Diagnostic utility of Gadolinium enhanced Coronary CT Angiography compared to Conventional Invasive Coronary Angiography in detection of obstructive Coronary Artery Disease

Waseem Ahmed, Imran Hafeez, Mohd Iqbal Dar, Feroze Shaheen, Jahangir Rashid Beig, Naseer A Choh and Ajaz Ahammad Lone

Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India

Corresponding author: Mohd Iqbal Dar, Department of Cardiology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, India, Tel: 919797020806; E-mail: darmohdizqbal@yahoo.in

Received date: October 04, 2016; Accepted date: November 22, 2016; Published date: November 30, 2016

Abstract

Background: The current gold standard for assessment of coronary artery disease, Invasive Coronary Angiography (ICA), has inherent risks of an invasive procedure including that of death. In addition use of iodinated contrasts in ICA and Coronary CT Angiography is often contraindicated due to its renal toxicity and hypersensitivity reactions. Gadolinium, though primarily an MRI contrast, has been shown to produce vascular luminal enhancement making it an attractive alternative contrast agent for use in angiography.

Objectives: To assess the possibility of use of Gd-enhanced 64-slice cardiac CT (CCT) for the diagnosis of obstructive coronary artery disease in comparison to invasive coronary angiography.

Methods: A total of 25 patients of CAD underwent Gadolinium Enhanced Coronary CT Angiography followed by Invasive Coronary Angiography. The data was analyzed by comparing coronary segments with ≥ 50% stenosis detected by ICA versus detection of the same by Gd-Enhanced CTA, as well as comparison on Per-Vessel basis.

Results: Mean age of patients in our study was 53.52 years (range 41-70 years). The total number of coronary segments evaluated by invasive coronary angiography was 379 of which 57 showed ≥ 50% stenosis. Gd-Enhanced CTA detected 47 of these lesions. In comparison to ICA, on Per-segment basis, Gd-Enhanced CTA showed Sensitivity of 82.46%, Specificity of 97.50%, PPV of 85.45% and NPV of 96.95%. Weighted Kappa value was 1, suggestive of strong agreement between the two modalities, excluding agreement by chance.

Conclusions: Our study shows Gadolinium Enhanced Coronary CT Angiography is safer alternative for assessment of CAD in patients who have a contraindication for ICA or Iodinated Contrasts with acceptable sensitivity and specificity. Results depend on BMI and coronary calcification.

Keywords: Coronary artery disease; Coronary angiography; CT angiography; Gadolinium

Abbreviations: CAD: Coronary Artery Disease; CCTA: Coronary CT Angiography; Gd: Gadolinium; BMI: Body Mass Index; LAD: Left Anterior Descending; LCX: Left Circumflex; RCA: Right Coronary Artery; HU: Hounsfield Units

Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in developed and developing countries [1]. The most widely used diagnostic technique for evaluation of CAD worldwide is invasive coronary angiography, which is associated with small but definite risk of life threatening complications [2]. In addition more than 1/3 of invasive coronary angiographic studies are done to rule out coronary artery disease and not followed by percutaneous or surgical intervention [3]. With the advance in the CT technology like Multiple detector computed tomography (MDCT), it allows CT to be used a more robust and reliable technique in the evaluation of coronary artery disease. A 2008 scientific statement from the American Heart Association [4], indicates that the potential benefit of noninvasive coronary angiography is likely to be the greatest for symptomatic patients who are at intermediate risk for coronary artery disease (CAD) after initial risk stratification, including patients with equivocal stress tests. While CT technology has evolved, the practice of CT intravenous contrast media administration has been continually debated and updated. The intravenous compounds used as contrast in CCT studies are iodinated compounds which offer high attenuation of the vascular territory and have low incidence of adverse physiological effects [5]. However, in patients with contraindications to iodinated contrast agents an alternative contrast media is preferable [6]. The major limitations of used of iodine contrast are prior severe anaphylactic reactions, thyrotoxicosis and renal insufficiency/renal failure. Use of intravascular iodinated contrast media is reported to be associated with 10%-30% of Contrast medium–induced nephropathy in patients with pre-existing renal insufficiency [7-10]. Though renal functions recover in majority of patients it can still be a serious problem in substantial percentage of patients and Permanent deterioration in renal function can occur and can land patient in end stage renal disease needing dialysis. Use of iodinated contrast is contraindicated in patients having previous life threatening allergy to...
iodinated contrast, in addition patient occasionally haven been asked “never” to receive iodinated contrast due to prior reaction which the patients may not be able to recall, creating the uncertainty regarding the use of iodinated contrast in these patients.

