European Journal of Radiology 83 (2014) 1816–1821

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Incidence and classification of neointimal proliferation and in-stent restenosis in post-stenting patients at 1-year interval: Findings from non-invasive coronary computed tomography angiography

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ARTICLE INFO

Article history:
Received 16 March 2014
Received in revised form 15 July 2014
Accepted 21 July 2014

Keywords:
Coronary artery disease
Computed tomography
In-stent restenosis
Neointimal proliferation

ABSTRACT

Objectives: To evaluate the incidence of coronary in-stent restenosis (ISR) and neointimal proliferation by coronary CT angiography (CCTA) at 1-year follow-up in asymptomatic patients.
Methods: 234 patients (mean age: 67 ± 10.2 years, range 39–88 years, 180 males and 54 females) with 379 stents were prospectively enrolled in this study. Binary ISR was classified by CCTA into 4 types using Mehran classification. Neointimal proliferation was similarly classified into focal and diffuse types. All patients with CCTA-revealed ISR or neointimal proliferation underwent further invasive coronary angiography (ICA) for validation. Fisher's exact test was used for comparison.
Results: ICA revealed patent stents with neointimal proliferation in 39 patients (16.7%, 39/234) and binary ISR in 23 patients (9.8%, 23/234). Lesion-based analysis showed 12 type I ISR lesions, 4 type II ISR lesions, 1 type III ISR lesion and 7 type IV ISR lesions. Among cases with neointimal proliferation, 27 lesions were classified as focal type whereas 13 lesions were classified as diffuse type. Patients with diabetes mellitus were associated with higher incidence of CCTA-revealed neointimal proliferation (21/77 vs. 18/157, $p = 0.002$) as well as ISR (12/77 vs. 11/157, $p = 0.038$), compared to patients without diabetes. CCTA was found to have good diagnostic performance for neointimal proliferation and ISR detection as well as classification, with an overall accuracy of 84.4% (54/64).
Conclusions: Silent ISR as well as neointimal proliferation is not uncommon findings in asymptomatic post-stenting patients at 1-year interval, as revealed by CCTA. Patients with diabetes are prone to have higher incidence of neointimal proliferation.

1. Introduction

Coronary artery stenting is currently the most widely employed revascularization strategy for treatment in patients with obstructive coronary artery disease [1,2]. Wide clinical adoption of drug-eluting stent (DES) has dramatically reduced the rate of in-stent restenosis (ISR) as well as target lesion revascularization (TLR) [3]. However, ISR and stent occlusion remains the major complication of this procedure [4,5].

Although the majority of the patients with ISR are symptomatic, a small portion remains clinically silent, even with occluded stents [6,7]. In addition, a late increase of neointimal tissue was also observed in DES group, which may give rise to the delayed restenosis [7]. Since the clinical outcomes in patients with ISR are worse than those with de novo lesions and interventional strategies are recommended for treatment [8], early detection of silent ISR could be of potential clinical significance. However non-invasive detection of ISR and neointimal growth in asymptomatic patients has not been reported previously. Therefore we aimed to evaluate the incidence of coronary silent ISR and neointimal proliferation by CCTA follow-up in asymptomatic patients.

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http://dx.doi.org/10.1016/j.ejrad.2014.07.015
0720-048X/

2. Methods

2.1. Patient population

From January 2010 to July 2012, consecutive asymptomatic post-stenting patients, who were at 1-year interval after previous percutaneous coronary intervention (PCI) and having DES stents diameter ≥3 mm, were prospectively enrolled in our study. Patients with stent diameters less than 3 mm were excluded from the study based on previous findings, which revealed a large percentage of unassessable stents with calibers smaller than 3 mm [9]. Other exclusion criteria included common contradictions of administration of contrast media (renal insufficiency defined as serum creatinine > 1.5 mg/dl, previous history of allergy to iodine-based contrast media), atrial fibrillation or other rhythm irregularity, inability to perform breath hold and uninterpretable CCTA image quality as well. Due to the mild diagnostic discrepancy between CCTA and ICA for stent imaging [10], further ICA was performed in all patients having CCTA-revealed ISR or neointimal proliferation for confirmation. The interval between CCTA and ICA was within two weeks. Written informed consent was acquired in all patients and the study protocol was approved by the hospital ethics committee.

