Comparison of synchrotron radiation angiography with conventional angiography for the diagnosis of in-stent restenosis after percutaneous transluminal coronary angioplasty

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Aims Synchrotron radiation angiography (SRA) is a novel tool for minimally invasive coronary artery imaging. The method uses subtraction of two images produced at energies bracketing the iodine K-edge after intravenous infusion of iodinated contrast agent. We investigated the accuracy of SRA for detecting in-stent restenosis (ISR).

Methods and results We recruited 57 men, 4–6 months after successful PTCA. We visualized the right coronary artery (RCA) in 27 patients with 36 stented segments [12 segments with ISR > 50% by quantitative coronary angiography (QCA)], and the left anterior descending artery (LAD) in 30 patients with 37 stented segments (10 ISR). SRA and QCA were performed within 2 days of each other. Two experienced observers unaware of QCA data evaluated the SRA results. Image quality was good or excellent in most patients. Global sensitivity was 64%, specificity was 95%, and positive and negative predictive values were 85%. Inter-observer kappa concordance coefficient was 0.86. False negatives involved short eccentric lesions and superimposed segments, most frequently of the LAD. False positives occurred in intermediate stenoses slightly overestimated by SRA.

Conclusion In men, this minimally invasive approach, using small radiation doses, detects significant ISR in the RCA, but the LAD poses difficulties because of superimposition with other structures.

KEYWORDS Angiography; Coronary disease; Restenosis; Stents; Synchrotron radiation

Introduction

In-stent restenosis (ISR) is now the most common form of restenosis. The incidence of ISR is between 20 and 40% with bare metal stents1 and between 3 and 9% with drug eluting stents.2,3 Up to half (20–50%) of restenoses are silent, but they may result in the same myocardium ischaemia as symptomatic ones. Electrocardiogram (ECG) stress tests have poor positive predictive value (PPV),4 and the more specific isotopic methods are rarely used. A minimally invasive technique permitting direct visualization of treated coronary arteries would therefore be useful.

Magnetic resonance imaging (MRI) and multi-detector computed tomography (MDCT) can provide non-invasive visualization of coronary arteries, with still some limitations, but stented segments pose particular problems and these techniques have not, as yet, been clinically validated.5 The shortest acquisition times achievable with MDCT scanners (of a few hundred milliseconds) cannot prevent motion artefacts,6,7 which reduce the accuracy of stenosis assessments. Arterial wall calcifications are well detected by MDCT and MRI, but an accurate quantification of the arterial lumen in calcified segments is often not possible. Advantages of MRI include the lack of irradiation and the fact that circulatory flux produces spontaneous contrast; although better results are achieved when intravascular contrast agents are used.8 However, the need to acquire data during several heartbeats limits the accurate measurement of stenosis in small distal coronary arteries. Thus, in the proximal parts, or in segments with a diameter > 2 mm9 of non-stented coronary arteries, MRI and MDCT can achieve sensitivities of >90%, and specificities >80%.5,10 Permeability control of arterial or venous grafts is also an important issue, which is now effective with these techniques.11,12

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In stented segments, the visualization of the lumen is still challenging. Despite the recently improved spatial resolution, the metal artefacts in MDCT images arising from the stent struts exaggerate the actual size of the stent, and obscure in-stent abnormalities within the lumen. In MRI images, the metal artefacts produced by conventional stents are larger, and jeopardize the in-stent lumen assessment. Up to now, no data on ISR imaging with MRI or MDCT, compared with selective angiography, have been published.

Selective coronary angiography remains the reference method for imaging the coronary lumen and for precise quantification of stenoses, but it is not recommended as a first line test for detecting restenosis. Synchrotron radiation angiography (SRA) after bolus injection of an iodinated contrast agent in a central vein, is an imaging method using the different attenuations of two X-ray monochromatic beams when energies bracket the sharp rise of the iodine mass attenuation at 33.17 keV. After subtraction of images simultaneous acquired at two different energies, the background is suppressed and iodine-containing structures are enhanced. The previous studies with SRA, performed in Stanford (SSRL), Hamburg (HASYLAB), Brookhaven (NSLS), and Tsukuba (KEK), demonstrated satisfactory feasibility. The aim of the current study was to compare the diagnostic accuracy of SRA with conventional angiography for the detection of ISR.

**Methods**

Adult patients who had undergone successful implantation of a bare metal stent 4–6 months previously were eligible to take part in this study to detect ISR. Restenosis was defined as a narrowing of >50% of the lumen diameter determined by QCA. SRA and conventional selective angiography were performed within 48 h of each other. Conventional angiography was performed using 4F or 5F catheters according to the normal practice of our centre. Twelve SRA imaging sessions were carried out in a period of 28 months.

