Quantification of Myocardial Perfusion Using Multi-Detector Computed Tomography: Validation Against Invasive Coronary Angiography

N Kachenoura[1], T Gaspar[2], JA Lodato[1], DME Bardo[1], B Newby[1], S Gips[2], N Peled[2], RM Lang[1], V Mor-Avi[1]

[1]University of Chicago, Chicago, Illinois, USA
[2]Lady Davis Carmel Medical Center, Haifa, Israel

Abstract

While CT coronary angiography (CTCA) has been validated, the potential of CT to evaluate perfusion has not been explored. We sought to: (1) develop and test a technique for quantitative assessment of myocardial perfusion from CT images, (2) identify the underlying causes of perfusion abnormalities detected by CT, (3) determine the added diagnostic value of CT perfusion. We studied 84 consecutive patients undergoing clinical CTCA. Accuracy of automated detection of perfusion abnormalities was determined against invasive coronary angiography findings combined with known prior myocardial infarction (MI). Perfusion abnormalities were detected in 29/64 patients in 47 vascular territories, of which 36 were confirmed as abnormal. Of these 36, 10 were associated with prior MI, while 26 corresponded to significant stenosis. The addition of perfusion to CTCA improved its diagnostic accuracy. In conclusion, myocardial perfusion is a potentially valuable addition to CT tools for the evaluation of coronary artery disease without additional cost in radiation dose or contrast load.

1. Introduction

Multidetector computed tomography (MDCT) is the most recent addition to the arsenal of cardiac imaging modalities, which is increasingly used as an alternative to invasive coronary angiography (ICA) [1]. The diagnostic value of CTCA has been established against conventional techniques used for the detection of coronary artery disease (CAD), including ICA and SPECT myocardial perfusion imaging (MPI) [2].

Nevertheless, the value of CTCA is limited in patients with severe coronary calcification, intracoronary stents that interfere with visualization of the coronary lumen and high heart rates that may result in motion artifacts. Thus, studies in unselected patients have reported low levels of agreement between CTCA and ICA [3]. It has been suggested that intramyocardial distribution of contrast may be related to perfusion. Studies have demonstrated hypo-enhanced areas corresponding to myocardial scar tissue in a small number of patients post MI [4,5], and in animal models of acute MI [5,6]. The visualization of these perfusion defects is operator-dependent and sometimes difficult, because it requires repeated manipulations of the contrast window.

Because information on coronary stenosis and myocardial perfusion is not physiologically identical but rather complementary, we hypothesized that perfusion information, which can be extracted from images acquired for CTCA without additional radiation exposure or contrast load, could improve the diagnostic accuracy of MDCT evaluation of CAD, especially in patients with equivocal CTCA results. This information could provide the basis for a quantitative technique for detection of perfusion defects, which would overcome the subjective nature of the visual assessment of myocardial perfusion.

Accordingly, this study was designed to determine the value of myocardial perfusion assessment in consecutive patients referred to CTCA, irrespective of calcium scores, presence of stents or heart rate. Our specific aims were: 1) to develop a technique for quantitative assessment of myocardial perfusion using analysis of MDCT images, 2) to identify the underlying causes of perfusion abnormalities detected by MDCT; 3) to test the accuracy of this technique against ICA, 4) to determine the added value of perfusion when combined with CTCA.

2. Methods

We studied 84 consecutive patients who underwent CTCA for the evaluation of CAD who also had ICA and/or MPI. Patients with coronary bypass grafts and patients who underwent percutaneous coronary interventions between the diagnostic ICA and CTCA or MPI, were excluded. 20/84 patients who had a normal MPI study and no hemodynamically significant stenosis on CTCA (<50% stenosis) were used as controls (age: 62±10, 12 male). The remaining 64/84 patients comprised the main study group (age: 58±13, 48 male).

2.1. MDCT imaging

All CTCA studies were clinically indicated and performed according to the standard clinical protocol. Patients received the beta-blocker metoprolol to achieve a target heart rate of <70 bpm. Standard contraindications to CTCA were observed. Images were obtained using an MDCT scanner (64-channels, Philips) with retrospective ECG-gating. A nonionic iodinated contrast agent was used (40-80 ml iv at 5-6 ml/sec).

