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Incremental value of myocardial perfusion over coronary angiography by spectral computed tomography in patients with intermediate to high likelihood of coronary artery disease

Patricia M. Carrascosa*, Alejandro Deviggiano, Carlos Capunay, Roxana Campisi, Marina López de Munain, Javier Vallejos, Carlos Tajer, Gaston A. Rodriguez-Granillo

Department of Cardiovascular Imaging, Diagnóstico Maipú, Buenos Aires, Argentina

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ABSTRACT

Purpose: We sought to explore the diagnostic performance of dual energy computed tomography (DECT) for the evaluation of myocardial perfusion in patients with intermediate to high likelihood of coronary artery disease (CAD).

Materials and methods: Consecutive patients with known or suspected CAD referred for myocardial perfusion imaging by single-photon emission computed tomography (SPECT) constituted the study population and were scanned using a DECT scanner equipped with gemstone detectors for spectral imaging, and a SPECT. The same pharmacological stress was used for both scans.

Results: Twenty-five patients were prospectively included in the study protocol. The mean age was 63.4 ± 10.6 years. The total mean effective radiation dose was 7.5 ± 1.2 mSv with DECT and 8.2 ± 1.7 mSv with SPECT ($p = 0.007$). A total of 425 left ventricular segments were evaluated by DECT, showing a reliable accuracy for the detection of reversible perfusion defects [area under ROC curve (AUC) 0.84 (0.80–0.87)]. Furthermore, adding stress myocardial perfusion provided a significant incremental value over anatomical evaluation alone by computed tomography coronary angiography [AUC 0.70 (0.65–0.74), $p = 0.003$].

Conclusions: In this pilot investigation, stress myocardial perfusion by DECT demonstrated a significant incremental value over anatomical evaluation alone by CTCA for the detection of reversible perfusion defects.

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1. Introduction

Computed tomography coronary angiography (CTCA) has been established as an accurate non-invasive diagnostic tool able to evaluate the presence and severity of obstructive lesions in patients with intermediate likelihood of coronary artery disease (CAD) [1,2].

Notwithstanding, obstructive lesions detected by CTCA have also shown a weak correlation with the presence of ischemia, being this relevant mainly in patients with intermediate to high likelihood of CAD [3]. The assessment of the functional significance of coronary stenoses by means of cardiac computed tomography has been therefore the focus of intense research during the last decade, and one of the available strategies is myocardial perfusion assessment under pharmacological stress [4–8].

Dual energy CT (DECT) imaging provided with gemstone detectors for spectral imaging appears as an interesting technique for myocardial perfusion imaging, mainly driven by its ability to obtain synthesized monochromatic image reconstructions that might attenuate some technical issues related to the polychromatic nature of X-rays and the energy dependency of X-ray attenuation [9].

We therefore sought to explore the diagnostic performance of DECT for the evaluation of myocardial perfusion versus single-photon emission computed tomography (SPECT) and its potential incremental value over anatomical assessment in patients with intermediate to high likelihood of CAD.

Abbreviations: DECT, dual energy computed tomography; SPECT, single-photon emission computed tomography; CT, computed tomography; CTCA, computed tomography coronary angiography; CAD, coronary artery disease.

* Corresponding author at: Av Maipú 1668, Vicente López (B1602ABQ), Buenos Aires, Argentina. Tel.: +54 11 48377596; fax: +54 11 48377596.
E-mail address: investigacion@diagnosticomaipu.com.ar (P.M. Carrascosa).

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2. Methods

2.1. Study population

The present was a single-center, investigator driven, prospective study, that involved patients with known or suspected CAD clinically referred for myocardial perfusion imaging by SPECT. All patients included were more than 40 years old, in sinus rhythm, able to maintain a breath-hold for 15 s; without a history of contrast related allergy, renal failure, or hemodynamic instability. Additional exclusion criteria comprised a body mass index > 32 kg/m^2, a history of previous myocardial infarction within the previous 30 days, percutaneous coronary revascularization within the previous 6 months, chronic heart failure, chronic obstructive pulmonary disease, high degree atrioventricular block, or low estimated pre-test probability of CAD.

