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Research paper

Diagnostic accuracy of semi-automatic quantitative metrics as an alternative to expert reading of CT myocardial perfusion in the CORE320 study

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ABSTRACT

Aims: To determine the diagnostic accuracy of semi-automatic quantitative metrics compared to expert reading for interpretation of computed tomography perfusion (CTP) imaging.

Methods: The CORE320 multicenter diagnostic accuracy clinical study enrolled patients between 45 and 85 years of age who were clinically referred for invasive coronary angiography (ICA). Computed tomography angiography (CTA), CTP, single photon emission computed tomography (SPECT), and ICA images were interpreted manually in blinded core laboratories by two experienced readers. Additionally, eight quantitative CTP metrics as continuous values were computed semi-automatically from myocardial and blood attenuation and were combined using logistic regression to derive a final quantitative CTP metric score. For the reference standard, hemodynamically significant coronary artery disease (CAD) was defined as a quantitative ICA stenosis of 50% or greater and a corresponding perfusion defect by SPECT. Diagnostic accuracy was determined by area under the receiver operating characteristic curve (AUC).

Results: Of the total 377 included patients, 66% were male, median age was 62 (IQR: 56, 68) years, and 27% had prior myocardial infarction. In patient based analysis, the AUC (95% CI) for combined CTA-CTP expert reading and combined CTA-CTP semi-automatic quantitative metrics was 0.87(0.84–0.91) and 0.86 (0.83–0.9), respectively. In vessel based analyses the AUC's were 0.85 (0.82–0.88) and 0.84 (0.81–0.87), respectively. No significant difference in AUC was found between combined CTA-CTP expert reading and CTA-CTP semi-automatic quantitative metrics in patient based or vessel based analyses($p > 0.05$ for all).

Conclusion: Combined CTA-CTP semi-automatic quantitative metrics is as accurate as CTA-CTP expert reading to detect hemodynamically significant CAD.

1. Introduction

Myocardial computed tomography perfusion imaging (CTP) when combined with coronary computed tomography angiography (CTA) has been shown in single and multicenter studies to have high diagnostic accuracy in defining the hemodynamic significance of a coronary stenosis.[1–7] The implementation of CTA into clinical practice has flourished over the past decade; however, the implementation of combined CTA-CTP has been limited by the level of expertise needed to interpret CTP images. Myocardial CTP image interpretation is visual and qualitative, in most published clinical studies[1,4,7,8] which requires training by expert readers in the identification and interpretation of

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Abbreviations list

CTA	Computed tomography angiography
CTP	Computed tomography perfusion
SPECT	Single photon emission computed tomography
ICA	Invasive coronary angiography
CAD	Coronary artery disease
ROC	Receiver operating characteristic
AUC	Area under the curve
LAD	Left anterior descending
LCX	Left circumflex
RCA	Right coronary artery

myocardial attenuation in all layers of the myocardium. Previous studies showed that visual assessment by expert readers is superior to the computer generated metrics for CTP image interpretation such as transmural perfusion ratio (TPR), when used alone.[9] We hypothesized that combination of TPR with other semi-automatic quantitative metrics improves its diagnostic accuracy to detect hemodynamic significance of coronary artery disease (CAD), while eliminates the dependence on high level of readers' expertise. The primary purpose of this study was to test whether the CTA expert reading plus combination of limited user input semi-automatic computer-derived quantitative CTP metrics is as accurate as the combined CTA-CTP both by expert reader visual interpretation to detect a hemodynamically significant coronary stenosis defined by combined invasive coronary angiography (ICA) and single photon emission computed tomography (SPECT) myocardial perfusion imaging.

2. Methods

2.1. Study population

The CORE320 multicenter diagnostic accuracy clinical study (www.clincialtrials.gov, NCT00934037) enrolled patients between 45 and 85 years of age with suspected or known CAD who were clinically referred for ICA between November 2009 and July 2011. The study design has been previously described.[10] In brief, the study was conducted at 16 international sites, 5 in North America, 2 in South America, 3 in Europe, 4 in Japan, and 2 in Singapore. Study participants underwent combined CTA-CTP and also SPECT prior to ICA. Study exclusion criteria included: known allergy to iodinated contrast media, elevated serum creatinine ($>$ 1.5 mg/dL) or calculated creatinine clearance of $<$ 60 mL/min, atrial fibrillation, second or third degree atrio-ventricular block, previous cardiac surgery, coronary intervention within the past 6 months, evidence of acute coronary syndrome with thrombolysis, Thrombolysis in Myocardial Infarction (TIMI) score $\geq$ 5 or elevated cardiac enzymes in the past 72 h, high radiation exposure ($\geq$ 50 mSv) in the 18 months before consent, and body mass index $>$ 40 kg/m^2 among others. All sites received study approval from their local institutional review boards, and all patients gave written informed consent.

