What is the benefit of CT-based attenuation correction in myocardial perfusion SPET?

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Abstract

In multimodality imaging, CT-derived transmission maps are used for attenuation correction (AC) of SPET or PET data. Regarding SPET myocardial perfusion imaging (MPI), however, the benefit of CT-based AC (CT-AC) has been questioned. Although most attenuation-related artifacts are removed by this technique, new false defects may appear while some true perfusion abnormalities may be masked. The merits and the drawbacks of CT-AC in MPI SPET are reviewed and discussed in this editorial. *In conclusion*, CT-AC is most helpful in men, overweight in particular, and in those with low or low to intermediate pre-test probability of coronary artery disease (CAD). It is also useful for the evaluation of myocardial viability. In high-risk patients though, CT-AC may underestimate the presence or the extent of CAD. In any case, corrected and non-corrected images should be viewed side-by-side and both considered in the interpretation of the study.

Introduction

Myocardial perfusion imaging (MPI) with single photon emission tomography (SPET) is a well-established method for the identification of haemodynamically significant coronary artery disease (CAD), the assessment of major adverse cardiac event (MACE) risk and the evaluation of myocardial viability [1-3]. However, artifacts from tissue attenuation of radioactivity frequently degrade the quality of MPI studies and sometimes pose diagnostic dilemmas. Attenuation artifacts commonly located in the inferior wall of male and the anterior wall of female patients mostly present as mild to moderate non-reversible tracer concentration defects and are usually easily recognizable by experienced interpreters. Occasionally, however, they are rather severe and sometimes appear as reversible defects mimicking ischemia. Furthermore, myocardial viability is probably underestimated in myocardial areas affected by attenuation artifacts. Several methods have been proposed to overcome the attenuation handicap: Gated-SPET, prone imaging, external radioactive sources which provide a transmission map for attenuation correction (AC), as well as various software techniques [4, 5]. Proponents of these methods claim there is a substantial improvement in MPI specificity after the application of each technique. However, certain drawbacks have hindered their universal acceptance. For example, gated-SPET can distinguish between attenuation artifacts and myocardial scars but cannot differentiate artifacts from ischemia; prone imaging requires an additional imaging sequence, while it frequently introduces new artifacts; external radioactive sources entail additional imaging time, produce transmission images of suboptimal quality, face the problem of radioactivity cross-talk between emission and transmission energies and require source replacement due to radioactivity decay [6, 7]; tomographic reconstruction using iterative algorithms is superior to filtered back-projection but does not eliminate attenuation artifacts, while incorporation of Monte Carlo-derived attenuation models into the iterative reconstruction procedure is probably more efficient [5] albeit not widely available.

The advent of hybrid SPET/CT technology gave rise to the potential for computed tomography (CT) images to serve as transmission maps for the AC of SPET data. Images produced by CT hold many advantages: they are obtained in seconds or a few minutes (depending on the CT device) and generally provide high quality transmission maps, there is no radioactivity cross-talk with emission images and the life of the x-ray tube is very long. The additional radiation dose to the patient varies considerably between scanners and different protocols but is generally low; with low-dose CT devices used in the first-generation hybrid SPET/CT systems in particular, the effective dose is about 1 mSv or less [7]. Computed tomography-based AC (CT-AC) procedure, however, is not as straightforward as that by an external radioactive source. The energy spectrum of x-rays is continuous while that of gamma photons discrete. This disparity can be solved by adopting an average or so-called "effective" energy for x-rays. Most importantly, x-ray interaction with matter is disparate from that of gamma-photons. Hence, the relationship between Hounsfield units (HU) and emission attenuation coefficients is not linear. Based on phantom experiments this relationship can be simplified and represented by a bilinear curve. The first component of the curve (HU≤0 with 0 corresponding to water) is used to correct for photons attenuated in air, water and low-density soft tissue, while the second component (HU>0) for more dense soft tissues and bone [7]. The effectiveness of AC is also largely dependent on the good quality of the transmission map. Common factors that may degrade CT maps are patient movement during CT acquisition and excessive beam hardening created by selective low-energy x-ray attenuation in bone structures or