2.2. MDCT image analysis

MDCT image analysis was performed using Extended Brilliance Workspace software (Philips). Regional myocardial perfusion was measured on the same phase of the cardiac cycle used for CTCA (75% of RR interval). After the long axis of the left ventricle was identified, 3 short axis planes were selected (figure 1). Slice thickness was set at 1 mm. These 3 slices were used to define 16 myocardial segments (6 basal, 6 mid-ventricular, 4 apical) using standard segmentation. In each segment, subendocardial and subepicardial regions of interest (ROI) were drawn, while excluding coronary arteries, papillary muscles and endocardial trabeculae. In each ROI, mean x-ray attenuation was measured. Mean attenuation was also measured in an elliptical ROI placed inside the LV cavity adjacent to each myocardial segment (figure 1). Perfusion index was then calculated as attenuation measured in the myocardial ROI divided by that in the adjacent LV cavity ROI.
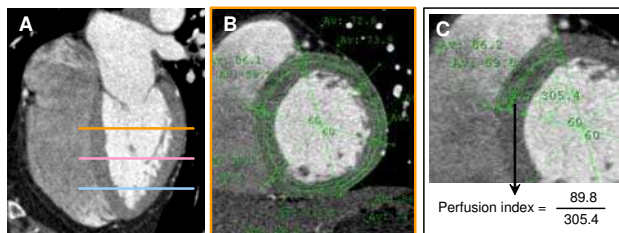

Figure 1. Perfusion analysis of MDCT images. An apical view of the left ventricle (A) was used to select 3 short-axis slices, and mean x-ray attenuation was measured in each myocardial ROI (B). Segmental perfusion index was calculated (C).

2.3. Detection of perfusion abnormalities

Perfusion indices obtained in the control group were averaged for each segment and used as normal values. In each segment, [median – SD] of the control group was used as a threshold for objective detection of perfusion abnormalities. A territory of an individual coronary artery was considered abnormal when the perfusion index was abnormal in at least two contiguous segments. For the patient-by-patient analysis, abnormal perfusion was diagnosed when at least one territory was abnormal.

2.4. Inter-technique comparisons

To allow comparisons of MDCT perfusion against coronary stenosis noted on ICA, coronary anatomy depicted on each patient's MDCT volume rendering of the heart was used to determine the perfusion territory of each artery and its major branches (figure 2). This approach was chosen, rather than using standardized perfusion maps, to avoid assigning myocardial segments to incorrect vascular territories. The specific location of stenosis, when detected on CTCA or ICA, was used to determine which myocardial segments would be affected.
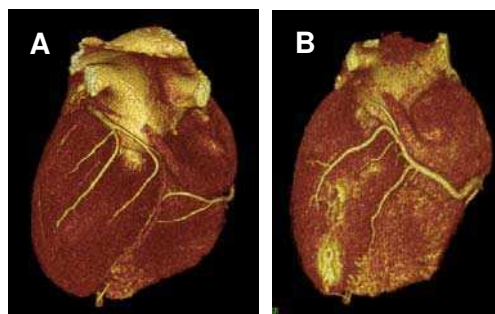

Figure 2. Examples of 3D renderings obtained in patients with different coronary anatomy: infero-lateral wall supplied by LCX and its marginal branches (A) and RCA (B).

CTCA data on coronary stenosis were mapped into myocardial segments by assigning to each segment a grade on a 0 to 3 scale (0: supplied by a normal artery, 1: supplied by an artery with <50% stenosis, 2: 50-70% stenosis, 3: >70% stenosis).

ICA findings were interpreted in a similar manner with one difference. To create a reference technique, against which all other techniques in this study would be compared, the possibility of abnormal perfusion despite patent arteries due to previous interventions was taken into account by combining ICA findings with history of MI, irrespective of current vessel status. To this effect, each myocardial segment was assigned a grade on a 0 to 4 scale (0: supplied by a normal artery, 1: supplied by an artery with <50% stenosis, 2: 50-70% stenosis, 3: >70% stenosis, 4: documented previous MI).

For both techniques, ICA and CTCA, grade >1 indicated abnormality, and a territory of a coronary artery was considered abnormal when at least one abnormal myocardial segment was detected in that territory. Abnormality was diagnosed in a patient when at least one abnormal territory was present.

2.5. Statistical analysis

The agreement between each of the tested techniques and the reference technique was assessed by calculating sensitivity, specificity, positive and negative predictive

values (PPV, NPV) and accuracy. In addition, histograms of myocardial segments by perfusion index were plotted separately for segments classified by the reference technique as normal and abnormal. Normal distribution was fitted to each histogram to calculate the overlap between normal and abnormal segments. These data were used to obtain cut-off values for ruling out perfusion abnormality with different levels of confidence.

3. Results

On ICA, 32/64 patients (50%), had stenosis >50%. Nineteen of 64 patients had prior coronary interventions (30%), including 18 with stent implantation. Thirteen patients had documented MI, including six patients with stents. Thus, according to the reference technique, 45/64 patients (70%) had abnormalities (77 vascular territories: 33 LAD, 23 LCX, 21 RCA).

Values of segmental perfusion index calculated in the control group showed a consistent pattern among subjects with the highest values in the anteroseptal wall. Segmental thresholds, defined as the lower limit of the normal range, were used for detection of perfusion abnormalities (figure 3).