The Grenoble 2 Research Ethical Committee approved the protocol as a study without direct benefit to the participants; for this reason, the total irradiation dose was strictly limited to 200 mSv skin dose per patient (2 mSv effective dose). All patients gave written consent to participate. Patients with severe myocardial dysfunction (left ventricular ejection fraction <35%), cardiac arrhythmia (atrial fibrillation or presence of extra ventricular beats), allergy to iodine, renal insufficiency (creatinemia >150 μmol/L), small superficial veins of the upper limbs, or obese patients (weight superior to 120 kg) were excluded. The sample size was determined by the accessibility to the European Synchrotron Radiation Facility (ESRF) with scheduled time periods. First, patients were imaged after right coronary artery (RCA) stenting (n = 27), then after left anterior descending artery (LAD) stenting (n = 30).

**Synchrotron radiation technical set-up**

High intensity X-rays with a broadband spectrum were delivered via the ESRF medical beamline that permits monochromatic beams to be generated at any energy. Image contrast can be enhanced by selecting the most effective energy level for each procedure. The K-edge subtraction technique uses the sharp rise in the photoelectric component of the attenuation coefficient of iodine at the binding energy of the K-electron (33.17 keV for iodine). Two images obtained with monochromatic X-rays are simultaneously acquired, just below (E−) and just above (E+) the K-edge energy of the contrast agent. The resulting logarithmically subtracted image (or ‘iodine image’) allows quantification of the contrast agent concentration in the sample because other materials are subtracted. Using the same principle, a so-called ‘tissue image’ can be generated, in which the iodine contribution is eliminated. The monochromator, a single bent-Laue silicon crystal, generates the E− and E− beams. The X-ray fan formed by the two beams crossing at the sample position is 0.8 mm high and 150 mm wide. The two beams diverge after the sample and are recorded independently with a dual-line detector (pixel size 0.350 mm.

The patient is translated up and down in order to construct a two dimensional image.

**Image analysis**

The synchrotron images were analysed by two physicians unaware of QCA findings but aware of the initial coronary angiogram and of the prior angioplasty location. They were asked to classify the stented segment(s) first into two categories.
(occlusion more or less than 50%), and then, more precisely, into four categories using the ranking: no restenosis if reduction in lumen diameter < 30%, no significant restenosis if ≥ 30 and < 50%, significant restenosis if ≥ 50 and < 70%, and severe restenosis if ≥ 70%. SRA sensitivity and specificity were determined both globally and separately for the RCA and LAD images. An independent cardiologist, blinded to the SRA findings, assessed results of conventional angiography offline using Cantor® System CAAS II version 4.0 on Dicom recorded angiograms. The lesions were quantified in the incidence exhibiting the highest stenotic degree; if necessary, manual corrections were carried out according to the examiner’s visual assessment.

**Statistical analysis**

Sensibility, specificity, and kappa concordance coefficient were assessed with 95% confidence intervals.

**Results**

**Study participants**

We enrolled 57 patients, all men, mean age 58 ± 10 years (range 38–78), mean weight 80 ± 11 kg (range 60–111) following successful coronary angioplasty with bare metal.
stents. This study was limited to men, only because of the necessity of naked chests procedure in a non-exclusive medical environment (engineers, physicists). This might have been uncomfortable for most of the women. Twenty-nine patients had single-vessel disease, 24 had two-vessel disease, and 4 had three-vessel disease. Thirty had previous myocardial infarction, none had previous bypass, and the mean ejection fraction was 61 ± 11% (range 40–80).

Conventional angiography findings

The RCA was visualized in 27 patients with 36 stent implantations: 6 on the first horizontal segment, 26 on the second descending, and 4 on the third up to the crux.

During the study period, ISR occurred in 10 patients and in 12 segments: four patients had angina, six were symptom-free, but four had ischaemia documented either with thallium or a stress test. Arteries analysis by QCA showed for the RCA, a mean reference diameter of the analysed segments equal to 3.30 ± 0.59 mm (2.14–4.46) and a mean minimal lumen diameter (MLD) equal to 2.0 ± 0.9 mm (0.24–3.76). ISR looked focal in eight segments, diffuse in three, and proliferative in one. The ISR rate for the RCA as determined by QCA was 33% (12/36).

