

Original Article

A single CT for attenuation correction of both rest and stress SPECT myocardial perfusion imaging: a retrospective feasibility study

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Abstract: Purpose: In the effort to reduce radiation exposure to patients undergoing myocardial perfusion imaging (MPI) with SPECT/CT, we evaluate the feasibility of a single CT for attenuation correction (AC) of single-day rest (R)/stress (S) perfusion. Methods: Processing of 20 single isotope and 20 dual isotope MPI with perfusion defects were retrospectively repeated in three steps: (1) the standard method using a concurrent R-CT for AC of R-SPECT and S-CT for S-SPECT; (2) the standard method repeated; and (3) with the R-CT used for AC of S-SPECT, and the S-CT used for AC of R-SPECT. Intra-Class Correlation Coefficients (ICC) and Choen's kappa were used to measure intra-operator variability in sum scoring. Results: The highest level of intra-operator reliability was seen with the reproduction of the sum rest score (SRS) and sum stress score (SSS) (ICC > 95%). ICCs were > 85% for SRS and SSS when alternate CTs were used for AC, but when sum difference scores were calculated, ICC values were much lower (~22% to 27%), which may imply that neither CT substitution resulted in a reproducible difference score. Similar results were seen when evaluating dichotomous outcomes (sum scores difference of ≥ 4) when comparing different processing techniques (kappas ~0.32 to 0.43). Conclusions: When a single CT is used for AC of both rest and stress SPECT, there is disproportionately high variability in sum scoring that is independent of user error. This information can be used to direct further investigation in radiation reduction for common imaging exams in nuclear medicine.

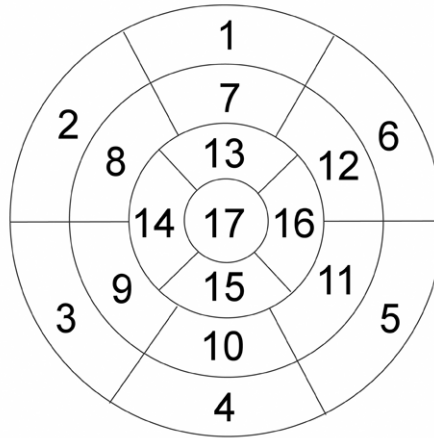
Keywords: Tomography, emission-computed, single-photon, myocardial perfusion imaging, "reproducibility of results", tomography, X-ray computed, radiation dosage

Introduction

Myocardial perfusion imaging (MPI) using rest and stress single photon emission computed tomography (SPECT) with Technetium-99m (Tc-99m) based radiotracers is a common method for detecting flow-limiting coronary artery disease [1]. Millions of patients every year receive this kind of exam. Thallium-201 (Tl-201) is less commonly used for MPI; due to higher ionizing radiation exposure compared to Tc-99m agents. The application of attenuation correction (AC) to SPECT attempts to produce qualitative and quantitative data that more accurately represents relative myocardial perfusion that is used to diagnose limitations in blood flow (ischemia) or the absence of blood

flow (myocardial infarct) [1]. Information about the blood flow from MPI is used to guide further treatment options. During the last decade, "low dose" CT became available for AC of SPECT MPI. Initially, the use of AC use was accompanied by some reluctance to quickly accept it without extensive study of the confounding artifacts that are unique to or accentuated by AC [2-4]. Specifically, the artifacts that are the result of AC with CT are the subjects of study, and much effort goes into the minimization of these errors [5-7].

Favorable cost-benefit analysis has been conducted on the use of MPI to quantify ischemia and myocardial viability, which in turn has led to greater reliance on quantitative MPI when



- | | | |
|------------------------|-----------------------|---------------------|
| 1. basal anterior | 7. mid-anterior | 13. apical anterior |
| 2. basal anteroseptal | 8. mid-anteroseptal | 14. apical septal |
| 3. basal inferoseptal | 9. mid-inferior | 15. apical inferior |
| 4. basal inferior | 10. mid-inferior | 16. apical lateral |
| 5. basal inferolateral | 11. mid-inferolateral | 17. apical |
| 6. basal anterolateral | 12. mid-anterolateral | |

Figure 1. Example of a 17-segment American Heart Association polar map used in our analysis.

deciding whether or not to revascularize coronary arteries with an invasive procedure vs treatment with medical therapy alone [8-10]. Concomitantly, the use of CT for AC is now becoming common in clinical practice [11]. Consequently, now more than ever, the quantitative methodology that physicians use to interpret MPI must be as accurate as possible.