metallic implants. Also, in hybrid systems with a CT field of view smaller than that of SPET, exclusion of part of the thorax from CT slices, the so called "body truncation", inevitably impacts on the accuracy of AC in patients with large body habitus. Motion artifacts are common when using slow-CT devices. Fast multi-detector CT scanners acquire images of the chest within a few seconds while the patient is holding his breath, thereby avoiding such artifacts. Misregistration of emission-transmission slices can result from a software misalignment error or, more frequently, from patient motion between SPET and CT acquisition, a change in the breathing pattern between acquisitions, flexing of the examining table as it moves inside the gantry and upward creeping of the heart after the cessation of vigorous stress [8]. Single photon emission tomography-CT misregistration of some degree is unavoidable with fast CT scanners which take "frozen" images of the chest, because SPET acquisition is much slower including several respiratory cycles and representing an average of the chest motion during respiration [9]. Actually, misregistration of emission and transmission slices is quite common in MPI SPET/CT studies [10, 11]. This misalignment may introduce false defects in MPI images and give rise to interpretation errors if left uncorrected. The occurrence and the severity of such artifactual defects are related to the magnitude and the direction of misregistration but are also case-specific and thus hardly predictable [12]. Software tools for the manual correction of misregistration have been developed by gamma-camera manufacturers. However, the correction procedure relies on visual evaluation of co-registration, is fairly reproducible [10, 12] and has not been adequately validated.

After the implementation of CT-AC the reconstructed SPET slices look somehow different from those of the uncorrected study (non-AC). Apart from the elimination of attenuation artifacts, other common features of corrected images include apical thinning, more intense delineation of the right ventricular wall and accentuation of extra-cardiac subdiaphragmatic activity. Also, the myocardial wall of the left ventricle appears thicker and the cavity smaller. These normal patterns should be kept in mind when interpreting AC studies [13]. In addition, true perfusion defects, particularly in the inferior and inferolateral wall, usually appear smaller in corrected compared with uncorrected images. The presentation of apical defects on AC images has drawn the attention of several investigators as to whether it represents a true thinning of the apex or a new artifact; the results of these studies are controversial [14-16]. Whichever their origin, apical defects frequently create interpretation uncertainties, particularly when these extend to the apical portion of the anterior wall or appear as partly or fully reversible at rest.

The value of CT-AC in clinical practice has been addressed by a number of studies. Despite converging to a general gain in MPI SPET specificity and normalcy rate, the results are not uniform concerning test sensitivity and accuracy. Massod et al. (2005) in studying 39 patients with low probability of CAD and 118 patients with subsequent invasive coronary angiography found that CT-AC consistently improved overall diagnostic performance of readers with different interpretive attitudes and experience [17]. Similar results have been produced by other studies [18-20]. However, some investigators have pointed out certain weaknesses of the correction method. Genovesi et al. (2011) in a multi-center study enrolling 104 patients compared standard technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) gated-SPET with CT-AC. They found that CT-AC yielded higher specificity than gated-SPET (100% vs. 67%, P<0.05) for the evaluation of right coronary artery (RCA) only in overweight men; in the other study subgroups specificity was not affected while sensitivity was frequently reduced [21]. In line with these results Tamam et al. (2016) reported that the improvement achieved by CT-AC is significantly greater in obese patients [22]. However, patients with normal body mass index may also benefit from CT-AC [20]. In another study involving 99 patients, although there was an increase in the overall specificity and accuracy with the use of CT-AC the specificity in the left anterior descending (LAD) artery territory was decreased. Moreover, CT-AC was less effective in eliminating breast artifacts and thus less useful in women [23]. In a larger cohort of 171 patients Sharma et al. (2012) reported that in the RCA territory the sensitivity of CT-AC with ^{99m}Tc-tracers was lower than that of conventional SPET, the specificity was higher, while the accuracy did not differ [24]. In our institution we have examined 120 patients with thallium-201-chloride (^{201}Tl-Cl) who subsequently underwent invasive coronary angiography. The overall sensitivity of CT-AC was lower than that of non-AC (70% vs. 87%, P=0.04), overall specificity was higher but not to a statistically significant degree (62% vs. 54%) while accuracy did not differ substantially (66% vs. 69%). However, the accuracy in evaluating RCA was significantly higher with CT-AC (73% vs. 55%, P<0.05). Figure 1 depicts a case in which non-AC images were misleading as regards the existence of ischemia in the inferior wall whereas CT-AC findings were more accurate. On the other hand, CT-AC was less effective in identifying multi-vessel CAD [25]. An example is given in Figure 2.

