REVIEW ARTICLE

Drugs 2004; 64 Suppl. 2: 1-7
0012-6667/04/0002-0001/$34.00/0

Atherosclerosis Imaging: Intravascular Ultrasound

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Abstract

Most acute coronary syndromes result from the rupture or erosion of high-risk plaques. Clinical imaging studies have shown that atherosclerotic plaque formation and rupture are widespread processes that are often asymptomatic. The rationale for atherosclerosis imaging is the *in-vivo* identification of high-risk lesions, which may subsequently lead to prevention of future cardiovascular events. Although intravascular ultrasound (IVUS) imaging studies demonstrated that echolucent appearance of the plaque and expansive (positive) remodelling are associated with unstable clinical presentation, these characteristics were not adequate for accurate plaque characterisation. Recent technical developments in ultrasound equipment and analytical methods, utilising several characteristics of the digitised ultrasound signal with radiofrequency analysis and elastography, promise accurate tissue characterisation. Other imaging modalities, including optical coherence tomography, also contribute to a more precise characterisation of the composition of atherosclerotic plaques. A non-imaging approach is the focal assessment of temperature differences using sensitive intravascular thermography catheters, presumably reflecting focal inflammatory changes of vulnerable lesions. Although the histological characteristics of the atheroma are critically important in the sequence of events leading to acute coronary syndromes, the clinical relevance of identifying these characteristics is not yet clear.

There is increasing evidence that identifying and treating individual culprit lesions may not be enough to prevent the ischaemic cardiac events in most patients, because the acute coronary syndrome is not a disease of a single site or a few discrete segments, but rather a systemic disease that involves the entire coronary tree. In addition to detection and quantitation of early coronary atherosclerosis and disease activity, accurate and reproducible methods could help to identify high-risk patients and allow serial monitoring during various therapeutic interventions. Serial IVUS imaging makes it possible to visualise the vessel wall that harbours the atheroma at different time points. Typically, serial IVUS allows the assessment of the percentage change in atheroma volume, with considerable statistical power to detect small changes. Using this methodology, aggressive lipid lowering by a high-dose statin agent has been shown to stop the progression of atherosclerosis, and a new mutant high-density lipoprotein complex was found to be effective in regressing atheroma burden.

Although intravascular ultrasound is very accurate for quantification of atheroma burden, widespread application and accurate and reproducible non-invasive imaging

modalities are needed for large-scale risk assessment algorithms. Cardiovascular computed tomography is at the forefront of the non-invasive imaging modalities. Future prospective imaging studies will be necessary to identify focal or systemic characteristics of high-risk lesions and to demonstrate the relationship between plaque burden, biochemical markers and clinical events.

1. Introduction

Coronary artery disease is the leading cause of mortality in industrialised societies.[1,2] Most acute coronary syndromes result from the rupture or erosion of high-risk plaques. Frequently, these plaques are not obstructive. Autopsy studies of patients who died from coronary events demonstrated certain morphological characteristics of high-risk lesions, including the lipid-rich necrotic core, fibrous cap and expansive arterial remodelling.[3] Animal experiments and clinical imaging studies have shown that atherosclerotic plaque formation and rupture are widespread processes that are often asymptomatic.[4] Atherosclerosis is a diffuse disease process, and inflammation plays a central part in this process. Acute coronary syndromes are the focal manifestation of this systemic inflammatory disease process.[5-7]

The rationale for atherosclerosis imaging is the *in vivo* identification of high-risk lesions, which may subsequently lead to prevention of future cardiovascular events. Invasive, high-resolution imaging modalities are aimed at identifying high-risk lesions. In contrast, the observation that plaque vulnerability is a focal manifestation of a systemic disease process has led to quantitative assessments of disease burden and activity. Several invasive and non-invasive imaging modalities are already used to assess atheroma burden. Our understanding of the relationship between the biochemical markers and disease activity is thus increasing.

Atherosclerosis imaging has the potential to become an integral part of atherosclerotic disease prevention. However, current data are incomplete, demonstrating the need for prospective clinical studies evaluating the relationship between plaque burden, biochemical markers and clinical events.[8-10]

2. Focal Identification of High-Risk Lesions

Our understanding of vulnerable plaques has been derived from *post-mortem* studies of patients who died suddenly from acute coronary syndromes.[11-14] Culprit lesion sites are typically characterised by large, often eccentric, plaques containing necrotic core and lipid-rich elements, separated from the lumen by a thin fibrous cap. Because of the positive arterial remodelling, the lumen size is often preserved.[15-19] A consistent characteristic of vulnerable plaques is a prominent inflammatory response.[20-23] Macrophages are abundant in the plaque, particularly in the shoulder region of the fibrous cap at the border of necrotic areas.[24-26] The accumulation and activation of macrophages and other inflammatory cells induces the secretion of enzymes, including the matrix metalloproteinases. Weakening of the connective tissue framework (extracellular matrix) of the fibrous cap by these enzymes is the pathophysiological process that underlies arterial remodelling and plaque rupture.[27,28]

