ORIGINAL ARTICLE

# Risk stratification with attenuation corrected stress Tc-99m sestamibi SPECT myocardial perfusion imaging in the absence of ECG-gating due to arrhythmias

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***Background.*** **Despite growing recognition of attenuation correction (AC) utilizing an external radiation source, prognostic studies using AC are lacking.**

***Methods.*** **Consecutive patients (n = 419) who underwent stress Tc-99m sestamibi SPECT imaging with AC but without ECG-gating, due to arrhythmia, were followed for cardiac death or non-fatal myocardial infarction (MI). A 17-segment model and the summed stress score (SSS) were used to classify both the non-AC and AC images.**

***Results.*** **The 419 patients had a mean age of 71.5 ± 11.7 years and most (70.6%) underwent pharmacologic stress. In follow-up, 35 (8.4%) patients suffered an adverse cardiac event. Patients with AC-SSS 1-3 and AC-SSS 4-8 had similar cardiac event rates (11.4% vs 10.5%, *P* = NS). Accordingly, AC-SSS cutoffs of 0, 1-8, and >8 were selected to classify perfusion as normal, mildly abnormal, and moderately to severely abnormal with annualized event rates of 2.1%, 10.8%, and 18.7%, respectively (*P* < .001). In multivariable analysis, AC-SSS >8 was the most powerful predictor of cardiac events followed by AC-SSS 1-8, history of CAD, age >75 and pharmacologic stress.**

***Conclusions.*** **AC provides powerful risk stratification when added to clinical variables in patients undergoing stress Tc-99m sestamibi SPECT imaging without ECG-gating. Moreover, smaller/less severe defects on AC data are more significant than if the same defects were seen on non-AC data. (J Nucl Cardiol 2009;16:533–9.)**

**Key Words: Attenuation correction • SPECT • prognosis • ECG-gating**

**See related editorial, pp. 490–492**

## INTRODUCTION

Despite advances in camera technology, artifact created from soft-tissue attenuation presents a continuing serious diagnostic challenge. Various techniques have been developed to address this problem, such as reviewing rotating planar images, prone or ECG-gated SPECT imaging. The most efficient and accurate approach, however, is to measure soft-tissue attenuation during acquisition of SPECT data using an external source of irradiation (either line source or x-ray). The positive role of attenuation correction (AC) in improving image quality and diagnostic accuracy is based on multiple studies.[1-9] In 2004, the American Society of Nuclear Cardiology (ASNC) and the Society of Nuclear Medicine (SNM) released a joint position statement that strongly endorsed AC.[10]

AC and ECG-gating are complementary for identifying attenuation artifacts and may improve diagnostic accuracy when used in combination.[4] AC may be of particular value in the absence of ECG-gated data, such as patients with arrhythmias preventing its use. A major limitation surrounding the routine clinical utility of AC is the lack of studies demonstrating effective risk

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stratification.[11] Therefore, the aim of this study was to define the role of AC in the risk stratification of patients with SPECT myocardial perfusion imaging studies in patients unable to undergo ECG-gating.

## METHODS

### Patient Selection

This study was approved by the institutional review board of Hartford Hospital. From the Nuclear Cardiology Laboratory clinical database at Hartford Hospital, consecutive patients who underwent stress Tc-99m sestamibi SPECT imaging without ECG-gating, secondary to an arrhythmia, between October 2001 and June 2004 were identified.

### Stress Testing and Image Acquisition

Patients were instructed to fast ≥8 hours prior to testing and to withhold caffeinated beverages. Patients taking beta-blockers or oral dipyridamole were instructed not to take those medications before the test. Patients underwent exercise or pharmacologic stress according to standard techniques.[12]

Images were acquired using a dual-headed Cardio-60 camera (Phillips Medical Systems), equipped with AC utilizing VantagePro/ExSPECT II devices using of two gadolinium 153 line sources for transmission acquisition.[13] Images were acquired over 180° non-circular orbit from 45° right anterior oblique to left posterior oblique, with a 64 × 64 matrix (pixel size of approximately 0.64 cm) for the emission images and a 128 × 128 matrix (pixel size 0.32 cm) for the transmission images. A total of 64 emission, transmission, and scatter projections were obtained, 30-35 seconds/projection. Attenuation corrected transverse images were reconstructed by first prefiltering the emission projections with a fifth-order 0.6 Nyquist Butterworth filter followed by reconstruction via an iterative maximum likelihood expectation maximization algorithm. Attenuation maps were reconstructed by the use of Bayesian prior approach with Butterworth filter processing at 0.66 Nyquist critical frequency and an order of 5. The attenuation map reconstruction used 12 iterations with a uniform initial estimate. The emission transaxial images were reconstructed by use of a maximum likelihood algorithm with 30 iterations and a uniform initial estimate. The scatter distribution obtained from the scatter window was used to correct both the scatter from the patient onto the photopeak window and scatter from the patient onto the transmission energy window. All attenuation maps were assessed for adequate counts, field uniformity, and truncation.

