Dipyridamole Stress and Rest Myocardial Perfusion by 64-Detector Row Computed Tomography in Patients With Suspected Coronary Artery Disease

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Recently, stress myocardial computed tomographic perfusion (CTP) was shown to detect myocardial ischemia. Our main objective was to evaluate the feasibility of dipyridamole stress CTP and compare it to single-photon emission computed tomography (SPECT) to detect significant coronary stenosis using invasive conventional coronary angiography (CCA; stenosis >70%) as the reference method. Thirty-six patients (62 ± 8 years old, 20 men) with previous positive results with SPECT (<2 months) as the primary inclusion criterion and suspected coronary artery disease underwent a customized multidetector-row CT protocol with myocardial perfusion evaluation at rest and during stress and coronary CT angiography (CTA). Multidetector-row computed tomography was performed in a 64-slice scanner with dipyridamole stress perfusion acquisition before a second perfusion/CT angiographic acquisition at rest. Independent blinded observers performed analysis of images from CTP, CTA, and CCA. All 36 patients completed the CT protocol with no adverse events (mean radiation dose 14.7 ± 3.0 mSv) and with interpretable scans. CTP results were positive in 27 of 36 patients (75%). From the 9 (25%) disagreements, 6 patients had normal coronary arteries and 2 had no significant stenosis (8 false-positive results with SPECT, 22%). The remaining patient had an occluded artery with collateral flow confirmed by conventional coronary angiogram. Good agreement was demonstrated between CTP and SPECT on a per-patient analysis (kappa 0.53). In 26 patients using CCA as reference, sensitivity, specificity, and positive and negative predictive values were 88.0%, 79.3%, 66.7%, and 93.3% for CTP and 68.8, 76.1%, 66.7%, and 77.8%, for SPECT, respectively (p = NS). In conclusion, dipyridamole CT myocardial perfusion at rest and during stress is feasible and results are similar to single-photon emission CT scintigraphy. The anatomical-perfusion information provided by this combined CT protocol may allow identification of false-positive results by SPECT. © 2010 Elsevier Inc. All rights reserved.

In the previous few years, multidetector computed tomography has emerged as a powerful tool to evaluate patients with suspect coronary artery disease. Sixty-four–slice multidetector computed tomography has demonstrated high accuracy to detect significant coronary stenosis.1–8 A diagnostic tool that can provide detailed information on myocardial perfusion and coronary angiography at the same time will not only help in the prognostic assessment of the patient but also be valuable in choosing appropriate therapeutic strategies. The purpose of this study was to evaluate the feasibility of dipyridamole stress computed tomographic perfusion (CTP) and compare the diagnostic accuracy of dipyridamole stress myocardial CTP and single-photon emission CT perfusion defects to detect significant coronary stenosis (>70%) using CT angiography (CTA) and conventional coronary angiography (CCA) as the reference standards.

Methods

This is a prospective cohort study of consecutive patients with a positive single-photon emission CT/Myocardial perfusion image (MPI) examination who met eligibility criteria and agreed to sign informed consent to participate in this CT research stress perfusion study.

Patient selection for the study included 523 consecutive patients in our institution who underwent scintigraphic stress testing in the previous 2 months for suspected coronary artery disease and had a positive stress test result with a high probability clinically indicating invasive angiography (Figure 1). The decision to undergo cardiac catheterization was made on clinical basis and single-photon emission CT
results. Results of coronary CTA and CTP were blinded to the attending physician.

Thirty-six patients with suspected coronary artery disease and positive single-photon emission CT results 2 months previously underwent a customized (20-minute) multidetector CT protocol with myocardial perfusion evaluation at rest and during stress and coronary CTA. Multidetector computed tomography was performed in a 64-slice scanner (Aquillion 64, Toshiba, Ottawara/Japan). Exclusion criteria included asthma, pregnancy, renal insufficiency (serum creatinine >1.5 mg/dl), and known allergy to iodinated contrast or dipyridamole. All patients signed informed consent and our institutional ethic review board approved the study. All patients were instructed to have a diet free of caffeine 24 hours before examination. Multidetector CT customized protocol included 2 contrast-enhanced scans. Calcium score was not performed (Figure 2). The first scan was a stress CT perfusion only, with low resolution. The second scan was done for coronary arteries (Table 1). In addition, perfusion information was sought. Stress CTP image was obtained 2 minutes after intravenous infusion of dipyridamole 0.56 mg/kg every 4 minutes. During dipyridamole infusion, heart rate, blood pressure, electrocardiogram, and patients’ symptoms were monitored continuously. Helical acquisition for CTP was initiated, using a real-time bolus tracking technique, at the time of peak left atrial filling with contrast, which was determined visually (no specific threshold in Hounsfield units was used). Immediately after the stress scan, infusion with aminophylline (USP - São Paulo/Brazil) 240 mg was started to revert vasodilatation induced by dipyridamole. Before a second perfusion/CT angiographic scan at rest, intravenous metoprolol was administered until a maximum dose of 20 mg to lower heart rate and improve image quality. Scanning at rest was performed using automatic trigger detection on the descending aorta set to 180-HU signal density.