Early studies in humans have focused on imaging of the culprit lesions in patients presenting with acute coronary syndromes. Intravascular ultrasound imaging demonstrated that echolucent appearance of the plaque and expansive (positive) remodelling are associated with unstable clinical presentation.[3,29-33] We have studied 85 patients with unstable and 46 patients with stable coronary syndromes using intravascular ultrasound (IVUS). Expansive (positive) remodelling and plaque echolucency were significantly more frequent in unstable than in stable lesions, whereas constrictive (negative) remodelling was more frequent in stable lesions.[3] In further work we demonstrated that increased matrix metalloproteinase-3 is found more frequently in expansive remodelled lesions.[34]

The above studies described characteristics of highly stenotic lesions that had already caused clinical manifestations. However, the proof of high-risk characteristics identifying vulnerable plaques could only come from prospective, serial examinations. This has become feasible with *in-vivo* imaging modalities, but the data are very limited. Yamagishi et al.[35] prospectively examined IVUS images to identify those morphological features in mild-to-moderately stenotic plaques that would be associated with acute coronary syndrome during follow-up. In 106 patients, they identified 114 atherosclerotic coronary sites without significant stenosis by angiography (<50% diameter stenosis). After follow-up, 12 of the 106 patients had an acute coronary event at a previously examined coronary site. The pre-existing plaques that led to the subsequent acute coronary event demonstrated an eccentric location and the percentage plaque area was greater than in the patients without acute events; lumen areas were similar in the two groups of patients. Among the 12 future culprit sites, 10 contained echolucent zones, probably representing a lipid-rich, necrotic core at baseline. In contrast, of the 90 sites without acute events, an echolucent zone was seen at only four sites. The findings of this study suggest that echolucent zones probably representing the necrotic core could in fact identify lesions at increased risk for future instability. The study also confirmed prospectively that, despite significant accumulation of plaque, lumen area is preserved at the time of initial study, secondary to expansive remodelling of the vessel wall.

Recent technical developments in ultrasound equipment and analytical methods, utilising several characteristics of the digitised ultrasound signal with radiofrequency analysis and elastography, promise to yield accurate tissue characterisation.[36-40] Other imaging modalities, including optical coherence tomography, also contribute to a more precise characterisation of the composition of atherosclerotic plaques.[41,42] A non-imaging approach, using sensitive intravascular thermography catheters, is the focal assessment of temperature differences, which presumably reflect focal inflammatory changes in vulnerable lesions.[43,44]

The results of these preliminary studies need to be confirmed in larger, prospective studies. Eventually, the clinical significance of identifying individual high-risk lesions will need to be examined in clinical outcome studies.

3. Limitations of Focal Lesion Identification

Although the histological characteristics of the atheroma are critically important in the sequence of events leading to acute coronary syndromes, the clinical relevance of identifying these characteristics is not yet clear. There is increasing evidence that identifying and treating individual culprit lesions may not be enough to prevent the ischaemic cardiac events in most patients.[9,10] There are several reasons for this. A number of studies demonstrated that plaque destabilisation and rupture are common, and frequently asymptomatic.[45-48] Thrombosis without occlusion, followed by a 'healing' process, which is characterised by fibrosis, appears to represents the most frequent and silent mode of lesion progression. Observations in patients with acute coronary syndrome support these histological findings. In the setting of unstable angina or myocardial infarction, several ruptured plaques are found distant from the 'culprit' lesion throughout the coronary tree.[4,6]

Presumably, such patients have an underlying milieu conducive to the development of multifocal plaque ulceration, explaining the high propensity for recurrent acute coronary events.[4,49,50] Similar results have been described in angiographic, IVUS and angioscopic studies.

The studies cited above demonstrate the limitations of identifying morphological characteristics of focal vulnerable plaques *in vivo*. The acute coronary syndrome is not a disease of a single site or a few discrete segments, but rather a systemic disease that involves the entire coronary tree. It is unlikely that we will be able to change the course of the disease by focusing solely on the most severe

lesions. Identification of patients at high risk for future events may be achieved by assessment of plaque morphology and plaque burden with imaging modalities integrated with systemic markers of disease activity (e.g. serum markers of inflammation).[51-55]

4. Assessing Atherosclerotic Disease Burden and Activity. A Better Indicator of Future Risk?

There are a number of imaging modalities that aim to detect and quantitate early coronary atherosclerosis and disease activity. Accurate and reproducible methods could help to identify high-risk patients and allow serial monitoring during various therapeutic interventions.