### Image Interpretation

Images were interpreted without clinical information during daily clinical reading sessions by a consensus of two or more experienced readers using a 17-segment model and scoring system.[14] In visual assessment of perfusion, each segment was scored on a scale of 0-4 (0 = normal, 1 = mild, 2 = moderate, 3 = severe, 4 = absent photon activity). A summed stress score (SSS) was calculated by adding the segment scores at stress.

### Definition of Normal and Abnormal Perfusion

With non-attenuation corrected images, cutoffs were determined from previous studies. Accordingly, a SSS <4 was considered normal, 4-8 mildly abnormal, and >8 moderately to severely abnormal perfusion.[15] No accepted cutoffs exist for SSS with attenuation-corrected images; thus, cutoffs were determined after examining annualized cardiac event rates in patients with an attenuation-corrected SSS (AC-SSS) of 0, 1-3, 4-8, and >8.

### Follow-up

Patient follow-up was obtained by scripted telephone interviews and mailed questionnaires. An investigator unaware of clinical, stress testing and SPECT imaging data confirmed events by reviewing hospital admission records, the public Social Security database and death certificates. The endpoint for this study was cardiac death or nonfatal myocardial infarction (MI). Patients were censored at the first cardiac event.

### Statistical Analysis

Clinical characteristics were expressed as mean ± standard deviation or as proportions. Inter-group comparisons were performed using the $\chi^2$ or Fisher exact test for categorical variables. Survival curves were generated by the Kaplan-Meier method. Differences between survival curves were tested with the log-rank test. Cox proportional hazards regression was performed in a stepwise forward fashion to identify independent predictors of cardiac events with AC-SSS entered as a categorical covariate. Only variables that achieved statistical significance by univariate analysis were entered in Cox regression. A $P$ value <.05 was considered significant in all analyses. SPSS 15.0 was used for statistical analysis.

## RESULTS

### Clinical Characteristics

Of the 480 patients, follow-up was complete in 90.8% over 1.3 ± 0.6 years. Patients who underwent either percutaneous coronary intervention or coronary artery bypass grafting ≤60 days (n = 13) after SPECT imaging were excluded, leaving 419 patient studies for

analysis. The 419 patients had a mean age of 71.5 ± 11.7 years and 43.4% were female. In addition, 24.3% had prior history of coronary artery disease (CAD), 29.1% had diabetes, and 70.6% had undergone pharmacologic stress. In follow-up, 35 (8.4%) patients had an adverse cardiac event, of which 29 (6.9%) suffered cardiac death while 6 (1.4%) sustained a non-fatal MI. Patients with an adverse cardiac event were more likely to be elderly (age >75 years), had a history of CAD, more often underwent pharmacologic stress, and had higher SSS or AC-SSS than those who were event-free (Table 1).

## Impact of Attenuation Correction on Interpretation of Myocardial Perfusion

The effect of AC upon interpretation of images was examined (Figure 1). For studies in which no abnormalities were found without AC (SSS = 0), AC interpretation was the same (180/419, 43%). However, 79 patients (18.9%) had a mild defect (SSS ≤ 3) without AC (14 reversible and 65 fixed) and in 59 (74.7%) interpretations was considered normal after AC. For 90 patients with SSS 4-8 (33 reversible, 57 fixed), 37.8% were reclassified as normal including 9 patients with

**Table 1.** Association between clinical and stress testing variables and cardiac death

| Variable | Cardiac event free N = 384 | Cardiac event N = 35 | *P*-value |
|---|---|---|---|
| Age >75 | 159 (41.4%) | 24 (68.6%) | .002 |
| Female gender | 168 (43.8%) | 14 (40.0%) | .668 |
| History of CAD (MI, revascularization) | 82 (21.8%) | 20 (57.1%) | <.001 |
| Risk factors | | | |
| Diabetes mellitus | 120 (31.3%) | 11 (31.4%) | .983 |
| Hypertension | 267 (69.5%) | 20 (57.1%) | .131 |
| Elevated cholesterol | 179 (46.6%) | 13 (37.1%) | .282 |
| History of smoking (former or current) | 104 (27.2%) | 12 (34.3%) | .367 |
| Pharmacologic stress | 263 (68.5%) | 33 (94.3%) | .001 |
| SSS (mean ± SD) | 3.6 ± 5.1 | 10.1 ± 8.4 | <.001 |
| AC-SSS (mean ± SD) | 2.5 ± 5.0 | 8.9 ± 8.9 | <.001 |