With SPECT/CT MPI, It is standard to acquire a separate and unique CT for AC of both rest and stress portions of the exam. Recently, it has been proposed that a single CT may be sufficient for AC of both rest and stress data to reproduce accurate quantitative information [12-15]. There are several benefits if one CT is sufficient for AC of both rest and stress data without significantly changing quantitation of relative myocardial perfusion: (1) Eliminate a CT scan in order to reduce radiation exposure to patients, (2) reduce the time necessary to evaluate both rest and stress CT scans in cases where dissimilar scanning margins/fields of view were used for rest- and stress-CTs, (3) reduce scan time and complexity.

The aim of this study was to measure the reliability of myocardial perfusion quantification

when only a single CT was used for attenuation correction of both rest and stress SPECT MPI in order to determine the feasibility of using one CT to suffice for AC of both exams vs the convention of using two.

Materials and methods

Study population

Retrospectively, a total of 40 *abnormal* MPI exams were selected. The study population was selected to meet certain inclusion criteria, which included (1) scans that were determined to be “abnormal” by a multi-disciplinary team which included a nuclear medicine physician (with > 20 years of experience), and a cardiologist (with > 10 years of experience), (2) held an equal proportion of males and females, and (3) had an equal distribution of TI-201 - Tc99m (dual isotope) to Tc99m - Tc99m (single isotope) single day rest-stress MPI protocols (further detailed in “MPI Technique” section). The most recent and available abnormal single and double scans were selected to meet the above criteria, which sourced from an 8-month time period in mid-late 2009. For a scan to be selected as “abnormal”, the original interpreta-

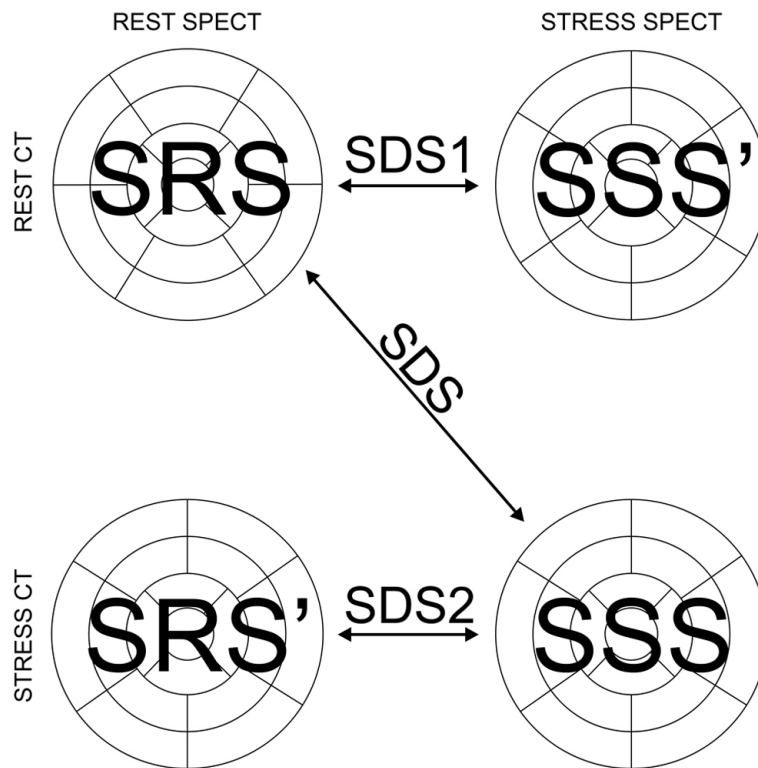


Figure 2. Study design grid. SRS = Sum rest score using standard processing with rest-CT. SSS = Sum stress score using standard processing with stress-CT. SRS' = Sum rest score using alternate processing with stress-CT. SSS' = Sum stress score using alternate processing with rest-CT. SDS = Sum difference score using standard processing (SDS = SRS - SSS). SDS1 = Sum difference score when only rest-CT is used for processing (SDS1 = SRS - SSS'). SDS2 = Sum difference score when only the stress-CT is used for processing (SDS2 = SRS' - SSS).

tion of the exam included either a fixed (decreased on both rest and stress images) or a reversible (decreased on stress but not rest images) perfusion defect that was reported in the medical record. The original quantification in defect size was not known. The indication for an exam, clinical outcomes, subsequent treatment, or further imaging was not part of any inclusion or exclusion criteria. Original indications for examinations included acute or chronic chest pain (60%), pre-surgical evaluation (20%), and monitoring of known cardiovascular disease (20%). Average age was 63 ± 13 years. The group included 18 females (45%) and 22 (55%) males. Prior to the acquisition of stress images, eleven (27.5%) of the patients received Regadenoson (Astellas Pharma Inc.), three (7.5%) received Dobutamine (Hospira Inc.), ten (25%) received Adenosine (Astellas Pharma Inc.), and two (5%) received combined exercise and Adenosine. Twelve (30%) followed the

Bruce protocol while two (5%) followed the modified Bruce protocol for stress [11].

