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The Value of Added CT-based Attenuation Correction Technique in the Era of Contemporary High Technology Gated ^{99m}Tc-MIBI Myocardial Perfusion Scintigraphy.

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ABSTRACT:

Background: accurate selection of the patients with known or suspected coronary artery disease (CAD) who will benefit from additional CT-based attenuation correction (CT-AC) images to gated ^{99m}Tc -MIBI myocardial perfusion scintigraphy (MPS) is mandatory to compromise the increased sensitivity demand for the unnecessary radiation doses exposure concerns. **Aim of the work:** to evaluate the value of added CT-AC to gated MPS in the clinical diagnosis of CAD for appropriate selection of the patient who will benefit from this additive technique. **Patients and methods:** 90 patients (53, SD ± 12 year-old, 66%males) were retrospectively included in the study. Two days protocol gated MPS and additional CT-AC images were performed for all patients. The final clinical diagnosis was reached by consensus after interpreting the gated MPS images and correlating them with the clinical risk factors and other available cardiac diagnostic modalities. Comparison was done between the final diagnosis and the CT-AC images to evaluate the performance of the latter. **Results:** 159 segmental perfusion defects were elicited; 93 (58%) and 66 (42%) perfusion defects were finally interpreted as attenuation artifact and true ischemic defects respectively. The CT-AC images show good performance with 100% sensitivity and specificity in the inferior and lateral walls perfusion defects while it shows poor performance in the anterior and septal walls due to false positive results resulting in reduced specificity of 75 %.

Conclusion: CT-AC is a fast and easy technique for accurate diagnosis of the inferior and lateral walls perfusion defects which will be potentially useful if the final clinical diagnosis cannot be reached. Whereas high false positive result is seen in anterior and septal wall defects with diminished specificity which may need additional other AC methods.

Key Words: Gated MPS, CT-AC, ^{99m}Tc -MIBI, Myocardial perfusion scintigraphy, Attenuation correction, Coronary artery disease.

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INTRODUCTION:

Coronary artery disease (CAD) is an increasing cause of disease-related morbidity and mortality, especially, in the developing countries; therefore, there is a mandatory need for an early and accurate diagnosis for risk stratification and proper management of the disease [1].

Gated ^{99m}Tc -MIBI myocardial perfusion scintigraphy (MPS) has been considered as one of the most sensitive non-invasive imaging modalities used in patients with known or suspected CAD, with its potentially important role regarding different aspects of management of these patients; however, this procedure does have many physical and technical limitations [2].

Attenuation artifacts resulting from attenuation of activity in the myocardial walls from the surrounding soft tissue structures such as the diaphragm and the breast come on the top of this list of limitations [3, 4]. Low dose CT-based attenuation correction (CT-AC) maps were used to reduce this inherent limitation and thus overcoming one of the commonest challenges encountered during clinical practice [5].

Currently, there is evident progress regarding myocardial perfusion scintigraphy (MPS) procedures related to the advances in instrumentation resulting in improved study quality together with raised concern towards unnecessary radiation exposure doses [6]. According to the new International Commission on Radiological Protection (ICRP) models ; the radiation exposure from the stress and rest ^{99m}Tc -MIBI MPS studies is 0.0066and 0.0070mSv/ MBq respectively with an additional 0.5–1.0 mSv absorbed radiation dose given to the patient if the study is combined with CT for attention correction (CT-AC) purposes [7,8].

Therefore, accurate selection of the patients who will benefit from additional CT-AC is mandatory to compromise the benefit of the increased sensitivity and specificity versus the risk of the radiation doses exposure.

Aim of the work: evaluate the value of added CT-AC to gated MPS in the clinical diagnosis of coronary artery disease (CAD) for appropriate selection of the patient who will benefit from this additive technique.

PATIENTS AND METHODS:

Study design and patient selection: this is a retrospective study performed in Nuclear Medicine Unit in NMROCK Center, faculty of medicine, Cairo University included 90 eligible gated ^{99m}Tc-Sesta-MIBI- myocardial scintigraphy studies among the 300 studies performed from January 2017 to December 2017 after excluding the studies with no CT-AC images, post pharmacologic stress, and those showing no segmental defects (normal) or showing multiple segmental defects that would account for multi-vessel disease.