Patients were advised to refrain from vasodilator medications for the previous 24 h, as well as from smoking and caffeine beverages. Coronary risk factors and clinical status were recorded at the time of the CT scan, and clinical variables were defined as indicated by the Framingham risk score assessment. The estimated pretest likelihood of obstructive CAD was calculated using the Duke Clinical Score, which includes chest pain features, age, gender, and traditional risk factors. Patients were thus categorized as having low (1–30%), intermediate (31–70%), or high (71–99%) estimated pretest likelihood of obstructive CAD. [10,11]

Patients were scanned using a DECT scanner equipped with gemstone detectors with fast primary speed and low afterglow designed for spectral imaging (Discovery HD 750, GE Medical Systems, Milwaukee, USA). The same pharmacological stress was used for DECT and SPECT scans. Dipyridamole (0.56 mg/kg) and iodinated contrast (iobitridol, Xenetix 350^{TM}, Guerbet, France) were administrated using two independent antecubital intravenous lines. After dipyridamole infusion, aminophylline (1–2 mg/kg) was administrated intravenously to revert the vasodilator effect.

The primary endpoint of the study was to evaluate the diagnostic performance of DECT on a per segment basis by means of receiver-operating characteristic (ROC) curve analyses. Finally, we sought to explore whether within this population the addition of CT perfusion would improve the diagnostic accuracy over CTCA alone.

The institution's Ethics Committee approved the study protocol, which complied with the Declaration of Helsinki, and written informed consent was obtained from all patients.

2.2. CT perfusion acquisition

Stress myocardial perfusion imaging was performed after intravenous administration of dipyridamole using prospective ECG gating including 150–200 ms of temporal padding aimed to comprise approximately 40–75% of the R–R interval, since systolic as well as diastolic phases were required for the analysis. DECT was performed by rapid switching (0.3–0.5 ms) between low and high tube potentials (80–140 kV) from a single source, thereby allowing the reconstruction of low and high energy projections and generation of monochromatic image reconstructions with 10 keV increments from 40 to 140 keV. Iterative reconstruction was performed in all cases at 40% ASIR (Adaptive Statistical Iterative Reconstruction). 60 keV is so far the lowest monoenergetic level available for the reconstruction of images utilizing an iterative reconstruction algorithm [12]. Three minutes after dipyridamole administration, a dual phase protocol with 50–70 mL of iodinated contrast followed by a 30–40-mL saline flush was injected through an arm vein. A bolus tracking technique was used to synchronize the arrival of contrast at the level of the coronary arteries with the start of the scan.

For rest-DECT imaging, patients with a heart rate of more than 65 bpm received 5 mg intravenous propralonol if needed in order to achieve a target heart rate of less than 60 bpm. Image acquisition at rest was performed using the same protocol as for stress-DECT, after sublingual administration of 2.5–5 mg of isosorbide dinitrate. As only a mid-diastolic window was required for rest acquisitions, the scan was performed using a 100 ms padding centered at 75% of the cardiac cycle.

2.3. Single-photon emission computed tomography (SPECT) myocardial perfusion imaging

At the time of the stress CT perfusion scans, 2 min after dipyridamole administration and immediately before the CT scan, 10–15 mCi of technetium-99m-methoxy isobutyl isonitrile (99mTc-MIBI) were administrated. Stress-SPECT image acquisition was performed 60 min after the administration of the radiotracer using a dual head gamma camera over a 90° circular orbit (GE Medical Systems. Millennium MG, Milwaukee, USA). Data were acquired in a 128 × 128 matrix for 32 projections in a step and shoot format. Rest-SPECT image acquisition was completed within 24–48 h after stress-SPECT, after administration of 10–15 mCi of 99mTc-MIBI.

2.4. CT angiography analysis

CTCA image analysis was performed off-line on a dedicated workstation, using a commercially available dedicated software tool (AW 4.6, GE Healthcare) by consensus of two experienced level 3 – certified coronary CTA observers (PC, AD), blinded to the clinical data and to the SPECT results. A coronary segment was considered interpretable if image quality was adequate for evaluation of coronary lesions in all segments ≥1.5 mm.