Cardiac event, cardiac death or non-fatal myocardial infarction.
*CAD*, Coronary artery disease; *MI*, myocardial infarction; *ECG*, electrocardiogram; *SSS*, summed stress score; *AC-SSS*, summed stress score after attenuation correction.

**Figure 1.** Impact of attenuation correction on stress perfusion.

**Figure 2.** An example of a patient with typical anginal symptoms and mild reversible perfusion abnormality in the anterior wall that persists with attenuation correction. **A**, Before attenuation correction. **B**, After attenuation correction.

reversible defects. Finally, for patients with SSS >8, the vast majority (83%) remained in the same classification.

Figure 2 demonstrates SPECT MPI images (A, non-attenuation corrected; B, attenuation corrected) from a patient with typical anginal symptoms. There was a small, apical to mid-anterior, mild, reversible perfusion abnormality that persists after AC (SSS = 2). At cardiac catheterization, the patient was found to have an 80% proximal left anterior descending artery stenosis.

## Establishing Cutoffs for AC-SSS in Risk Stratification

The outcomes of the study population were examined in the absence of AC. Similar to numerous previous studies, cardiac events in patients with SSS of 0-3 was low, and accelerated with higher SSS categories (Figure 3), using previously described cutoffs.[15,16] However, the assumption for these "cutoffs" was based upon attenuation artifacts in a high percentage of patients with low, but not normal SSS (1-3). A reasonable assumption with AC would be to expect any remaining abnormality to be consistent with CAD, and SSS = 0 to be normal.

Thus, we examined AC outcomes assuming normal to be SSS of 0, and "mild" to be SSS 1-3 (Figure 4). The cardiac event rate in patients with AC SSS of 1-3 was significantly higher compared to patients with SSS of 1-3 without AC (11.4% vs 2%, $P = .01$). This cardiac event rate was similar to the group with AC SSS 4-8 (11.4% vs 10.5%, $P = .89$) or SSS 4-8 (11.4% vs 8.2%, $P = .53$). Furthermore, the cardiac event rate in the 20 patients who had SSS 1-3 before and after AC was similar to the patients with AC SSS 4-8 (8.7% vs 10.5%, $P = .80$) or SSS 4-8 (8.7% vs 8.2%, $P = .94$). Thus, the cardiac event rate in this group was high even prior to combining it with the 12 patients who changed from SSS 4-8 into AC SSS 1-3.

We combined the two groups with either a SSS of 1-3 or SSS of 4-8 after AC. Figure 5 demonstrates

**Figure 3.** Cardiac event rate in different risk groups with and without attenuation correction.

**Figure 4.** Justification for using a new cutoff for attenuation corrected summed stress score.

| | | | | | |
|---|---|---|---|---|---|
| AC-SSS = 0 | 274 | 260 | 246 | 63 | 33 |
| AC-SSS 1-8 | 87 | 77 | 67 | 21 | 10 |
| AC-SSS ≥ 9 | 58 | 46 | 40 | 8 | 2 |

**Figure 5.** Kaplan-Meier estimates for survival free of cardiac events according to new AC-SSS risk categories. Numbers at bottom of graph indicate patients available for analysis at given time points.

Kaplan-Meier estimates for survival free of cardiac events utilizing these new AC-SSS risk categories with a clear separation into three risk groups ($P < .001$).

## Predictors of Adverse Cardiac Events

In multivariate analysis, AC-SSS >8 was the most powerful predictor of cardiac events followed by AC-SSS 1-8, history of CAD, age >75 and pharmacologic stress (Table 2). In addition, attenuation corrected perfusion data significantly increased the overall $\chi^2$ value over clinical variables (33.3-58.8, $P < .001$).

## DISCUSSION

This study investigated the prognostic value of AC in a group of patients with known or suspected CAD having undergone stress myocardial perfusion imaging without the added benefit of ECG-gating. Our results demonstrate successful risk stratification with AC that is comparable to non-AC data. Importantly, we identified a subset of new at risk group (AC SSS 1-3) which would have been previously considered normal.