The included patients were indicated either due to presence of symptoms suggestive of CAD such as dyspnea on exertion and chest pain (90%) or as part of routine preoperative check-up (10 %).

^{99m} Tc-sesta-MIBI myocardial perfusion scintigraphy (MPS) procedure

All patients underwent two days protocol (rest & exercise stress) according to the updated 2015 EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT [(6)].

Patient preparation: cardiac medication including beta blockers, theophylline derivatives, nitrates, and calcium channel blockers were stopped 48 hours prior to the study. Patients were also instructed to fast for 4 to 6 hours before the test.

Stress protocol: Graded treadmill exercise was performed according to the modified Bruce protocol [(9)]. 555 to 925 MBq (calculated according to the body weight) of ^{99m}Tc Sesta-MIBI was injected when the patient had achieved >85% of maximum predicted target heart rate (MPTHR) or at peak patient tolerance, and the exercise study was continued for further one minute to reach maximum tracer extraction.

Imaging protocol:

The rest/stress gated images were acquired with a dual-head SPECT system equipped with an integrated x-ray transmission system (Siemens Medical Systems).

Emission SPECT data were acquired by use of parallel hole low-energy high-resolution collimators, with the patient in the supine positions with raised left arm. The acquisition orbits were body contour over a 180° arc, via 30 stops and 30 seconds per stop. The image acquisition matrix was 128 X 128. Images were acquired on the 140-keV photo peak with a 20% symmetric window.

The total SPECT/CT time was approximately 25 minutes. Stress SPECT images were acquired 30 to 45 minutes after exercise and after administration of the radiopharmaceutical. While resting SPECT images were acquired 45 to 60 minutes after administration of the radiopharmaceutical. The resting and stress SPECT images were electrocardiogram synchronized with R wave trigger (RR time acceptance window was 20%., 8 frames / cardiac cycle to generate a total of 32 projections (40 s per projection).

Transmission data based on low-dose CT for attenuation-correction (AC) was started immediately after the emission scan was completed; it was acquired at a slice step 1mm. a current of 80 mA.

Tomographic images reconstruction:

SPECT reconstruction parameters: Filter: Butterworth, Reconstruction: iterative (3D Flash), Images: Short-axis, vertical long-axis, and horizontal long-axis. All raw data sets were corrected with isotope decay factor and checked for patient motion by reviewing a rotating cine display. The projection data from the ECG-gated SPECT scan were summed and perfusion images were reconstructed with 3D ordered subsets expectation maximization (OSEM) algorithm and built-in processing that preserved the linearity between photon counts in projection data and pixel values in reconstructed images. Cardiac SPECT software reconstructed cross-sectional cardiac images along the short and long axes of the heart to form: transaxial (short axis), coronal (horizontal long axis) and sagital (vertical long axis).

Tc-sesta-MIBI myocardial perfusion scintigraphy (MPS) evaluation:

All (90 stress/rest ^{99m}Tc-MIBI-gated SPECT) studies were interpreted by consensus of 2 experienced nuclear medicine physicians centering on the established 17 segment model and the quantitative gated-SPECT (QGS/QPS) in multiple color scales. The gated MPS images were also evaluated for myocardial thickening, contractility, and left ventricular ejection fraction estimation.

The final clinical diagnosis was concluded by consensus after interpreting the gated MPS images and correlating them with clinical history, clinical risk factors and other available diagnostic cardiac modalities.

Statistical methods:

The quantitative data was summarized as mean and standard deviation, whereas the frequency data was summarized as percentage.Agreement was tested using kappa statistic. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

The following criteria were accepted as our standard of reference to differentiate a true perfusion defect from an attenuation defect: (a) gated MPS findings; (b) clinical findings e.g. history of previous infarction; (c) ECG changes; (d) segmental wall motion abnormalities on a recent echocardiographic study; (e) prior MPS; and (f) recent left cardiac catheterization results. The final results were compared with the findings of the CT-AC images on a per-defect basis; the performance of both SPECT alone and the CT-AC images was evaluated through comparison with our reference standard. The findings were classified as

True Positive (TP): a defect not corrected in CT-AC confirmed to be positive for perfusion abnormality.