Perfusion abnormalities were detected in 29 patients (173 segments, 47 territories). Figure 4 shows the breakup of the abnormal territories by grades assigned to them by the reference technique. First, the majority of these territories (36/47, 77%) had abnormal reference grades 2, 3 (stenosis >50%) and 4 (prior MI), thus confirming the causes of MDCT perfusion abnormalities. Importantly, grade 3 was assigned to most of these abnormal territories (22/32, 69%), indicating that perfusion abnormalities can be detected at rest not only in post MI scar, but also in myocardial tissue with severely restricted blood supply. Of note, the relatively large number of false positive perfusion abnormalities reflected by references grades 0 or 1 (11/47 or 23% territories) was related to image quality: the proportion of images with

suboptimal quality (8/11 or 72 % territories) was considerably higher than in correctly identified abnormal territories (11/36 or 31%).
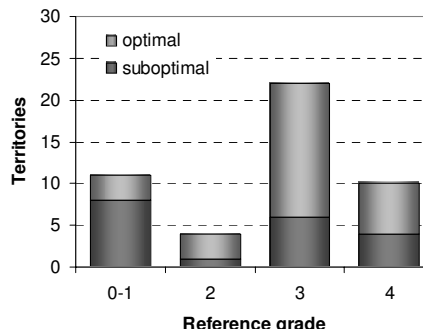
Figure 4. Breakup by reference grade and by image quality of vascular territories with abnormal CT perfusion.

	Sens.	Spec.	PPV	NPV	Accur.
CTCA	0.87	0.79	0.91	0.71	0.84
CT perfusion	0.60	0.89	0.93	0.49	0.69
CTCA + CT perfusion	0.96	0.68	0.88	0.87	0.88

Table 1. Agreement with the reference technique (ICA+history of MI) in 64 non-selected patients referred for CTCA, calculated on a patient-by-patient basis.

Table 1 shows side-by-side statistics of agreement between subendocardial MDCT perfusion, CTCA and the combination of these techniques against the reference technique on a patient basis. Analysis of transmural MDCT perfusion showed lower levels of agreement.

MDCT perfusion agreed with the reference technique in 44/64 patients, corresponding to accuracy 0.69 (Table 1). While sensitivity and NPV were moderate, specificity and PPV were high (>0.85). CTCA alone agreed with the reference technique in 54/64 patients (84%). The addition of perfusion to CTCA findings improved the diagnostic accuracy with a considerable increase in sensitivity and NPV, despite a decrease in specificity and PPV (Table 1).
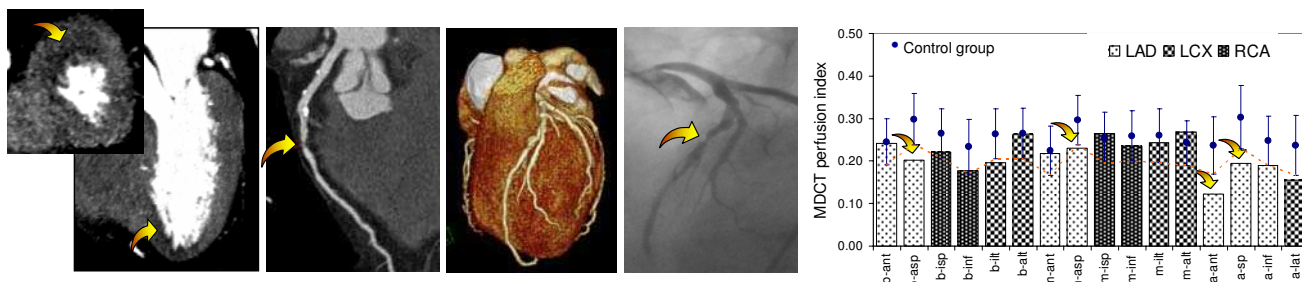
Figure 3. MDCT images obtained in a patient with no history of cardiac events. The patient had unstable angina and no conclusive evidence of acute myocardial infarction. CTCA revealed severe stenosis in the LAD, distal to the first diagonal branch, which was confirmed by ICA. MDCT images revealed a subendocardial area of subtle hypoenhancement in the apical anterior wall extending to the septum. Regional perfusion index (bar diagram shown with the normal values) was below the lower limit of the normal range (dashed line) in the mid anteroseptal and the apical segments (green bars), while the mid-anterior segment supplied by the first diagonal branch retained normal perfusion.