Two independent blinded observers with no knowledge of clinical data or other examinations performed visual and semiquantitative analyses for each method to include CTP, CTA and CCA and any discordance was resolved by consensus. Data analysis was performed to correlate myocardium CTP and single-photon emission computed tomography (SPECT) and to compare diagnostic accuracy of myocardium CTP and SPECT to the reference standards (CTA and CCA; coronary stenosis >70% as reference).

The standard American College of Cardiology/American Heart Association 17-segment model was used to identify perfusion defects. For comparison of perfusion data (CTP vs SPECT) with coronary anatomical data derived from CTA/CCA, we consolidated the segmental data into 3 territories according to the American College of Cardiology/American Heart Association recommendation (per-vessel analysis). CTP datasets were evaluated on a true short axis, with 2- and 4-chamber views, with 8-mm-thick multiplanar reformatted images. Thicker slices were used to improve low-contrast resolution for visual myocardium perfusion analysis, as de-
scribed previously.\textsuperscript{10} Narrow window and level were also used (350 W and 150 L). Initial evaluation of perfusion defects started in the diastolic phase, and for potential artifacts readers could use the systolic phase to confirm the perfusion defect. True perfusion defects were defined as subendocardial hypoenhancement, encompassing $\geq 25\%$ of transmural extent, present in different phases of the cardiac cycle and within a specific coronary territory.

CT angiographic raw data analysis was evaluated by 2 level-3 1-year fellowship-trained experts on coronary CTA, and stenoses were graded as 0\% to 50\% (mild), 51\% to 70\% (moderate), and $>70\%$ (severe). Coronary segments with severe calcification and smaller stents with no lumen visualization were graded as uninterpretable. Quantitative coronary assessment was performed in all patients who underwent CCA. Blinded readers considered coronary stenosis $\geq 70\%$ as a hemodynamically significant lesion.

Statistical analysis was done using STATA 8.0 (STATA Corp., College Station, Texas). Continuous variables were expressed as mean $\pm$ SD and categorical variables as absolute number and percentage. Comparison between discrete variables used chi-square or Fisher's exact test, as appropriate. Tables of frequency were used for sensitivity, specificity, and predictive values. Diagnostic values for perfusion methods were compared using test of proportions and McNemar test. Kappa analysis was performed to evaluate agreement.

Figure 3. Positive CTP images during stress (A, white arrow) and at rest (B) with matched single-photon emission CT images during stress (C, white arrow) and at rest (D) and anatomic concordance by CT angiogram (E) and conventional coronary angiogram (F) showing in-stent restenosis.

Figure 4. Single-photon emission CT-by-CTP correlation shows false-positive anterior single-photon emission computed tomogram (B) and CTP images at rest (C) and stress (A) and normal left anterior descending coronary artery on curved reformatted image by computed tomography (D). The arrow in (B) indicates mild anterior myocardial perfusion defect.
Results

Thirty-six patients (62 ± 8 years old, 20 men) were enrolled in this protocol and underwent SPECT and multi-detector computed tomography (stress perfusion and CTA). Clinical data are listed in Table 2. The most common clinical symptoms were chest pain in 75% and dyspnea in 22%. All 36 patients completed the protocol with no adverse event, with a mean total radiation dose of 14.7 ± 3.0 mSv (minimum 11.4 mSv, maximum 20.3 mSv) and with interpretable scans. Mean, minimum, and maximum radiation doses for CTP scans were 3.4 ± 0.3, 3.0, and 4.1 mSv, respectively, and those for CT angiographic scans were 11.6 ± 2.3, 8.4, and 16.2 mSv.

Mean basal heart rate was 64 ± 9 beats/min. After dipyridamole stress, heart rate increased to 82 ± 12 beats/min; scan acquisition at rest (after aminophylline and metoprolol administration) showed that heart rate returned to 64 ± 7 beats/min.

In the 36 patients, comparing SPECT to CTP (Figures 3, 4, and 5) by per-patient analysis showed good agreement of 75% with a kappa value of 0.53 (p < 0.01; Figure 6).

Diagnostic accuracy, using per-territory analysis, of CTP and SPECT (Figure 7) was calculated using CTA as the reference standard (coronary stenosis >70%) with sensitivity, specificity, and positive and negative predictive values of 29 of 42 (69%), 54 of 61 (89%), 29 of 36 (81%), and 54 of 67 (81%) for CTP and 27 of 42 (64%), 47 of 61 (77%), 27 of 41 (66%), and 47 of 62 (76%) for SPECT, respectively (p = NS).