This study was approved by the institutional review board of the Medical University of South Carolina and informed consent was waived due to the retrospective nature of the research.

Study design

We selected automated quantitative values for statistical analysis opposed to a qualitative interpretation in an effort to eliminate inter-individual variability of MPI interpretation as a study variable. Quantitative MPI information is typically displayed in the form of sum scoring, represented by a two-dimensional polar map that relates to the three dimensional anatomic distribution of relative myocardial perfusion [16, 17]. Corridor4DM (Invia Medical Imaging Solutions) applies sum scoring with the American Heart Association 17-segment polar map for quantita-

tive measurement of myocardial uptake as an adjunct to MPI interpretation (Figure 1). With Corridor4DM, sum scores were automatically produced when the rest- or stress-SPECT images were compared to a gender-specific normal database of patients that were scanned with the same technique (e.g. CT for AC, without AC, supine, etc.) [18, 19]. If a segment demonstrated no significant perfusion defects, it was assigned a value of 0. A significant defect compared to the database ranged from mild to severe, where it is assigned a value of 1 to 4, respectively. Sum scores were produced for a given set of SPECT data by summing all 17 numeric values to produce a sum rest score and a sum stress score. A sum difference score (SDS) was used to determine and quantify the presence or absence of blood flow differences between rest and stress perfusion images. The specific calculation of SDS is subject to inter-institutional variability. For the purposes of this

research, in order to form a positive number when the sum stress score is subtracted from the sum rest score ($SDS = SRS - SSS$), normal blood flow is indicated as a *high* rest or stress score and relative perfusion deficits result in comparably *low* sum scores. We used a sum difference score of “4” as a threshold for clinically significant defects to suggest stress-induced ischemia which is a method derived from evidence-based research, and represents at least a 5% change in sum score [20]. Likewise, we used the same number to represent any (reversible or non-reversible) variability in defect characterization by Corridor4DM.

A single operator repeated post-processing for all exams using the standard method of using a concurrent rest-CT for AC of rest-SPECT and a stress-CT for AC of stress-SPECT. This baseline intra-operator variability was used as a frame of reference to help investigate the research aim. For the purposes of nomenclature for this study, a schematic for the organization of polar map processing is shown in **Figure 2**. The standard method of processing rest-SPECT with the rest-CT and stress-SPECT with the stress-CT is labeled “SRS” and “SSS”, respectively. The resultant sum difference score produced from the standard SRS and SSS is labeled “SDS”. Not shown in **Figure 2**, sum scores from repeated processing attempts are referred to as “SRSrpt”, “SSSrpt”, and “SDSrpt”. To measure the reliability of single CT substitution for AC, the stress-CT was used for AC of rest-SPECT (labeled SRS’) and the rest-CT was used for AC of stress-SPECT (labeled SSS’).

For rest-SPECT, the sum rest score using the stress-CT (SRS’) was compared to the standard method of processing with the rest-CT (SRS). Likewise, for stress-SPECT, the sum stress score using the rest-CT (SSS’) was compared to the standard method of processing with the stress-CT (SSS). To measure variation in sum difference scores, the scores that were calculated with standard methods were compared to both the sum difference score when only the rest-CT is used for AC (labeled SDS1) and the sum difference score when only the stress-CT is used for AC (labeled SDS2).

A single operator conducted reprocessing of all exams for intra-operator variability and a second operator reprocessed 10 of these studies to determine inter-operator variability.

MPI technique

Stated previously, 20 patients with a dual isotope (Thallium-201 for rest and Tc99m-Tetrofosmin for stress) and 20 patients with single-isotope (Tetrofosmin Tc-99m for both rest and stress) were included. Our standard dual-isotope protocol utilized 148 MBq (4 mCi) Thallium-201 at rest and 1,110 MBq (30 mCi) Tc-99m Tetrofosmin at stress. Our standard single-isotope protocol utilized 370 MBq (10 mCi) Tc-99m Tetrofosmin at rest and 1,110 MBq (30 mCi) at stress. A single day rest/stress SPECT/CT MPI protocol was used for all exams [11]. For Thallium-201 and Tc-99m Tetrofosmin resting injections, there was a 30- and 60-minute interval between injection of radiotracer and SPECT/CT imaging, respectively. For both rest and stress, patients were scanned in a supine position with arms raised with efforts to replicate identical positioning between scans. Following rest or stress injection of radiotracer for any protocol, cold water was ingested in an attempt to reduce bowel uptake. Following stress, patients received a light meal 20 minutes post-injection to reduce bowel activity. For all stress portions of an exam, the period between radiotracer injection and image acquisition was one hour.