IVUS studies allow visualisation of the vessel wall that includes the atheroma. Typically, in serial imaging studies, a motorised pullback of the IVUS catheter is performed through a long target segment (>40mm) with moderate disease (angiographic stenoses <50%). Frames at 1mm distance are selected and plaque area is measured in the individual frames. In quantitative, volumetric coronary IVUS, consecutive plaque area measurements are integrated along the vessel segment. When the patient returns for a repeat IVUS examination after follow-up periods of 12–24 months, and the same methodology is used. This methodology allows the assessment of the percent change in atheroma volume with considerable statistical power to detect small changes.[56]

In the recently reported Reversal of Atherosclerosis with Aggressive Lipid lowering (REVERSAL) trial,[57] IVUS was performed in patients with serum low-density lipoprotein (LDL) cholesterol concentrations of 125–210 mg/dL. Individuals were allocated randomly to groups to receive 80mg atorvastatin or 40mg pravastatin for 18 months. At completion of the study, a repeat IVUS examination was performed under identical conditions and the results analysed in a blinded core laboratory. At 34 centres in the USA, 655 patients were randomised and 502 completed the procedure. The baseline serum LDL cholesterol concentration (mean 150.2 mg/dL) was reduced to 110 mg/dL with pravastatin and to 79 mg/dL with atorvastatin ($p < 0.0001$). Plasma C-reactive protein concentrations decreased by 5.2% with pravastatin and by 36.4% with atorvastatin ($p < 0.0001$). The primary endpoint (percent change in atheroma volume) showed progression in the pravastatin-treated cohort (+2.7%; $p = 0.001$ compared with baseline). Atheroma volume decreased slightly in the atorvastatin group (−0.4%; $p = 0.98$ compared with baseline), indicating absence of progression. Comparing the two groups, the rate of progression was significantly lower in the atorvastatin cohort ($p = 0.024$), and this was independent of baseline serum LDL cholesterol concentrations. These results show that intensive treatment using 80mg atorvastatin can arrest progression of coronary atherosclerosis.

A smaller trial[58] assessed the effect of intravenous recombinant ApoA-I Milano/phospholipid complexes (ETC-216), a variant of apolipoprotein A-I, on atheroma burden in patients with acute coronary syndromes. In this double-blind, randomised, placebo-controlled multicentre study 123 patients consented, 57 were randomly assigned to study groups and 47 completed the procedure. In a ratio of 1:2:2, patients received five weekly infusions of placebo or ETC-216 at 15 mg/kg or 45 mg/kg. Intravascular ultrasound was performed within 2 weeks of acute coronary syndrome and was repeated after five weekly treatments. The primary efficacy parameter was the percentage change in atheroma volume (follow-up minus baseline) in the combined ETC-216 cohort. The atheroma volume decreased by $1.06 \pm 3.17\%$ (mean ± SD) in the combined ETC-216 group (median −0.81%, 95% confidence interval −0.34 to −1.53%; $p = 0.02$ compared with baseline). In the placebo group, atheroma volume increased by $0.14 \pm 3.09\%$ (median 0.03%; $p = 0.97$ compared with baseline). The absolute reduction in atheroma volume in the combined treatment groups was $-14.1 mm^3$ or a 4.2% decrease from baseline 0.001).

Although intravascular ultrasound is very accurate for quantification of atheroma burden, wide-

spread application and accurate and reproducible non-invasive imaging modalities are needed for large-scale risk assessment algorithms. Cardiovascular computed tomography is at the forefront of the non-invasive imaging modalities. The effect of pharmacological intervention on (calcified) coronary plaque burden has been observed in computed tomography 'calcium scoring' studies.[59,60] More recently, the differentiation between calcified and non-calcified plaque has become possible non-invasively, with contrast-enhanced multidetector computed tomography (MDCT).[61-64] Results from this technique suggest that advances in temporal and spatial resolution of MDCT will allow the non-invasive detection of atherosclerotic plaque, but future studies are needed to confirm the accuracy and reproducibility of disease quantification before MDCT can be applied to research and clinical settings in the same way as is currently possible with IVUS. Corresponding results have been described with other non-invasive modalities, including B-mode ultrasound and magnetic resonance imaging.[64-68]

A quantitative assessment of the disease burden with tomographic imaging modalities, and of disease activity using C-reactive protein or more specific markers of inflammation, including myeloperoxidase, could identify individuals at high risk for future events.[69] Future developments in multimodality imaging and plaque-specific imaging could provide much needed information regarding atheroma content and activity and lead to innovative preventive strategies.[70,71]

5. Conclusion

Future prospective imaging studies will be necessary to identify focal or systemic characteristics of high-risk lesions and demonstrate the relationship between plaque burden, biochemical markers and clinical events.

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