techniques. Obviously, the combined use of all three techniques should only be done in a "research setting" and is not recommended in routine clinical use.

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