The reference technique detected 352 abnormal segments out of 1024. Histograms of x-ray attenuation showed almost complete overlap between normal and abnormal segments (figure 5A). Following normalization by attenuation in regional LV cavity, the distribution of the perfusion index differed between these two groups of segments (figure 5B). The lack of overlap in the higher range allowed us to define cut-off values for ruling out abnormalities with different levels of confidence.
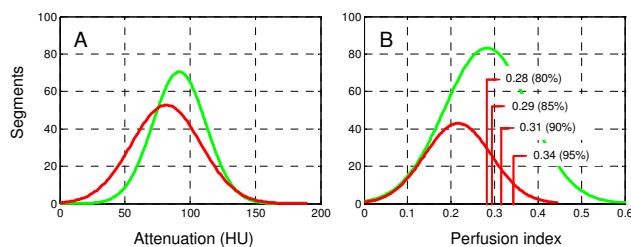

Figure 5. Distribution of x-ray attenuation (A) and perfusion index values (B) in normal (green) and abnormal (red) segments.

4. Discussion and conclusions

This is the first study to validate quantitative MDCT evaluation of myocardial perfusion against an ICA-based reference technique. Our primary goal was to test the hypothesis that perfusion abnormalities detected by MDCT in consecutive patients referred for CTCA, irrespective of calcium load, heart-rate and/or previous interventions including stenting, have an underlying etiology, such as coronary stenosis or history of MI.

Since x-ray attenuation depends on the specific location of a myocardial ROI because of beam hardening and varies among patients depending on body habitus, cardiac output, contrast dose and infusion rate, we normalized myocardial attenuation by that in the adjacent LV cavity to obtain a standardized perfusion index.

Because it is known that resting perfusion can be normal despite the presence of obstructive CAD, we did not expect to see high levels of agreement between CT perfusion and the reference technique. Nevertheless, when tested in a relatively large group of unselected patients, our perfusion index objectively detected abnormalities with surprisingly high levels of accuracy. Importantly, the majority of perfusion abnormalities detected at rest were associated with either prior MI, as previously reported [4,5,7], or reduced blood supply secondary to significant stenosis. This latter previously unknown finding may prove to be clinically useful.

A limitation of our methodology is that perfusion measurements were performed in only three manually selected slices of the left ventricle. This approach is subjective and may potentially lead to missing small perfusion abnormalities. To overcome this limitation, a volumetric technique is currently in development.

Quantitative assessment of myocardial perfusion is a valuable addition to MDCT tools for the noninvasive evaluation of CAD without additional radiation dose or contrast load. Our results support its use in every patient referred for CTCA, especially the problematic patients with high calcium scores and/or stents.

References

[1] Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de FP, George R, Kaufmann P, Kopp AF, Knuuti J, Ropers D, Schuijf J, Tops LF, Bax JJ: Cardiac computed tomography: indications, applications, limitations, and training requirements: Report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. Eur Heart J 2008;29:531-56

[2] Schuijf JD, Wijns W, Jukema JW, Atsma DE, de RA, Lamb HJ, Stokkel MP, bbets-Schneider P, Decramer I, De BP, van der Wall EE, Vanhoenacker PK, Bax JJ: Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol 2006;48:2508-14

[3] Kuettner A, Kopp AF, Schroeder S, Rieger T, Brunn J, Meisner C, Heuschmid M, Trabold T, Burgstahler C, Martensen J, Schoebel W, Selbmann HK, Claussen CD: Diagnostic accuracy of MDCT angiography in patients with angiographically proven coronary artery disease. J Am Coll Cardiol 2004;43:831-9

[4] Mahnken AH, Koos R, Katoh M, Wildberger JE, Spuentrup E, Buecker A, Gunther RW, Kuhl HP: Assessment of myocardial viability in reperfused acute myocardial infarction using 16-slice computed tomography in comparison to magnetic resonance imaging. J Am Coll Cardiol 2005;45:2042-7

[5] Gerber BL, Belge B, Legros GJ, Lim P, Poncelet A, Pasquet A, Gisellu G, Coche E, Vanoverschelde JL: Characterization of acute and chronic myocardial infarcts by MDCT: comparison with contrast-enhanced magnetic resonance. Circulation 2006;113:823-33

[6] Hoffmann U, Millea R, Enzweiler C, Ferencik M, Gulick S, Titus J, Achenbach S, Kwait D, Sosnovik D, Brady TJ: Acute myocardial infarction: contrast-enhanced multi-detector row CT in a porcine model. Radiology 2004;231:697-701

[7] Nikolaou K, Sanz J, Poon M, Wintersperger BJ, Ohnesorge B, Rius T, Fayad ZA, Reiser MF, Becker CR: Assessment of myocardial perfusion and viability from routine contrast-enhanced 16-detector-row computed tomography of the heart: preliminary results. Eur Radiol 2005;15:864-71

Address for correspondence:

Victor Mor-Avi, PhD
University of Chicago MC5084,
5841 S. Maryland Ave., Chicago Illinois 60637.
E-mail: vmoravi@medicine.bsd.uchicago.edu