Gadolinium is a contrast agent primarily used in magnetic resonance imaging (MRI) and it has also been proposed as an alternative contrast agent for CT vascular studies [11-14] in the subset of patients with normal renal function who have relative or absolute contraindications to both MRI and iodinated contrast agents. Diagnostic quality images can be produced with gadolinium using digital subtraction imaging (DSA) by exploiting the gadolinium's ability to attenuate the X-rays [15-18]. Use of gadolinium chelate at MR imaging recommended doses in angiography is reported to result in reduced incidence of contrast media induced nephropathy in comparison with use of iodinated contrast. The safety of gadolinium chelate for MR studies in patients with pre-existing renal insufficiency has been reported by multiple authors [19-21]. Gadolinium can remain 10 times longer in blood stream of patients of with reduced renal function creating a theoretical concern of accumulation of gadolinium chelate in body [22] but no adverse effects have been reported in humans [23]. A number of studies have shown no deterioration of renal function or gadolinium induced toxicity who undergo MR imaging with intravenous gadollium chelate and have underlying renal dysfunction [19-21,24-26]. Should the need arise; gadolinium is a readily dialyzable compound with haemodialysis [24]. There is ample evidence regarding the safety of gadopentate dimeglumine, gadodiamide, and gadoteridol in the literature adverse reaction however do occur with total incidence of less than 5% and incidence of any single adverse event is approximately 1% or less in all patients [27]. The most common events are nonlife threatening like headache, nausea and emesis. Anaphylactic reactions are reported very infrequently with each of these agents with incidence one in 100,000 to one in 500,000 administrations [28].

Our study intended to evaluate the utility of Gadolinium Enhanced CT Angiography in diagnosing Obstructive Coronary artery disease as Compared to conventional Invasive Coronary Angiography that is presently the “Gold Standard” so that the results could be used to assess the feasibility of using Gadolinium as the contrast agent in those patients of Coronary Artery Disease who have a contraindication for iodinated Contrast agents.

Material and Methods

25 patients with Coronary Artery Disease were enrolled in the study who, after informed consent, agreed to undergo Invasive Coronary Angiography (ICA) followed/preceded by Gadolinium Enhanced Coronary CT Angiography. ICA and Gd-Enhanced Coronary CTA were done sequentially with time duration of minimum 2 days and not more than 7 days between the two modalities. Clinical worsening between the two modalities of investigation was excluded from the study. Other Exclusion Criteria were clinical instability, previous Revascularization (CABG/Stenting), inability to have adequate intravenous access to give Contrast, baseline creatinine Clearance <30 ml/min, contraindication to administer Heart Rate controlling drugs (Beta Blockers), any associated illness that would require separate use of CT scan (radiation) for evaluation like malignancy etc.

Invasive coronary angiography

It was performed with the standard Judkins Technique through Trans femoral Route. Those segments having a diameter >1.5 mm were analyzed. Stenosis ≥ 50% was considered as a true- positive finding. ICA was chosen as the standard of reference to validate CCT. The coronary 15-segment model was used for analysis. Renal functions were monitored before and 48 hours after ICA.

Protocol for gadolinium enhanced CCTA

CCT studies were performed with a 64-slice CT scanner. Patients with a heart rate of >60 bpm received 50 to 100 mg Metopolrol orally the night before and 1 h before the scan. If the heart rate was still >60 bpm at the time of the scan, intravascular Metopolrol in 2.5 mg aliquots up to a total of 10 mg was used to achieve a target heart rate of <60 bpm. The amount of Gadolinium used was as per body weight, with a maximum dose of 0.4 mmol/kg of body weight. The contrast was injected at a rate of 5 ml/s followed by 50 ml of isotonic saline solution injected into an antecubital vein through an 18 gauge canula. Injection protocol was as described by Carracosa et al. [29] and is as follows follows: bolus tracking was performed with a region of interest (ROI) placed into the left atrium and CT image acquisition was started 4 s after the signal density reached a predefined threshold of 80 Hounsfield units (HU). Cross-sectional images were reconstructed with a slice thickness of 0.675 mm in 0.3 mm intervals with the use of an ECG-gated reconstruction algorithm centered at 0%, 50%, 75% and 95% phases of the cardiac cycle, using a medium soft tissue convolution kernel.