Axial planes, curved multiplanar reconstructions, and maximum intensity projections were used at 1–5 mm slice thickness, according to the previously reported American Heart Association 17-segment model. Each segment was graded as follows: normal; non-significant stenosis (<50%); significant stenosis (≥50%); or uninterpretable. Uninterpretable segments due to artifacts or severe calcification were assumed as positive.

2.5. Myocardial perfusion analysis

CT perfusion analysis was performed at least 30 days after CTCA analysis using the same dedicated workstation, and by the same observers blinded to the CTCA results.

CT images were analyzed at mid diastole using a smooth filter in axial planes and multiplanar reconstructions. However, if movement artifacts were present additional phases complemented the analysis. Short axis views were obtained initially using 5 mm average multiplanar reconstructions from base to apex, with the full dataset available for the reader. Evaluation of the presence of perfusion defects was carried out using the American Heart Association left ventricular 17-segment model [13]. DECT images were evaluated using monochromatic data in gray scale and color scale. Different energetic levels from 40 to 100 kev were applied so as to confirm or to rule out the presence of a perfusion defect, and in order to validate a positive finding it was required to be identified at all the energetic levels explored. Using standarized regions of interest of 20 mm^2 localized at the interventricular septum over normally perfused myocardium, myocardial signal density (SD) was determined [14]. Myocardial perfusion defects were initially identified in a qualitative manner (Fig. 1), and subsequently complemented with a semiquantitative analysis that defined defects as myocardium having a signal density (SD) two standard deviations below the mean myocardial SD. The combined evaluation determined the presence of perfusion defects. In addition, we performed