ECG-gated SPECT imaging provides improved specificity by identifying soft-tissue attenuation in patients with fixed perfusion defects and normal function.[17-19] It also increases reader confidence while reducing the chance of equivocal interpretation and providing incremental prognostic information to perfusion results.[20,21] In our study we included only cases in which ECG-gating could not be performed. As such we were able to focus on AC results while making certain that interpreters of the AC images were not influenced by ECG-gating. AC may also have an important larger risk stratification role in these patients.

The role of SPECT myocardial perfusion imaging without AC in risk stratification is well established.[22-28] Conversely, the only study addressing risk stratification with AC was by Gibson et al demonstrating the safety of a normal study mainly in a low risk group referred for chest pain. Although the current endorsement for AC by national societies is based on multiple studies demonstrating improved diagnostic accuracy for the detection of significant CAD, data providing risk stratification for this procedure are lacking.[1-9] This concern was recently reflected in an article by Germano et al.[11]

Traditionally, a summed stress score <4 is considered to represent normal perfusion in risk stratification.[16] In our study, an AC-SSS of 0 was introduced as the cutoff to represent normal based upon the significantly higher cardiac event rate in patients with AC-SSS 1-3. This underscores that although there is a high prevalence of attenuation artifact in patients with SSS 1-3 in previous prognostic studies, there are still patients in that group with real CAD. Without AC, there is a reduced ability to differentiate between truly abnormal and artifact. Therefore, we suggest an AC-SSS 1-8 to represent mild perfusion abnormalities and an AC-SSS >8 to represent moderate to severe perfusion abnormalities in risk stratification. Justification at this approach lies in the clear separation into different risk levels with the Kaplan-Meier curve and the multivariate analysis, in which

**Table 2.** Cox proportional hazards regression analysis: significant predictors of cardiac events

| Variable | Wald $\chi^2$ | OR | 95% CI | *P*-value |
|---|---|---|---|---|
| Age >75 | 5.1 | 2.34 | 1.12-4.88 | .024 |
| History of CAD | 5.4 | 2.28 | 1.14-4.57 | .020 |
| Pharmacologic stress | 3.9 | 4.33 | 1.01-18.58 | .049 |
| AC-SSS 1-8 | 6.7 | 3.53 | 1.35-8.35 | .009 |
| AC-SSS >8 | 20.7 | 7.85 | 3.23-19.09 | <.001 |

*OR*, Odds ratio; *CI*, confidence interval; *Wald* $\chi^2$, Wald chi-square; *CAD*, coronary artery disease.

AC-SSS >8 and 1-8 emerged as the most powerful predictors of adverse cardiac events with a higher $\chi^2$ and incremental prognostic value compared to clinical variables.

Having an incremental value is an important factor in any diagnostic study and should translate into altered patient management. An important implication from this study is that smaller/less severe defects on AC data (AC-SSS 1-3) are more significant than if the same defects were seen on non-AC data and require aggressive coronary risk factor modification similar to SSS values 4-8. Without AC, this group of patient which represents 8.4% of our abnormal studies may have been denied life-saving medical treatment. A more invasive approach could be employed in patients with AC-SSS $\geq$ 9.

The cardiac event rates in our study are high relative to most prognostic studies even when compared to the AC study performed by Gibson et al.[29] This is most likely due to the selection of a high-risk population in our study. The patients tended to be elderly while the vast majority had either known CAD or had undergone pharmacologic stress imaging. Our results are consistent with a previous meta-analysis by Navare et al[30] which demonstrated a doubling of the cardiac event rate in patients undergoing pharmacologic stress.

## STUDY LIMITATIONS

Although data were prospectively collected, this study is retrospective with all the limitations inherent to similar analysis such as the possibility of unknown confounders. Furthermore, this was a highly selective group and the number of patients and events limited the statistical analysis and did not allow examination of risk stratification with AC in key subgroups. This study is hypothesis generating and should be corroborated with more extensive research. Furthermore, we utilized a sealed source for AC as detailed above and results may not apply to other AC approaches utilizing sealed sources or computerized tomography.

## CLINICAL IMPLICATIONS

In patients with known or suspected CAD who cannot undergo ECG-gating during SPECT acquisition, AC provides a powerful risk stratification tool that is incremental to clinical variables. Our results also identified a new "at risk group" of patients with a smaller/less severe defect and a summed stress score after AC of 1-3 which previously would have been considered normal and denied appropriate medical treatment.

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