2.2. Scan protocol of CCTA

Patients with a pre-scan heart rate of 65 beats/min or higher were given 25–75 mg of metoprolol (Betaloc ZOK, AstraZeneca, China) orally 1 h prior to scanning. CCTA was acquired using a 128-slice multidetector CT (Definition AS, Siemens Medical Solutions, Forchheim, Germany) after sublingual administration of nitroglycerin in all patients. A double-head power injector (Tyco, Cincinnati, US) was used to inject contrast media (Iopamidol, 370 mg iodine/ml, Schering AG, Berlin, German) in an antecubital vein. A test bolus (10–20 ml contrast agent followed by a 20 ml saline flush) with injection rate of 4.5–5 ml was used to determine the timing of scan delay and image acquisition time. Depending on patient weight and delayed time, 50–90 ml contrast media was injected and followed by 40 ml saline flush. Retrospective ECG-gated CTA was performed in all patients with final heart rate no less than 70 bpm. The scanning parameters were as follows: 128-slice detectors; 0.6 mm individual detector width; 300 ms gantry rotation time; 120 kV tube voltage, pitch and current were ECG modified and the effective current was set as 200 mA (ECG-dependent dose modulation technique was applied, full dose during the R–R interval of 40–70%). Patients with final heart rate less than 70 bpm underwent prospective ECG-triggered CTA with same acquisition parameters except that the center of the triggering window was set at 70% of the RR interval.

2.3. Image reconstruction and analysis

Two sets of axial images with smooth (B26f smooth ASA) and sharp kernels (B46f sharp heartview ASA) were manually reconstructed with slice thickness of 0.6 mm in order to reduce the beam hardening artifact of stent strut and therefore enhance visualization of stent lumen [11]. The optimal cardiac phase displaying the minimum motion artifact was individually determined. All images were sent to an offline workstation (Syngo, Siemens Medical Solutions) for further analysis. Image sets available on the workstation included curved planar reformation (CPR), angiographic view maximum intensity projection (MIP) and short axis view of the stents with sharp kernel reconstruction using dedicated post-reconstruction software (Circulation, Siemens Medical Solutions).

Binary ISR is considered as an in-stent neointimal proliferation with diameter stenosis ≧50%. According to Mehran classification, the angiographic patterns of binary ISR were further classified by CCTA into 4 types [12]: focal, diffuse intrastent, diffuse proliferative and total occlusion. The angiographic patterns of neointimal proliferation were also similarly classified into 2 types: focal (≤10 mm) and diffuse (>10 mm).

Total lesion length was measured on CPR images and defined as the length from the proximal to distal shoulder of the in-stent neointimal proliferation. ISR involving two or more overlapping stents was considered as one lesion.

Image quality of stent was assessed by using a 3-point semi-quantitative scale as previously reported [9]: 3 = excellent (absence of artifact), 2 = acceptable (presence of less artifact, but still diagnostic), 1 = poor (presence of severe artifact, non-diagnostic). All images were evaluated independently by two radiologists who were blinded to the number, location, diameter, and type of stents, to the clinical history of patients. Disagreements between the two readers for any image set were resolved by consensus, and the consensus findings were used in all assessments of diagnostic performance.

2.4. ICA procedure and analysis

The ICA was performed with standard techniques, and at least 2 different views were obtained for each main vessel. Angiographic binary restenosis was defined as luminal stenosis >50% occurring within stents by visual assessment. All segments were evaluated by 2 skilled observers who were blinded to the results of CCTA. Disagreements between the two readers were resolved by consensus. Angiographic patterns were classified into 4 types, employing the same grading system as of CCTA. Balloon angioplasty was performed for treatment of focal ISR while stent implantation was used in patients with diffuse ISR or stent occlusion.

2.5. Statistical analysis

Statistical analysis was performed using a commercial available statistical software (SSPS, V13.0, SPSS Inc., Chicago, USA). The diagnostic accuracy was evaluated by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Intraobserver and interobserver agreement was expressed in Cohen's kappa value (k) for categorical variables. Fisher's exact test was used to make comparison of proportions. A probability value of $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

335 patients who were asymptomatic at 1-year interval after PCI were initially included in the study. 81 patients were excluded for having one or more stents with diameter less than 3 mm. 12 patients were excluded because of concomitant rhythm irregularity whereas further exclusion of 8 patients was due to uninterpretable CCTA images (image quality score 1). Therefore, a total of 234 patients with 379 stents was finally included in the study (mean age: 67 ± 10.2 years, range 39–88 years, 180 males [mean age: 65.8 ± 10.2 years, range 39–88] and 54 females [mean age: 70.8 ± 9.6 years, range 39–88], $p = 0.002$). Among the total 379 stents, the image quality of 264 stents was assessed as score 3 whereas 115 stents were graded as score 2. The dose length product (DLP) of CCTA was 433.3 ± 133.9 mGy cm (range 219–718 mGy cm). The mean contrast used for CCTA was 82.4 ± 8.6 ml (range 65–105 ml). ICA was performed in 62 patients with an interval of