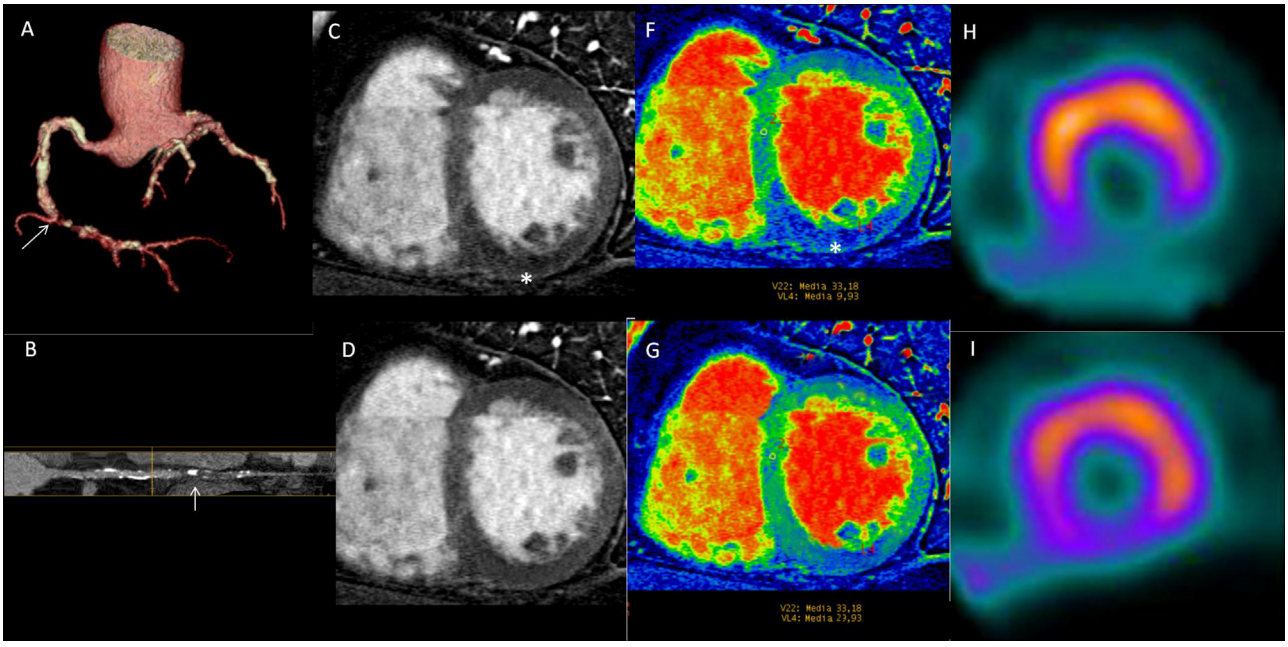

Fig. 1. Myocardial perfusion imaging by dual energy CT (DECT) in a 53-year-old male with diabetes and hypertension as coronary risk factors, and chest pain, referred for myocardial perfusion imaging by single-photon emission computed tomography (SPECT). Computed tomography coronary angiogram depicts diffusely calcified coronary arteries, with total occlusion of the mid right coronary artery (arrow, panels A and B). Stress-DECT at monochromatic reconstruction (panels C and D) and color coded (panels F and G) demonstrate a perfusion defect at the inferior wall, with almost complete normalization at rest (asterisk, panels C–G). Stress–rest single-photon emission computed tomography confirm the findings.

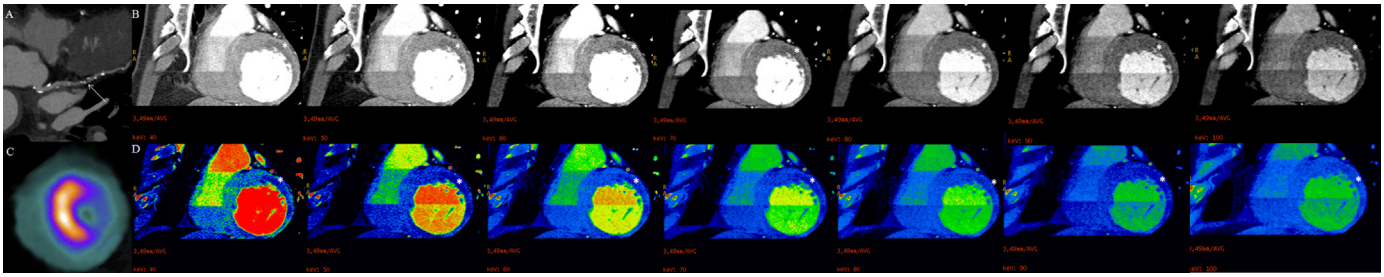

Fig. 2. Myocardial perfusion imaging by dual energy CT (DECT) in a 79-year-old male with hypertension and hypercholesterolemia as coronary risk factors, and typical chest pain, referred for myocardial perfusion imaging by single-photon emission computed tomography (SPECT). Curved multiplanar reconstruction showing a severe stenosis at the mid left circumflex artery (arrow, panel A). Monochromatic reconstruction of stress-DECT at 10 keV interval energy levels (panels B, from 40 to 100 keV) and color coded (panels D, from 40 to 100 keV) demonstrate a perfusion defect at the lateral wall that persists at all energy levels. Stress-SPECT (panel C) confirms the findings. Rest of the images (not shown) demonstrate normalization of perfusion defects.

a post hoc analysis that comprised the evaluation of myocardial signal density levels of all AHA myocardial segments by averaging signal density values at three different regions of interest within each segment, at energy levels from 40 to 80 keV. Signal density values were thus compared between segments with and perfusion defects and segments with normal perfusion, provided that observers were blinded to the previous definition of the presence of perfusion defects. SPECT analysis was carried out by consensus of two experienced observers (RC, MLM) blinded to the CT data. For that purpose, reconstruction into long and short axis projections perpendicular to the heart axis was initially performed, followed by an automated quantitative analysis of the perfusion images using polar map format (normalized to 100%). Myocardial perfusion defects were identified as segmental tracer activity <75% of maximum. Gated images were used to assess regional wall motion in order to enhance the discrimination between perfusion defects and attenuation artifacts (Fig. 2).

CT effective radiation dose was derived by multiplying the dose–length product with the weighting (k) value of 0.014 mSv/mGy/cm for chest examinations, as suggested by the Society of Cardiovascular Computed Tomography [10]. Radiation dosimetry of SPECT was estimated based on recommendations of recently published guidelines [11].