Twenty-six patients underwent invasive angiography without complications. On per-patient analysis, CTP was compared to CCA, showing a sensitivity of 17 of 18 (94%), specificity of 6 of 8 (75%), positive predictive value of 17 of 19 (89%), and negative predictive value of 6 of 7 (86%). In these patients, on per-territory analysis with CCA as the reference standard (stenosis >70%), diagnostic values for CTP were 22 of 25 (88%), 42 of 53 (80%), 22 of 33 (67%), and 42 of 45 (93%) and those for SPECT were 22 of 32 (69%), 35 of 46 (76%), 22 of 33 (67%), and 35 of 45 (78%), respectively (p = NS).

Discussion

In this study, the first to our knowledge, using dipyridamole to perform stress myocardial CTP imaging on a 64-slice CT scanner, we showed that a comprehensive protocol was able to assess myocardial perfusion imaging during stress and at rest and coronary anatomy with good diagnostic accuracy, in short duration, and with an acceptable radiation dose. Nuclear stress scintigraphy is the most clinically used method to evaluate myocardial ischemia and could be done in a hybrid positron emission tomographic/CT association.12,13 Recently, a few studies have evaluated stress myocardial perfusion by cardiac computed tomographic.14 –16 None used dipyridamole as a vasodilator stress perfusion agent, which has a lower cost. Another unique characteristic of our study is that we evaluated per-
fusion defects during stress and at rest on a 64-slice scanner with an acceptable radiation dose using a customized protocol that included low tube current during stress acquisition. One previous study that evaluated adenosine stress perfusion computed tomography on 64- and 256-slice scanners included only the stress perfusion phase, which was also used to evaluate coronary stenosis. It might be detrimental for image quality and diagnostic accuracy to perform coronary evaluation during the stress phase because adenosine infusion increases heart rate. In our protocol, coronary evaluation was performed at rest with lower heart rates and improved image quality.

Furthermore, only newer scanners with advanced technology are being considered to perform stress cardiac computed tomography (2 sources, 320 slices) due to radiation constraints. Our study reinforces that CTP imaging during stress and at rest on a 64-slice scanner is feasible, with mean total radiation dose of 14.7 mSv. Once 64-slice scanners are the standard CT equipment used for coronary CTA and much more available than advanced CT equipment, such as 2-source, 320-slice, and others, our data will be important to demonstrate that CTP can be done appropriately in a larger set of machines and therefore could reach a larger number of patients in need of such evaluation. A potential application of this protocol in newer-generation scanners is the possibility to assess first the coronary anatomy and grade the severity of coronary stenosis and, based on those results, decide to perform stress CTP, thus avoiding stress in patients with no disease, severe left main coronary artery stenosis, or 3-vessel disease.

The customized CT acquisition protocol used was feasible and accurate and had a duration of only 20 minutes compared to longer protocols for scintigraphy. On dipyridamole stress CTP acquisition heart rate increased 21% (median 18 beats/min), but this scan was used only to evaluate the stress myocardial perfusion component and not for coronary anatomy, which potentially would have poorer image quality due to a high heart rate. Image data to evaluate stress myocardial perfusion defects despite a higher heart rate present good image quality with no unevaluable scans. Qualitatively, it did not appear that levels of heart rate achieved with our stress perfusion CT scans negatively affected the quality of perfusion scans, but no formal testing was done to confirm this. Aminophylline was administrated before scanning at rest to revert the dipyridamole effect and metoprolol was used to decrease heart rate and improve CT scan image quality at rest and accuracy for evaluation of coronary stenosis. To reinforce this strategy resulting in an appropriate heart rate for CTA, heart rate at rest with our scan acquisition was similar to that at baseline. Total amount of contrast given at computed tomography was 140 ml and mean contrast dose at catheterization was 80 ± 10 ml. However, no patient developed contrast medium-induced nephropathy or allergy.
In this feasibility study, patient selection was based on a positive single-photon emission CT examination, which could have introduced verification bias. However, this study was performed to demonstrate, for the first time, the feasibility of dipyridamole stress myocardial CTP on a standard 64-slice CT scanner, our primary objective. It was not the purpose of our study to compare perfusion methods. Although our study was not planned to compare perfusion methods, we presented diagnostic performance data, such as accuracy, as a way to confirm the feasibility of our technique and possibly shed some light on the true accuracy of this novel technique, which should be investigated ideally in a large multicenter trial. Moreover, recent new techniques are available for decreased radiation dose. In our present study, these recent techniques, including dose modulation, prospective gating, and 100-kV protocols, were not used.17