Scanning was conducted on any one of three Siemens Symbia (Two T6 and one T2) dual-head SPECT/CT scanners at our institution. Scanning employed a low-dose CT transmission scan with adaptive exposure control.

Reconstruction method

Raw data reconstruction for all protocols used Siemens Syngo version 6.1. Emission data was reconstructed per Siemens recommendations using filters to smooth the data, scatter correction, followed by Siemens FLASH3D iterative reconstruction [21]. No methods for motion correction were used. Alignment of the SPECT and CT data was visually confirmed in axial, sagittal, and coronal fusion planes.

Left ventricular activity was masked from bowel or liver activity. All processed SPECT reconstructions were automatically compared to a normalized database within Corridor4DM version 8.5.10.3 to produce sum scores according to anatomic regions on a 17-segment American Heart Association polar map [18]. Methods to

Table 1. INTRA-operator variability. Results of analyses comparing sum rest score, sum stress score, and sum difference score measurements

Comparison	ICC	Mean Score Difference (95% Confidence Interval)	% of observations for which measurements differed by ≥ 4
Intra-Operator Variability			
SRS vs. SRSrpt	96.4%	0.6 (-0.0 to 1.2)	10.0%
SSS vs. SSSrpt	97.1%	0.3 (-0.3 to 0.9)	15.0%
SDS vs. SDSrpt	78.5%	-0.3 (-1.2 to 0.6)	27.5%
CT Substitution Variability			
SSS vs. SSS'	91.0%	-1.0 (-2.0 to 0.0)	40.0%
SSSrpt vs. SSS'	92.5%	-1.3 (-2.2 to -0.4)	37.5%
SRS vs. SRS'	86.7%	1.9 (0.7 to 3.1)	37.5%
SRSrpt vs. SRS'	87.1%	1.3 (0.1 to 2.6)	35.0%
SDS vs. SDS1	22.0%	-4.3 (-5.8 to -2.8)	47.5%
SDSrpt vs. SDS1	23.6%	-4.0 (-5.6 to -2.4)	62.5%
SDS vs. SDS2	26.7%	1.8 (-0.7 to 4.3)	52.5%
SDSrpt vs. SDS2	20.2%	2.1 (-0.6 to 4.8)	60.0%

ICC = Intra class correlation coefficient; SRS = sum rest score based on first standard processing; SRSrpt = sum rest score based on second standard processing; SRS' = sum rest score based upon the stress CT; SSS = sum stress score based on first standard processing; SSSrpt = sum stress score based on second standard processing; SSS' = sum stress score based upon the rest CT; SDS = SRS - SSS; SDSrpt = SRSrpt - SSSrpt; SDS1 = SRS - SSS'; SDS2 = SRS' - SSS.

anatomically align the left ventricle to the normal database for sum scoring were in line with software guidelines for Corridor4DM, which included a cut-off of the basal ventricle at the mid-mitral valve annulus.

Statistical analysis

Intra class correlation coefficients (ICCs) were used to measure both intra-operator and "CT substitution" reliability, by calculating the proportion of variation within and among subjects (e.g. by repeating the processing or by substitution of a stress-CT for a rest-CT or vice versa). Measurements that are highly reliable have a high ICC, ideally close to 100% [22]. Larger ICC values are associated with smaller within-subject variation, reflecting smaller amounts of variation attributable to repeated processing [22]. For each comparison of measurements, we calculated the proportion of observations for which the individual patient scores differed in absolute value by 4 or more. In addition, because sum difference scores greater than or equal to 4 were considered to be potentially clinically significant, Cohen's kappa (κ) coefficient was used to quantify the intra-operator

and "CT substitution" diagnostic agreement levels [23]. We consider a kappa value of greater than 0.6 as indicative of strong agreement.

Results

Intra class coefficients (ICCs) for SRS, SRSrpt, SSS, SSSrpt, SDS, and SDSrpt between the two operators were 97.4%, 90.1%, 99.0%, 98.9%, 78.1%, and 60.9%, respectively. These values represented reasonable inter-operator variability.