2.6. Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± SD, or medians (interquartile range) for continuous variables with non-uniform distribution. Comparisons among groups were performed using paired samples t-test, unpaired samples t-test, or Kolgomorov–Smirnov test (Lilliefors corrected), as indicated. The agreement between observers was tested using Kappa coefficient. To determine the accuracy of CT perfusion for the detection of perfusion defects by SPECT, we calculated the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and receiver-operating characteristic (ROC) curve analyses, accounting for potential non-uniform distribution (95% confidence intervals). Likelihood ratios were used instead of predictive values, since the latter are highly dependent on the prevalence of the disease [15,16].

Table 1
Demographical characteristics.

	N (%)
Age (years ± SD)	63.4 ± 10.6
Body mass index (kg/m^2)	27.6 ± 4.0
Male	16 (64%)
Diabetes	7 (28%)
Hypercholesterolemia	19 (76%)
Hypertension	21 (84%)
Smoking	6 (24%)

ROC curve analyses were performed using specific software for ROC analysis (MedCalc Software, Ostend, Belgium). Pairwise comparison of ROC curves were performed using the method of DeLong et al. for detection of differences between two AUCs, and calculated the binomial exact confidence interval for the area under the curve [17]. All other statistical analyses were performed using SPSS software, version 22.0 (Chicago, IL, USA). A two-sided *p* value of less than 0.05 indicated statistical significance.

3. Results

Twenty-five patients were prospectively included in the study protocol. The mean age was 63.4 ± 10.6 years, 16 (64%) patients were male, and 7 (28%) had diabetes (Table 1). Fifteen (60%) patients had typical chest pain, 8 (32%) patients had effort dyspnea, and 2 (8%) patients had atypical symptoms with a history of previous coronary revascularization. The mean heart rate 1 h before the CT scan was 63.0 ± 6.4 bpm, and the mean estimated pretest likelihood of obstructive CAD (Duke) was 68.7 ± 21.6%. The median coronary calcium score (Agatston), performed only in patients without previous PCI (*n* = 19), was 92.0 (1.0–532.0). The mean effective radiation dose was 7.5 ± 1.2 mSv with DECT (4.3 ± 1.1 mSv for stress scans and 3.2 ± 0.4 mSv for rest scans) and 8.2 ± 1.7 mSv with SPECT (*p* = 0.007).

3.1. Diagnostic performance of myocardial perfusion by DECT

A total of 425 left ventricular segments were evaluated by DECT. Two (0.47%) segments were deemed non-assessable due to motion artifacts and considered positive as pre-specified in the study protocol. SPECT detected reversible perfusion defects in 30/425 segments (7.1%). The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the ROC curve of stress-DECT for detection of reversible myocardial perfusion defects were 73.3% (53.8–87.0%), 94.7% (91.9–96.6%), 13.8 (8.6–22.0), 0.3 (0.2–0.5), and 0.84 (0.80–0.87), respectively.

The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and area under the ROC curve of DECT for detection of myocardial perfusion defects were 84.3% (74.7–90.8%), 94.3% (91.2–96.5%), 14.9 (9.5–23.3), 0.2 (0.1–0.3), and 0.89 (0.86–0.92); respectively. Table 2 depicts a detailed analysis of the diagnostic performance of DECT.

There was a good agreement between observers for the presence of myocardial perfusion defects evaluated by DECT (kappa = 0.89, $p < 0.001$).

3.2. Incremental value of myocardial perfusion over CTCA

CTCA alone for the detection of reversible perfusion defects showed a moderate diagnostic performance, with relatively low sensitivity [66.7% (47.1–82.7%)] and area under the ROC curve [0.70 (0.65–0.74)] (Table 2). The addition of stress myocardial perfusion by DECT over CTCA significantly improved the area under the ROC curve for prediction of reversible perfusion defects by SPECT, both considering the presence of DECT reversible defects alone (*p* = 0.003), and the combined CTCA and reversible perfusion defects (*p* = 0.01) (Table 2).

3.3. Signal density values of segments with perfusion defects and with normal perfusion

Myocardial signal density levels at segments with perfusion defects (*n* = 157) were significantly lower than those at normally perfused segments, and at all energy levels (Table 3). The difference between signal density levels at 40 keV and 80 keV was significantly

Table 3
Signal density values of segments with perfusion defects and segments with normal perfusion.