CCT image analysis

CCT datasets were evaluated by a single experienced observer blinded to the patient’s clinical history and results of invasive coronary angiography. Single experienced observer was chosen to eliminate the inter-observer variation. The reconstructed image datasets was transferred to an offline workstation for post processing. Coronary segments were defined according to the 15-segment model of the American Heart Association/American College of Cardiology guidelines. Those segments having a diameter >1.5 mm were analysed. Coronary artery stenosis with a diameter reduction ≥ 50% was considered as positive findings (Figure 1).

Results

The Study was a Prospective, comparative study conducted over a period of 2 years in a Tertiary care centre. 25 patients admitted for evaluation of CAD were enrolled in the study after obtaining an Informed Consent. Mean Age (S.D) was 53.52 years (10.038) with a Range between 41 to 70 years. All patients were males. Maximum number of patients were in the age group of 41-49 years with a number of 12 (48%). 7 (28%) were in the age group of 50-51 years. 3 (12%) were in 60-69 and 70-79 years each. Mean (SD) BMI was 26.12 kg/m² (17.48), Range 153-217 HU. In comparison to ICA, on Per-segment basis, Gd-Enhanced CTA showed Sensitivity of 82.46%, Specificity of 97.50%, PPV of 85.45% and NPV.
of 96.95% (Figure 1). Weighted Kappa value was 1, suggestive of strong agreement between the two modalities rather than on the basis of chance. Highest agreement between the two modalities was when only one segment was diseased and lowest when 5 segments were diseased. However 2 of our patients had very high Calcium Score (>800). If these patients were excluded then Gd-Enhanced Coronary CTA detected 41 segments compared to 47 segments by ICA. This improved the Sensitivity to 87.23%, Specificity to 99.1%, PPV of 93.18% and NPV of 98.22%. Of 47 segments detected by ICA, 21 segments were in LAD, 11 in LCX and 15 in RCA. Of 41 Segments detected by Gd-Enhanced CTA, 19 were in LAD, 8 in LCX, 14 in RCA. Highest Percentage agreement between ICA and Gd-Enhanced CTA was with lesion in RCA (93%), Followed by LAD (90%) and Lowest for LCX (72%). Multivariate Analyses revealed that the diagnostic accuracy of Gd-Enhanced Coronary CTA correlated with Body Mass Index (BMI) and Coronary Calcification. For BMI Area under ROC (S.E) was 0.988 (0.0135), p<0.001, BMI of ≤ 27 kg/m² yielded a sensitivity of 100% with a specificity of 85.71% (Figure 2). Youden index J was 0.8571 (Associated criterion ≤ 27). For Coronary Calcification Correlation Coefficient (r) was -0.479 and p<0.017. There was no significant alteration in renal functions after Gadolinium administration. Mean Creatinine Clearance before and after Gadolinium administration was 84.45 ml/min and 82 ml/min respectively. No adverse effects occurred after Gadolinium administration in any patient (Figure 2).

One patient had abnormal course of right coronary artery between pulmonary artery and aorta which was picked by CT angiography (Figure 3). Two of our patients had very high Calcium Score (>800). Diffuse calcification making it almost impossible to assess for coronary stenosis (Figure 4).

**Discussion**

The present study was conducted in the Department of Cardiology and the Department of Radiology of Sher-i-Kashmir Institute of Medical Sciences, a Tertiary care Hospital. 25 patients of CAD were enrolled in the study that underwent invasive coronary angiography and Gadolinium Enhanced Coronary CTA. Direct comparison between the two modalities on per-segment basis revealed an acceptable sensitivity and specificity of Gd-Enhanced Coronary CTA that could make it an attractive alternative for non-invasive assessment of CAD in patients with contraindication for iodinated contrasts.

The overall sensitivity of Gd-Enhanced Coronary CTA was 82.46%, specificity of 97.50%, positive predictive value of 85.45% and negative predictive value of 96.95%. The sensitivity in our study is lower than that reported by Carrascosa et al. [29]. In their study gadolinium-enhanced CCT showed a sensitivity of 90.3%, specificity of 96.8%, and positive predictive value of 77.8% and negative predictive value of 98.8%. However, in our study, after excluding patients with Coronary Calcium Score of > 800, Sensitivity improved to 87.23%, Specificity 99.10%, PPV 93.18% and NPV 98.22%. These values are comparable to the results of Carrascosa et al. The Mean Lumen Attenuation achieved in our study was 183.48 with SD 17.48 (Range 153-217 HU). These values are slightly more than that in the study of Caracossa et al who had Mean Lumen Attenuation of 140.1 Hounsfield units (HU). This difference may possibly be due to the lower BMI of our patients. Achenbach et al. [30] and Knez et al. [31] compared coronary artery scanning using 4-MDCT scanners with invasive coronary angiography.