As regards the prognostic value of CT-AC, previous studies have yielded conflicting results. Pazhekonttil et al. (2011) studied 876 patients with ^{99m}Tc-MIBI for a follow-up period of 2.3±0.6 years. They found that patients with zero summed stress score (SSS) had an excellent prognosis with a warranty period of at least 4 years. MACE rates for other SSS groups ranged from 3.7% to 7.5%. The authors concluded that CT-AC offered improved outcome prediction compared with conventional SPET [26]. In another study which included 935 patients with 2.2±0.8 years follow-up, similar MACE frequency between CT-AC and non-AC for those with normal or mildly abnormal scan (SSS 0-8) was reported, whereas for the moderately to severely abnormal group (SSS>8) MACE rate increased significantly after CT-AC (4.5 vs. 8.1%, P=0.03). The authors concluded that CT-AC allows for improved risk stratification over non-AC because it offers clearer separation between low risk and moderately to severely abnormal findings [27]. In contrast to previous studies, our results with the use ^{201}Tl SPET challenge the effectiveness of CT-AC for risk stratification. We studied 637

with a follow-up period of 3.5±1.1 years. Study endpoints were all-cause mortality and the composites of death/non-fatal acute myocardial infarction (AMI) and death/AMI/late revascularization. In the multivariate Cox proportional hazards analysis CT-AC yielded no significance for either study endpoint whereas non-AC SPET results proved significant and independent from other covariates for the composite endpoints [28].

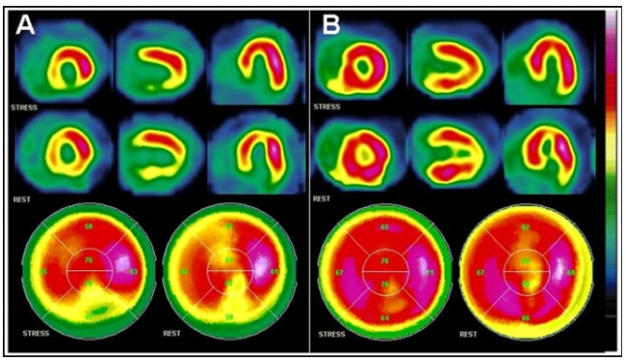

Figure 1. Selective 3-axis ^{201}Tl-Cl stress/redistribution SPET slices of a 69 years old male, smoker and hypertentive with 32.7Kg/m^2 BMI, who complained of mild dyspnea on exertion. He had an inconclusive exercise treadmill test due to inadequate heart rate increase. Myocardial perfusion imaging was performed via dobutamine stress. The achieved maximum heart rate was 96% of maximum predicted with no angina or ischemic ECG changes during the test. Non-AC images (A) show a partly reversible defect in the inferior wall. The CT-AC study (B) is normal. Invasive coronary angiography a few days later revealed no critical stenoses in the coronary vessels.

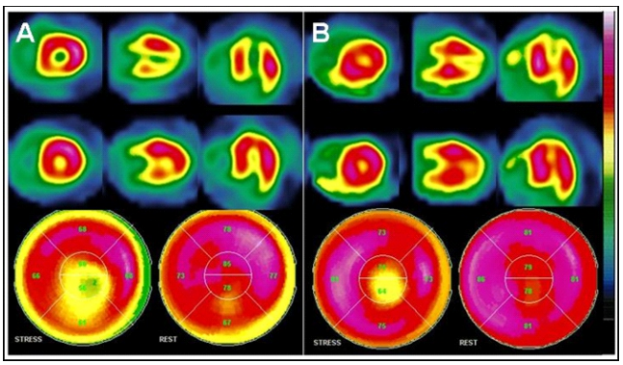

Figure 2. Thallium-201 stress/redistribution SPET images of a 79 years old diabetic male, with hypertention, dislipidemia and a BMI of 23.7Kg/m^2. He complained of angina-like substernal pain. Myocardial perfusion imaging was performed via dipyridamole stress, during which a horizontal ST depression 1-1.5mm in lateral ECG leads was recorded. Non-AC images (A) show a large reversible defect in the apex and the inferior wall. Transient ischemic dilation is also evident. Computed tomography-AC findings (B) are confined to a small area at the apex. Subsequent invasive coronary angiography revealed significant 3-vessel disease (75% ostial and 99% mid LAD, 99% mid RCA, and 90% obtuse marginal branch stenosis).