	Perfusion defects (*n* = 157)	Normal perfusion (*n* = 693)	*p* value
Signal density (HU)			
40 keV	110.0 ± 31.8	246.9 ± 37.9	<0.0001
50 keV	85.1 ± 23.8	169.2 ± 26.8	<0.0001
60 keV	66.5 ± 19.9	126.3 ± 18.9	<0.0001
70 keV	57.0 ± 16.6	97.3 ± 13.9	<0.0001
80 keV	48.6 ± 14.7	81.5 ± 10.2	<0.0001
Δ 40/80 kev	62.3 ± 24.9	165.3 ± 33.2	<0.0001

	Reversible perfusion defects		*p* value
	Presence (*n* = 30)	Absence (*n* = 395)	
Δ Rest–stress[a] (HU)			
40 keV	112.0 (82.3; 144.5)	−6.0 (−19.0; 17.3)	<0.0001
50 keV	58.5 (43.0; 83.5)	−4.0 (−15.0; 16)	<0.0001
60 keV	47.5 (30.5; 58.0)	−3.0 (−10.0; 10.3)	<0.0001
70 keV	28.0 (14.3; 45.8)	−4.0 (−11.0; 7.0)	<0.0001
80 keV	22.5 (14.0; 36.3)	−4.0 (−9.0; 5.0)	<0.0001

[a] Presented in medians (interquartile range), and *p* values calculated using Kolgomorov–Smirnov test (Lilliefors corrected).

Table 2
Diagnostic performance of dual energy computed tomography compared to single-photon emission computed tomography.

	Sensitivity	Specificity	LR+	LR−	AUC
Per segment (*n* = 425)					
Stenosis (CTCA)	66.7 (47.1–82.7)	72.4 (67.7–76.7)	2.4 (1.8–3.3)	0.5 (0.3–0.8)	0.70 (0.65–0.74)
Reversible defect	73.3 (53.8–87.0)	94.7 (91.9–96.6)	13.8 (8.6–22.0)	0.3 (0.2–0.5)	0.84 (0.80–0.87)*
Both	56.7 (37.7–74.0)	97.0 (94.6–98.3)	18.7 (9.8–35.3)	0.4 (0.3–0.7)	0.77 (0.73–0.81)**
Per patient (*n* = 25)					
Stenosis (CTCA)	92.9 (64.2–99.6)	72.7 (39.3–92.7)	3.4 (1.3–9.0)	0.1 (0.01–0.7)	0.83 (0.63–0.95)
Reversible defect	78.6 (48.8–94.3)	81.8 (47.8–96.8)	4.3 (1.2–15.6)	0.3 (0.09–0.7)	0.80 (0.60–0.93)***
Both	71.4 (42.0–90.4)	81.8 (47.8–96.8)	3.9 (1.1–14.4)	0.3 (0.1–0.8)	0.77 (0.56–0.91)†

LR refers to likelihood ratio, AUC refers to area under receiver-operating characteristic (ROC) curve; CTCA refers to computed tomography coronary angiography.
* Standard error = 0.05, *p* = 0.003 versus AUC stenosis.
** Standard error = 0.03, *p* = 0.01 versus AUC stenosis.
*** Standard error = 0.08, *p* = 0.76 versus AUC stenosis.
† Standard error = 0.09, *p* = 0.40 versus AUC stenosis.

lower for segments with perfusion defects compared to segments with normal perfusion (62.3 ± 24.9 HU vs. 165.3 ± 33.2 HU, $p < 0.0001$). Finally, segments with reversible perfusion defects showed a significantly larger difference in signal density levels between rest and stress with respect to segments without reversible perfusion defects, and this was observed at all energy levels (Table 3).

4. Discussion

The main finding of our study was that stress myocardial perfusion by DECT had a reliable accuracy for the detection of reversible perfusion defects as detected by SPECT, with an area under the curve of 0.84. Moreover, we demonstrated a significant incremental value of stress myocardial perfusion over anatomical evaluation alone by CTCA.

The DEFER and FAME studies, among others, have underscored the importance of the assessment of the hemodynamic significance of coronary obstructions, showing that deferring revascularization of lesions that do not cause ischemia is associated with very low rates of death or myocardial infarction [18,19].