Table 1 summarizes the findings of the comparisons investigating intra-operator reliability and CT substitution variability. ICCs are listed, along with the mean difference between scores and 95% confidence intervals on the difference.

The ICCs were $> 95\%$ when sum rest scores and sum stress scores were repeated and compared to their respective standard processing attempts (SRS vs. SRSrpt; SSS vs. SSSrpt), implying little variation due to the repeated processing (i.e. high intra-operator reliability). Intra-operator reliability was lower for sum difference scores based on repeated processing (SDS vs. SDSrpt: ICC = 78.5%), but acceptable. The ICCs for using the non-standard CT on the SPECT data (i.e. SRS vs. SRS'; SSS vs. SSS') were relatively high ($> 85\%$); however, variability in sum scoring was magnified when sum difference scores were calculated and compared among standard and non-standard methods for calculating a sum difference score (SDS vs. SDS1, SDS vs. SDS2), reflecting much lower ICC values (from 20.2% to 26.7%) with many of the 95% confidence intervals failing to include 0. The last column of **Table 1** further illustrates that when using a non-standard CT, there was more variability in measurements than when using the standard CT, indicated by the proportion of observations for which the measurements differed by 4 or more. When using the non-standard CT measurements, the sum difference score measure-

ments differed by 4 or more for a total of 47.5% to 62.5% of the time.

Cohen's kappa represents how well separate sum difference score calculations agree. The highest value of kappa ($\kappa = 0.66$) (i.e. best agreement) occurred when the SDS and SDSrpt calculations were used. This value is used as a frame of reference for non-standard CT substitution. When a non-standard CT was used to calculate a sum difference score (i.e. SDS1, SDS2), kappa values decreased substantially, demonstrating less agreement between SDS and either SDS1 ($\kappa = 0.32$) or SDS2 ($\kappa = 0.43$). Likewise, the kappas between SDSrpt values and SDS1/SDS2 were poor ($\kappa = 0.46$ and $\kappa = 0.20$, respectively). When SDS1 or SDS2 was used to classify a subject (≥ 4 vs. < 4), a substantial proportion (from 8 to 14, or 20% to 35%) of subjects were classified in a manner that was not consistent with the standard SDS (or SDSrpt).

Discussion

Visual or software-based methods for quantification of myocardial perfusion are used to make important clinical decisions that have significant effect on patient care [8-10]. This study evaluated if there could be a reduction in radiation exposure to patients by eliminating an "extra" CT for AC without compromising quantitative information of perfusion defects provided by a commonly used software suite. Because of disproportionately high variability in sum difference scoring when a single CT is used for AC, we found no evidence to suggest that a single CT would currently suffice as the sole source of AC of both rest and stress SPECT data, using the described technology.

To avoid the potential mistake of only looking at the metrics least or most likely to vary, we felt it was important to show the variation for all three sum score parameters independently. From a mathematical perspective, the fact that the sum difference score exhibited greater variability than either of its individual components (sum rest score and sum stress score) is to be expected, since it is known that the variance of a difference of two independent random variables is equal to the sum of the variances of each of the two variables [22].

Small studies (to date published in peer-reviewed abstract form only) used sum scores

and differences in anatomic measurements on CT as a metrics for evaluating if a single CT could be used for AC [12-15].

This feasibility study carries certain limitations, which may cause discordance in sum scoring. In order to avoid masking true perfusion defects at the later stress portion of the study, a single day MPI requires a lower-count density for the earlier rest portion of the study. Therefore, it is a reasonable hypothesis that lower-count rest myocardial perfusion images may be susceptible to higher variability in sum scores. Contrary to this hypothesis, we found the highest ICCs for SRS and SRSrpt. This may be due to more uniform "normal" perfusion of rest exams compared to stress exams that may be caused by true ischemia.

It is known that robust co-registration of CT and SPECT minimizes variation in relative myocardial perfusion due to errors in attenuation correction [7, 24-27], with as little as one pixel of mismatch. Automated, fiducially guided fusion of the CT to the SPECT may be useful for minimizing attenuation artifacts and may be advisable to eliminate co-registration errors if further evaluation of our primary aim is desired [28].

Conclusions

We found that a single rest or stress CT is not sufficient for attenuation correction of both the rest and stress portions of the exam. Anatomic or physiologic changes between rest and stress exams necessitate a time-specific recalculation of attenuation correction. This information can be used to direct further investigation in radiation reduction for common imaging exams in nuclear medicine.

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Disclosure of conflict of interest

The authors declare that they have no conflict of interests.

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