False Positive (FP): a defect not corrected in CT-AC confirmed to be negative for perfusion abnormality.

True Negative (TN): a defect corrected in CT-AC and confirmed to be negative for perfusion abnormality.

False Negative (FN): a defect corrected in CT-AC and confirmed to be positive for perfusion abnormality. The sensitivity, the specificity, the negative and positive predictive values of SPECT-CT/AC was calculated from the performance tables.

RESULTS:

The male to female ratio of the included patients is 2/1, with mean age of 53, SD ± 12 year-old. The main clinical characteristics of the included patients are summarized ***in table 1.***

Table 1: clinical characteristics of the studied group of patients

Clinical characteristic	Frequency (patients)	Percentage (%)
Male/female	60/30	67/33
Hypertension	48	53
Diabetes	21	23
Smoking	39	43

The segmental perfusion defects were analyzed according to their location the in the five left ventricular (LV) walls (i.e. apex, anterior, inferior, lateral and septal walls), A defect involving two regions e.g. antero-septal was considered to be two segmental defects in two cardiac walls. The total number of segmental perfusion defects (reversible/irreversible) elicited in the uncorrected gated MPS was 159 segmental perfusion defects; 93 (58%) and 66 (42%) perfusion defects were finally interpreted as attenuation artifact, and true ischemic defects respectively.

1- Anterior wall defects:

36 perfusion defects were noted in the anterior wall representing 22% of all perfusion defects. 12 defects were TB, 6 defects were FB, 18 defects were TN with sensitivity of 100 % and Specifity of 75 %. The performance of the CT-AC images in comparison to the final clinical diagnosis are summarized in ***(table 2)***; Overall, the CT-AC images results showed statistical agreement with the final clinical diagnosis with **p value = 0.014**.

Table (2): performance of the CT-AC images in the diagnosis of perfusion defects in the anterior wall

True Positive	12	**Sensitivity**	100%
False Positive	6	**Specificity**	75%
True Negative	18	**PPV**	66.6%
False Negative	0	**NPV**	100%

2- Inferior wall defects:

63 perfusion defects were noted in the inferior wall representing 39.6% of all perfusion defects; 21 studies were TP and 42 studies were TN in the CT-AC images with 100% sensitivity and specificity; Overall, the CT-AC images results showed high statistical agreement with the final clinical diagnosis (p<0.001) **.**

3- Lateral wall defects:

30 out of 159 defects were noted in the lateral wall representing 18.9% of all perfusion defects detected in all walls. ; 50% of the studies were TP and the other 50% were TN in the CT-AC images resulting into 100% sensitivity and specificity. Overall, the CT-AC images results showed statistical agreement with the final clinical diagnosis (**p=0.002**)**.**

4- Septal defects:

21 perfusion defects were noted in the septum representing 13.2% of all hypo-perfusion defects encountered in Non-AC images. The performance of the CT-AC images in comparison to the final clinical diagnosis are summarized in ***(table 5)***; Overall, the CT-AC images results showed statistical agreement with the final clinical diagnosis with **p value = 0.047**.

Table (3): performance of the CT-AC images in the diagnosis of perfusion defects in the septal wall

True Positive	9	**Sensitivity**	100%
False Positive	3	**Specificity**	75%
True Negative	9	**PPV**	75%
False Negative	0	**NPV**	100%

5- Apex:

Nine defects were detected in the apex; all of them were proven to be physiologic related to normal diminished activity in the region of the apex. The total defects were 42 defects (45 %) of the perfusion that was finally attributed as attenuation artifacts were located in the inferior wall with male/ female ratio (13/1), whereas 24 defects (26%) were located in the anterior wall with male/ female ratio (1/7), 15 defects (16%) were located in the lateral with male/ female ratio (4/1), 12 defects (13 %)

was located in the septum with male/ female ratio (1/3), and no attenuation defects were encountered in the apex. In reference to the final clinical diagnosis; the performance of the corrected CT-AC images in the whole group was 100% sensitivity and 90.3% specificity.