During the past decade, major technological advances in the field of computed tomography have lead to the feasibility of performing a comprehensive assessment of both CTCA and stress myocardial perfusion during a single procedure. Several clinical studies have validated this application using different scanners, pharmacological agents, and acquisition protocols. Myocardial perfusion can be assessed using mainly two different approaches; static CT perfusion, and dynamic CT perfusion. Static CT perfusion acquisitions, as used in our investigation, allow a qualitative assessment of CT attenuation-based myocardial perfusion evaluation. On the other hand, dual-source scanners enable a dynamic evaluation of myocardial perfusion and provide quantitative estimation of myocardial time-attenuation curves and other parameters such as myocardial blood flow. The main limitation of the latter is the significantly increased radiation dose compared to static CT perfusion [20]. It is noteworthy though, that both approaches have shown a high diagnostic performance for the detection of myocardial perfusion defects [20]. Moreover, a recent study has shown a good agreement between both methods [21].

Very few studies have explored the diagnostic performance of myocardial perfusion using other approach (source-oriented) for DECT imaging, while evidence regarding the diagnostic performance of detector-oriented DECT imaging is scarce [22–26]. DECT has emerged as an appealing technique toward myocardial perfusion imaging, owing to its ability to generate monochromatic image reconstructions that might improve some technical issues related to the polychromatic nature of X-rays.

It has been previously established that CTCA does not provide further significant diagnostic information in patients with a high pretest probability of CAD [27]. Accordingly, we evaluated the diagnostic performance of DECT perfusion in patients with intermediate to high likelihood of CAD. As expected in such population, CTCA alone showed only a moderate diagnostic performance for the detection of reversible perfusion defects, with an area under the curve of 0.70; whereas the addition of stress myocardial perfusion significantly improved the area under the curve (0.84, $p = 0.003$).

In line with the primary endpoint of the study and the population involved, stress myocardial perfusion imaging was prioritized and performed first, and rest imaging was performed 30 min after stress imaging. Late enhancement CT scans have demonstrated their ability to identify irreversible myocardial damage therefore aiding risk stratification even in scenarios such as early after primary PCI [28]. Nevertheless, late enhancement does not rule out the presence of ischemia, therefore stress scans cannot be neglected by the performance of late enhancement, at least in intermediate to high risk patients such as in our study.

It is noteworthy that DECT imaging, a prospective acquisition by itself, was associated to a significant reduction in effective radiation dose compared to SPECT. Such low radiation dose is considerably lower than doses associated to dynamic perfusion using double source CT, although it should be stressed that DECT radiation could have been lower since ECG padding (additional surrounding X-ray beam over time that results in supplementary available phases for analysis) is related to significant increments in radiation doses [29,30].

A study contemporaneous to our investigation has been published very recently and showed similar findings in a higher risk population, including more than 50% of the patients with a history of previous myocardial infarction and percutaneous revascularization [26]. In the study of De Cecco et al., additional methodological differences were observed compared with our investigation, including a different approach for DECT imaging (dual source), DECT analysis (iodine maps), and different stress agent (adenosine). Notwithstanding, in line with our findings, they reported that the combined analysis of coronary CTCA and DECT perfusion reduces the number of false-positives and outperforms CTCA alone for the detection of significant CAD. It should be noted that, as expected from DECT imaging using dual source CT, significantly higher radiation doses were observed in their study [20].

Our study has some limitations that should be granted. The relatively small sample size might lead to selection bias. Likewise and for the same reason, analyses on a per patient basis should be considered with caution. Finally, patients did not undergo invasive angiography in order to confirm the presence of obstructive CAD, therefore the reference standard (SPECT) is potentially subject to error.

5. Conclusions

In this pilot investigation, stress myocardial perfusion by DECT showed a reliable accuracy for the detection of reversible perfusion defects as detected by SPECT, with a significant incremental value over anatomical evaluation alone by CTCA.

Conflict of interest

We declare that Dr. Patricia Carrascosa is a consultant of GE. There are no competing interests related to the manuscript for any of the other authors.

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