The LAD was examined in 30 patients with 37 stents implanted on the proximal (n = 15), mid (n = 17), and distal (n = 2) segments of the LAD, or on a diagonal artery (n = 3). During the study period, nine patients had restenosis on QCA in 10 restenotic segments, two had angina, seven were symptom-free, but four had documented ischaemia. Arteries analysis by QCA showed for the LAD, a mean reference diameter of the analysed segments equal to 2.52 ± 0.46 mm (1.62–3.42) and a mean MLD equal to 1.59 ± 0.79 mm (0.0–3.14). ISR looked focal in six cases and diffuse in four. The ISR rate on the LAD as determined by QCA was 27% (10/37).

SRA findings

The SRA image quality was excellent in 31 patients (54%), good in 23 (40%), and fair or less in 3 (5%). However, one patient stented in the proximal LAD without restenosis on QCA was excluded because of the poor SRA image quality.

Patients with more than one stented-segment were imaged (1.3 stent/patient), which leads to potential biases due to a patient effect, as the independence assumption is not strictly obeyed. However, these biases sound acceptable since the ability of the method to detect intra stent stenosis depends much more on the stent location and lesion anatomy rather than on the patient himself.

With the two-category classification (less or more than 50% stenosis), five divergences between the SRA observers occurred, giving an inter-observer reproducibility of 93%. The inter-observer kappa was excellent: 0.86 (0.78–0.94). The divergences occurred in two short eccentric lesions, in two superimposed lesions of the LAD on the diagonal, and one unexplained.

With the two-category classification at the 70% threshold, the inter-observer kappa was 0.70 (0.37–1.03).

The four-category classification (thresholds: 30, 50, and 70%) led to a moderate overall unweighted kappa value: 0.52 (0.35–0.68) and 70% reproducibility.

Diagnostic accuracy

SRA successfully detected the presence of ISR (using the greater or less than 50% criteria) with a sensitivity of 64 ± 20% for both observers, specificity 94 ± 7% and 96 ± 5%, PPV 82 and 88%, negative predictive value (NPV) 85 and 86% (Table 1).

False positives (n = 3) were caused by other vessels superimposed on coronary segments (a right pulmonary vein on the RCA and a diagonal on the LAD) and a slight overestimation of a diffuse stenosis of an RCA third segment close to 50%. False negatives (n = 8) were due to superimpositions in two cases: proximal LAD-appendage, mid LAD-internal mammary artery; poor image quality in two patients weighing 94 and 98 kg, with large chest; slight underestimation of very short lesions (two of the RCA, one of the proximal LAD, and one eccentric lesion of the mid LAD which was only visible on LAO–cranial projection by QCA (Figure 4).

For RCA, the specificity (92%) and NPV (88 and 92%) remained excellent for detecting vessels with ≤30% stenosis. At the 70% threshold, the sensitivity was low (57 and 43%); once the diagnosis of severe restenosis was made, it was highly reliable (PPV: 100 and 83%).
For LAD, when stenosis on QCA was ≤30%, SRA ruled out restenosis with an NPV of 87 and 84% and a specificity of 91 and 87% for the two observers. At the 70% threshold, discrepancies between observers increased: sensitivity 66 and 33%, specificity 100%, PPV 100 and 50%. On the LAD, half of the lesions were underestimated or missed; however, this may not be significant because of the small number of patients with severe restenosis. On the other hand, the SRA diagnosis of no severe restenosis (70% threshold) was reliable (NPV: 94 and 88%).

Safety and tolerability
Patient tolerance of SRA was excellent and no major complications occurred. In one case, positioning of the pigtail catheter in the superior vena cava for synchrotron imaging was difficult because of a small and tortuous brachial vein. This difficulty was overcome by using a hydrophilic guide wire. The patient experienced periphlebitis, which resolved after a few days.

Discussion
Synchrotron technical aspects and radiation
SRA permits visualization of vessels as small as 1 mm without motion artefacts because of the small line-to-line interval in the images (0.35 mm and 1.4 ms). With venous catheterization, the coronary arteries are not artificially pressurized and the resulting images are therefore in a true physiological state. In patients with stents, SRA allows simultaneous visualization of the stent and the perfusion of the vessel. Calcification or the presence of the stent does not impair the evaluation of coronary artery perfusion as they are eliminated in the subtraction process. The disadvantages of the SRA are mainly the superimposition of venous structures over the arterial tree, and the filling of the ventricle with the contrast agent. The effective radiation dose delivered to the patient for the complete study is ~2 mSv (i.e. 200 mSv skin-entry dose), which compares favourably with ~5–7 mSv for conventional angiography and ~5 mSv for computed tomography. The total amount of iodinated contrast agent delivered was 50 mL.