![Figure 1: Diagnostic value of Gd-CTA compared with ICA.](image)
and reported similar negative predictive values of 96% and 98%. However, the percentages of nonevaluable coronary segments and arteries were 6% and 32%, respectively [30,31]. Nieman et al. [32] reported sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 86%, 80%, and 97%, respectively, for identifying stenosis of 50% or more while using only 12 of the 16 detectors because of technical limitations. When considering that no segments were excluded from the analysis, their results were deemed excellent. Ropers et al. [33] reported sensitivity, specificity, positive predictive value, and negative predictive value of 92%, 93%, 79%, and 97%, respectively, for identifying stenosis of 50% or more using all 16 detectors. However, in their series, 12% of the arterial segments were excluded from the statistical analysis after they were considered nonevaluable.

Gul et al. [34] conducted a phantom study to evaluate the attenuation of serial dilutions of Gd and iodinated agents. This study was done on a 64-slice multirow detector CT (MDCT) scanner and e-speed scanner and CT attenuation Hounsfield units (CTHU) were compared. The authors evaluated 35 consecutive patients who underwent Gd-enhanced CTA. CTHU of aorta was measured at first, mid, and lowest slice levels with and without contrast administration. The image quality was graded on the basis of visualization of the coronary arteries (scale I-III; III demonstrating diagnostic image quality of the distal-most vessels). In a sub study, four patients with borderline renal insufficiency underwent CTA using Gd and iodinated contrast agents admixed in a 50:50 ratio. The phantom study showed that enhancement of various dilutions of Gd and iodine resulted in near identical CTHU with both e-speed and 64-slice scanners (r (2) > or =0.997). Mean CTHU with contrast at the top slice was 116 HU, at middle slice was 125 HU, and at the lower slice was 93 (111.14 ± 22). Quality evaluation showed 2 grade III, 9 grade II, and 24 grade I images (average quality of images 1.35). Mean CTHU was 222. The study demonstrated that Gd-enhanced contrast medium provides adequate enhancement of coronary vasculature, allowing for diagnostic evaluation of coronary arteries with new CT systems. Use of newer generations of multirow detector CT scanners should further enhance the quality of images.

Our study revealed that the diagnostic accuracy of GD-Enhanced Coronary CTA was significantly related to Body Mass Index (BMI). ROC curve for BMI revealed that at a cutoff value of 27 kg/m² below which GD-Enhanced Coronary CTA had a sensitivity of 100% and a specificity of 85.71%. Hence GD-Enhanced Coronary CTA may be better suited for patients with a BMI of < 27 kg/m². Our Study also revealed that the highest agreement between ICA and GD-Enhanced CTA was for RCA, followed by LAD and lowest for LCX. Hence GD-Enhanced CTA may be best suited to assess RCA and LAD disease.

Furthermore GD-Enhanced Coronary CTA may detect anomalous origin and course of coronaries.
However the use Gadolinium enhanced Coronary CT Angiography for estimation of Flow fractional reserve and its use in Acute Coronary Syndrome, as routine CT coronary angiography is used [35] needs to be further evaluated.

**Limitations**

In our study we have excluded patients who had undergone coronary revascularization either in the form of Coronary Stents or Bypass Grafts. Hence there is a need for additional studies to assess feasibility of Gd-Enhanced Coronary CTA in patients who have undergone coronary revascularization.

Notwithstanding the benefits of Non-invasive assessment, it needs to be emphasized that Coronary CTA is associated with a higher radiation exposure, approximately 2-3 times more than conventional ICA. Radiation exposure from CT Angiography accounts for about 70% of radiation while accounting for only 15% of all radiological procedures. Though hypothetical, yet there is a significant concern about adverse effects of such large amounts of radiation exposure including that of malignancy. Such concerns call for cautious and justified use of Coronary CT Angiography as well as use of various algorithms for radiation dose reduction during CT angiography.

**References**