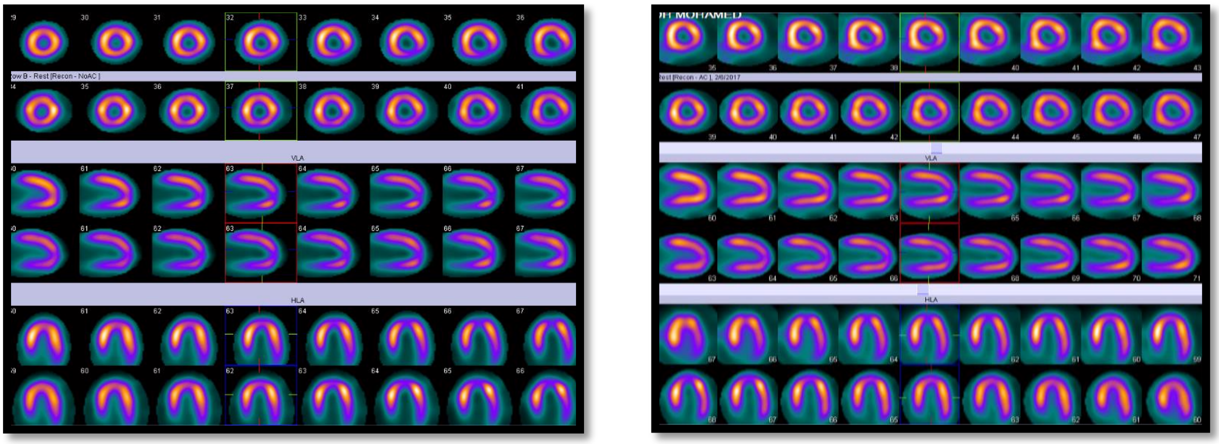

Figure 1: 30-year-old male patient presenting with typical chest pain and normal echo.
(a) Gated MPS shows medium sized fixed perfusion defect in the infero-lateral region, however the final clinical diagnosis was negative for true ischemic defect which is confirmed in the CT-AC images (b) the CT-AC images shows complete normalization of the perfusion defect in the infero-lateral region.

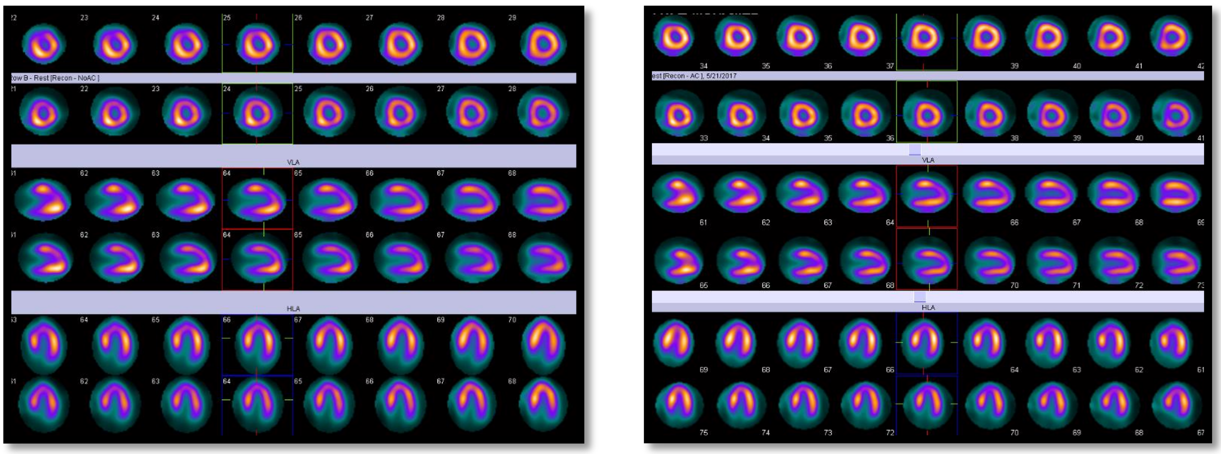

Figure 2: 50 year-old female patient with atypical chest pain, normal echo and coronary angiography showed no significant stenosis. (a) Gated MPS shows medium sized reversible perfusion defect in the antero-septal region, however the final clinical diagnosis was negative for true ischemic perfusion defect which is not confirmed in the CT-AC images (b) the CT-AC images shows partial improvement of the perfusion defect in the antero-septal region (FP result).