Regarding myocardial viability assessment, recent evidence supports the implementation of CT-AC as it correlates better than non-AC SPET with regional wall motion, infarct size and fluorine-18-fluorodeoxyglucose positron emission tomography findings [29, 30].

Computed tomography images of every SPET-CT MPI study should be reviewed for incidental pathology, even if these are of suboptimal quality and of limited range. Literature reports have pointed out that such incidental CT findings (noncalcified pulmonary nodules, interstitial lung disease, pleural effusion, pneumonia, aortic aneurysm, aortic dissection, enlarged mediastinal lymph nodes, mediastinal tumor, breast abnormalities, etc) are not uncommon and can be of particular importance for the patient [31].

In conclusion, CT-AC is a valuable innovation, particularly helpful in males and obese patients. It is also useful for the evaluation of myocardial viability. Moreover, the inspection of "non-diagnostic" CT images may reveal unsuspected concurrent pathology and thereby foster further investigation. Nevertheless, CT-AC studies should be interpreted with caution, side-by-side with non-AC images and in the context of clinical data. In males at low or low-to-intermediate risk for obstructive CAD, AC images greatly improve the specificity of MPI in the inferior, inferoseptal and inferolateral wall (Figure 1); equivocal test results are also substantially reduced. Consequently, in several cases a stress-only MPI study can be performed, which results in a marked reduction of radiation burden and improved laboratory logistics. In intermediate or high risk patients though, one should consider the possibility of underestimating the presence or the extent of CAD by CT-AC. In these cases, surrogate information from additional MPI signs such as left ventricular transient ischemic dilation, increased pulmonary tracer retention, as well as clinical and ECG stress results should be incorporated in the final diagnosis (Figure 2). In any case, findings in the anterior, anteroseptal, anterolateral wall and the apex should be interpreted with reference to non-AC rather than CT-AC images.

Bibliography

1. Hesse B, Lindhardt TB, Acampa W et al. EANM/ESC guidelines for radionuclide imaging of cardiac function. *Eur J Nucl Med Mol Imaging* 2008; 35: 851-85.
2. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol* 2004; 11: 171-85.
3. Nishina H, Slomka P, Abidov A et al. Combined supine and prone quantitative myocardial perfusion SPECT: method development and clinical validation in patients with no known coronary artery disease. *J Nucl Med* 2006; 47: 51-8.
4. Okkalides D. Recent international regulations: Low dose-low rate radiation protection and the demise of reason. *Hell J Nucl Med* 2008; 11(2):86-89.
5. Kalantari F1, Rajabi H, Saghar M. Quantification and reduction of attenuation related artifacts in SPET by applying attenuation model during iterative image reconstruction: a Monte Carlo study. *Hell J Nucl Med* 2011; 14: 278-83.
6. Garcia EV. SPECT attenuation correction: An essential tool to realize nuclear cardiology's manifest destiny. *J Nucl Cardiol* 2007; 14: 16-24.
7. Patton JA, Townsend DW, Hutton BF. Hybrid imaging technology: from dreams and vision to clinical devices. *Semin Nucl Med* 2009; 39: 247-63.
8. Stone CD, McCormick JW, Gilland DR et al. Effect of registration er-