The procedure
For this study, patients (only men) were inpatients; the SRA procedure was easy, and it could be performed on an outpatient basis. Measuring the bolus transit time (mean time 13 s with 5–10 mL iodine infusion) allowed precise timing for image acquisition and patient positioning with an appropriate incidence for a given known segment. The lumen was clearly seen without artefacts due to calcification, stents, or cardiac motion. When heart rhythm was regular, synchronization with the cardiac cycle could be achieved for at least one image regardless of the heart rate. However, such synchronization was not necessary as no motion artefacts were observed: atrial fibrillation would therefore not prevent the use of SRA.

Image interpretation
The acquisition of two images at different monochromatic X-ray energies leads, with a simple mathematical procedure,
to the iodine and tissue images. The pixel-to-pixel correspondence of these two images permits easy localization of the stent, even if it has a low radio-opacity (Figure 2A). A post-processing technique was used to enhance stent visualization. Of the five images acquired during the bolus transit, at least one was always optimal for lumen visualization without artefact.

In most cases, images of the RCA from the ostium to the crux were excellent in the first procedure using LAO 40°, with no superimposition on collaterals or the ventricular cavity. In the case of a tortuous segment, eccentric lesion, or occasional superimposition on a right pulmonary vein, a second session using LAO 80° was needed. Vessels with lumen diameters of \( < 1.0 \text{ mm} \) were clearly seen. False positives were due to a difficult analysis, in one case due to superimposition on the pulmonary vein. A divergence with QCA for one stenosis close to 50% (Figure 4) and two false negatives in very short lesions were due to the low signal-to-noise ratio. In this study, the radiation dose was limited; two false negatives occurred in overweight patients (94 and 98 kg) imaged with a low SNR and one patient (92 kg) was excluded because of the poor image quality. This might have been overcome by using higher X-ray doses (increased signal-to-noise ratio).

When compared with the conventional angiograms, satisfactory results were obtained with SRA for RCA images. The specificity and low false positive rate allowed a clear diagnosis of absence of restenosis.

Imaging of the left coronary artery was more difficult. The left main was not studied here because of the unsolved problem of superimposition on the aorta and because of the circumflex artery being superimposed on the full left ventricular cavity. For the LAD, the most useful approach is the RAO 40°, despite the problems of superimpositions on the left ventricle, the appendage or the aorta which must be carefully managed (Figure 5). The use of another orientation (mostly
RAO 60° provided only limited improvements. Proximal, mid, and distal segments were most often visualized. In our study, we noticed one superimposition of the proximal LAD on the left appendage, and two of the mid-LAD on the diagonal (Figure 6) or the LIMA. The distal LAD without superimposition was always clearly seen. One false negative occurred due to a highly eccentric mid-LAD lesion (Figure 7), which was classified as mild in RAO on QCA and synchrotron, but appeared as a severe stenosis only in the LAO—cranial view of the conventional angiogram. The major limitations of the SRA techniques were mainly because of projective images and a limited number of incidences. On the LAD, some restenoses were not detected and the sensitivity (observer 1: 40% and observer 2: 50%) was lower than for the RCA (observer 1: 75% and observer 2: 83%), (P = 0.03 Fisher exact test).

The SRA is currently the only minimally invasive technique allowing intra-stent stenosis follow-up which has been compared with the conventional gold standard technique. Because of concern about patients undergoing repeated techniques without benefit to themselves, the present study used a low X-ray dose of only 200 mSv to the skin for the entire imaging procedure (test infusion with five images plus two series of scans at different orientations) at relatively low energy (33 keV). Because the exposed skin surface is small (≤225 cm²), the whole body effective dose is <2 mSv. Use of higher radiation doses might improve image quality with regards to the signal-to-noise ratio.

The technique of subtracting images acquired at two energies closely bracketing the iodine K-edge permits the effective subtraction of all other structures, whether calcified or metallic; this is an important benefit of SRA. The iodine image allows quantification: even stenoses which do not appear as diameter reductions in the projection plane can be detected as the iodine thickness is reduced.

Limitations of the technique are related to the projective mode and the superimposition of other vascular structures. Some arterial segments, notably the left main and the circumflex, remain hard to distinguish. The knowledge of the segment one wants to image is therefore required. With regards to sensitivities and specificities, and assuming that our results are confirmed on larger studies, this SRA technique on stented segments can be favourably compared to CT and MRI techniques.

Clinical implications
SRA is accurate for the analysis of stented segments where other non-invasive techniques are less effective. It has the
advantages of being unaffected by artefacts due to the stents, calcifications, or cardiac motion. Stenosis in any part of the RCA can be accurately visualized, but visualization of the LAD may cause problems due to superimposition of other vascular structures. Such a minimally invasive procedure could be repeated to follow-up patients at high risk of ISR, and can identify most of patients without restenosis.

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