DISCUSSION:

Gated MPS is already validated in many studies as an essential diagnostic tool in the diagnosis, prognostication and risk stratification of patients with CAD [10, 11]. However, attenuation artifacts resulting from the surrounding soft tissue structures such as the diaphragm and the breasts and altering the homogeneity of tracer distribution within the LV still a frequently encountered challenge during its interpretation [3].

These artifacts can be seen in around 20 to 50% of the studies and they affect the diagnostic accuracy of the study in terms of reduced specificity and positive predictive values especially in the RCA and LAD territories [12, 13]. Various techniques have been proposed for compensation of these artifacts such as prone imaging and low dose CT-AC based techniques; however, the latter expose the patients to additional radiation burden [14, 15].

In the routine work-up of patients with suspected CAD, the final clinical diagnosis is reached relying not only on the result of a single imaging procedure but also on clinical history, examination and the results of other tests [16, 17], however, this information may be sometimes not available and time consuming [18] and in such cases CT-AC may be of great value though the debate on the risks related to low level radiation exposure in medical procedures [19].

In this study, we aim to evaluate the value of added CT-AC in in the clinical diagnosis of CAD. We retrospectively evaluated ninety (90) gated MPS studies with 159 segmental perfusion defects. Among these defects; the inferior wall defects were representing the majority of defects that was finally designed as attenuation artifacts (~45%) with male to female ratio 13/1, which is consistent with its known increased prevalence due to the diaphragmatic effect especially in obese patients [20].

The main finding of our study is that the additional CT-AC images shows an excellent diagnostic performance versus the standard of reference criteria in diagnosing **inferior and lateral wall perfusion defects** with 100% sensitivity and specificity ($p<0.001$ and $p=0.002$ in inferior and lateral walls respectively).

CT–derived attenuation maps has been reported in an earlier multicenter study published in 2005 to validate its clinical value that they significantly improve the diagnostic performance of MPS taking in consideration that their results were mainly based on normalization of inferior wall defects [21].

Similarly, other studies had concluded that hybrid SPECT/CT imaging is particularly beneficial in recognition of perfusion defects in the lateral and inferior walls than stand-alone SPECT [22, 23]. In the same line, more recent studies compared the value of added CT-AC to gated MPS performed in the state of the art gamma cameras and they concluded that it significantly increased performance accuracy only for the evaluation of the perfusion defects in the territory of RCA, mainly in the overweight male sub-groups [24, 25].

Moreover; we found that the additional CT-AC images shows poor performance in accurate characterization of true perfusion defects in **the anterior and septal wall** with 6 false positive defects with reduced specificity of 75%. It is known that anterior wall defects are usually more common in women and likely attributed to breast attenuation and many studies had concluded that positional change from supine to prone position may potentially decrease equivocal interpretation results in this group of patients with no increased radiation dose burden [26, 27]. Likewise, ***Malkerneker et al***., who also concluded that CT based attenuation correction technique imaging was not useful either in women or in anterior wall defects characterization [28]. Worden et al. also showed that patients with complete normalization of perfusion abnormalities during this alternative imaging position are at low risk for the worst cardiac events during their short term follow-up periods and that more wide use of this approach will have many cost effective consequences [29].Thus, there is evidence that prone-attenuation correction technique represents an alternative easy, and cost effective imaging approach applying the ALARA concept [30, 31].

In our study the **apical** perfusion defects didn't represent a diagnostic dilemma, however, the significance of the apical perfusion defects has been debatable since the early introduction of MPS, due to the phenomenon of physiological apical thinning [32], which can produce apparent perfusion artifacts in normal individuals, and this artifact that seems to be observed more frequently when an AC modality is used and must be interpreted with great caution [33].

There are two limitations for our study; the first is the relative small simple size and the second is the lack of clinical follow-up of patients. Both are attributed to the relative short experience as the hybrid SPECT/CT machine is recently introduced into our center.

CONCLUSION:

CT-AC is a fast and easy to perform additive tool for accurate diagnosis of the inferior and lateral walls defects which will be potentially useful if the final clinical diagnosis cannot be reached. On the other side, in evaluating the anterior and septal wall defects; there are some false positive results reducing the specificity of the study and other AC methods such as prone position may be needed.

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