rors between transmission and emission scans on a SPECT system using sequential scanning. *J Nucl Med* 1998; 39: 365-73.
9. Nye JA, Faber TL. Current state of hybrid imaging: attenuation correction and fusion. *J Nucl Cardiol* 2011; 18: 729-40.
10. Goetze S, Brown TL, Lavely WC et al. Attenuation correction in myocardial perfusion SPECT/CT: effects of misregistration and value of reregistration. *J Nucl Med* 2007; 48: 1090-5.
11. Kennedy JA, Israel O, Frenkel A. Directions and magnitudes of misregistration of CT attenuation-corrected myocardial perfusion studies: incidence, impact on image quality, and guidance for reregistration. *J Nucl Med* 2009; 50: 1471-8.
12. Apostolopoulos DJ, Gąsowska M, Savvopoulos CA et al. The impact of transmission-emission misregistration on the interpretation of SPET/CT myocardial perfusion studies and the value of misregistration correction. *Hell J Nucl Med* 2015; 18: 114-21.
13. Dvorak RA, Brown RK, Corbett JR. Interpretation of SPECT/CT myocardial perfusion images: common artifacts and quality control techniques. *Radiographics* 2011; 31: 2041-57.
14. Fricke H, Fricke E, Weise R et al. A method to remove artifacts in attenuation-corrected myocardial perfusion SPECT Introduced by misalignment between emission scan and CT-derived attenuation maps. *J Nucl Med* 2004; 45: 1619-25.
15. Purser NJ, Armstrong IS, Williams HA et al. Apical thinning: real or artefact? *Nucl Med Comun* 2008; 29: 382-9.
16. Okuda K, Nakajima K, Matsuo S et al. Cause of apical thinning on attenuation-corrected myocardial perfusion SPECT. *Nucl Med Commun* 2011; 32: 1033-9.
17. Masood Y, Liu YH, Depuey G, Taillefer R et al. Clinical validation of SPECT attenuation correction using x-ray computed tomography-derived attenuation maps: multicenter clinical trial with angiographic correlation. *J Nucl Cardiol* 2005; 12: 676-86.
18. Utsunomiya D, Tomiguchi S, Shiraishi S et al. Initial experience with X-ray CT based attenuation correction in myocardial perfusion SPECT imaging using a combined SPECT/CT system. *Ann Nucl Med* 2005; 19: 485-9.
19. Zafrir N, Shafir G, Kovalski G et al. Yield of a novel ultra-low-dose computed tomography device mounted on a dedicated cardiac SPECT system in improving the accuracy of myocardial perfusion imaging and the detection of chest abnormalities. *J Nucl Cardiol* 2012; 19: 303-10.
20. Shawgi M, Tonge CM, Lawson RS et al. Attenuation correction of myocardial perfusion SPET in patients of normal body mass index. *Hell J Nucl Med* 2012; 15: 215-9.
21. Genovesi D, Giorgetti A, Gimelli A et al. Impact of attenuation correction and gated acquisition in SPECT myocardial perfusion imaging: results of the multicentre SPAG (SPECT Attenuation Correction vs Gated) study. *Eur J Nucl Med Mol Imaging* 2011; 38: 1890-8.
22. Tamam M, Mulazimoglu M, Edis N et al. The Value of Attenuation Correction in Hybrid Cardiac SPECT/CT on Inferior Wall According to Body Mass Index. *World J Nucl Med* 2016; 15: 18-23.
23. Huang R, Li F, Zhao Z, Liu B et al. Hybrid SPECT/CT for attenuation correction of stress myocardial perfusion imaging. *Clin Nucl Med* 2011; 36: 344-9.
24. Sharma P, Patel CD, Karunanithi S et al. Comparative accuracy of CT attenuation-corrected and non-attenuation-corrected SPECT myocardial perfusion imaging. *Clin Nucl Med* 2012; 37: 332-8.
25. Savvopoulos C. CT-based attenuation correction in myocardial perfusion scintigraphy. Diagnostic and prognostic value. Doctorate thesis, University of Patras 2014, Patras, Greece. http://www.didaktorika.gr
26. Pazhenkottil AP, Ghadri JR, Nkoulou RN et al A. Improved outcome prediction by SPECT myocardial perfusion imaging after CT attenuation correction. *J Nucl Med* 2011; 52: 196-200.
27. Ou X, Jiang L, Huang R et al. Computed tomography attenuation correction improves the risk stratification accuracy of myocardial perfusion imaging. *Nucl Med Commun* 2013; 34: 495-500.
28. Savvopoulos CA, Spyridonidis T, Papandrianos N et al. CT-based attenuation correction in Tl-201 myocardial perfusion scintigraphy is less effective than non-corrected SPECT for risk stratification. *J Nucl Cardiol* 2014; 21: 519-31.
29. Giubbini RM, Gabanelli S, Lucchini S et al. The value of attenuation correction by hybrid SPECT/CT imaging on infarct size quantification in male patients with previous inferior myocardial infarct. *Nucl Med Commun* 2011; 32: 1026-32.
30. Nkoulou R, Pazhenkottil AP, Buechel RR et al. Impact of CT attenuation correction on the viability pattern assessed by ^{99m}Tc-tetrofosmin SPECT/^{18}F-FDG PET. *Int J Cardiovasc Imaging* 2011; 27: 913-21.
31. Husmann L, Tatsugami F, Aepli U et al. Prevalence of noncardiac findings on low dose 64-slice computed tomography used for attenuation correction in myocardial perfusion imaging with SPECT. *Int J Cardiovasc Imaging* 2009; 25: 859-65.