2.2. Combined CTA-CTP acquisition and interpretation

The combined CTA-CTP acquisition methods have been previously described.[11] In brief, all computed tomography images were acquired on a 320 × 0.5 mm detector row system (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). Prior to the CTA scan oral (75–150 mg) or intravenous (up to 15 mg) metoprolol and sublingual, fast acting nitrates were administrated. The rest computed tomography simultaneously acquired the CTA and rest CTP imaging data. Twenty minutes after the administration of the sublingual nitrates for the rest CTA-CTP, stress CTP images were acquired during a continuous 6 min intravenous infusion of adenosine at a rate of 0.14 mg/kg/min intravenously. CTA and CTP acquisitions were performed with 50–70 mL of iodinated contrast (Iopamidol 370 mg iodine/mL) injected intravenously at 4.0–5.0 mL/s for each of the separate, axial, prospectively ECG-triggered acquisitions. All images were reconstructed and processed in a centralized core laboratory at the Johns Hopkins Hospital.

The CTA images were interpreted manually in a centralized blinded core laboratory by two experienced readers (Level 3 certified) and differences were resolved through consensus. A 19 segments coronary artery model was used as previously described.[12] All segments were graded visually for stenosis on an ordinal scale (no disease, stenosis 1–29%, 30–49%, 50–69%, 70–99%, and 100%). Stenosis diameter for segments graded visually as 30% or greater were then delineated by a semi-automatic contour detection algorithm: The user identified the lesion and a reference segment and the electronic calipers were placed automatically by the commercial software (Vitrea™ fX version 3.0 workstation; Vital Images, Minnetonka, MN, USA). The user then visually assessed and edited the calipers, if needed and recorded the percent stenosis.

The CTP images were visually interpreted in a centralized blinded core laboratory by two experienced readers and differences were resolved through consensus. The CTP expert readers were blinded to the CTA interpretations. As previously described, a 13 segment myocardial perfusion model was used with the exclusion of the most apical segment (i.e 12 segments were included in analysis).[11] For each myocardial segment, rest and stress perfusion images were visually assessed using a categorical scale: 0, normal; 1, mild perfusion deficit; 2, moderate perfusion deficit; 3, severe perfusion deficit and a summed score was then calculated for all segments.[1] The quantitative CTP metrics were derived automatically with limited user input.[11] A technologist loaded the rest and stress CTP images into a software package (Advanced Myocardial Perfusion, Toshiba Medical Systems). The software automatically and equally divided the myocardium into three myocardial

Table 1
Computation of quantitative CTP metrics.

Quantitative Metric[a]	Definition
Transmural Myocardial Attenuation	Contrast attenuation density in the myocardial tissue
Subendocardial Attenuation[a]	Contrast attenuation density in the inner third of myocardial thickness (under the endocardium)
Subepicardial Attenuation[a]	Contrast attenuation density in the outer third of myocardial thickness (under the epicardium)
Transmural Perfusion Ratio	Subendocardial mean contrast attenuation density divided by subepicardial mean contrast attenuation density
Perfusion Index	Mean myocardial contrast attenuation density divided by mean left ventricular blood pool contrast attenuation density
Perfusion Index Reserve	Stress perfusion index divided by rest perfusion index
Myocardial/Arterial Input Function(AIF) Ratio	Mean myocardial contrast attenuation density divided by mean contrast attenuation density in descending aorta (area under the contrast curve)
Myocardial/AIF Reserve	Myocardial/AIF ratio at stress divided by myocardial/AIF ratio at rest

[a] The myocardial thickness was divided equally into three layers to obtain attenuation values in subendocardial, midmyocardial and subepicardial layers. All metrics are computed at a myocardial segment level.