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CT Attenuation correction and its impact on image quality of myocardial perfusion imaging in coronary artery disease: A systematic review

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ABSTRACT

Myocardial perfusion imaging is a non-invasive procedure that plays an integral role in the diagnosis and management of coronary artery disease. With the routine use of computerised tomography attenuation correction (CTAC) in myocardial perfusion imaging still under debate, the aim of this review was to determine the impact of CTAC on image quality in myocardial perfusion imaging. Medline, Embase and CINAHL were searched from the earliest available time until August 2019. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies version 2. Details pertaining to image quality and diagnostic accuracy were analysed, and results summarised descriptively. Three studies with 'unclear' risk of bias and low applicability concerns (1002 participants) from a yield of 2725 articles were identified. Two studies demonstrated an increase in image quality, and one study found no difference in image quality when using CTAC compared to no attenuation correction. Benefits of CTAC for improving image quality remain unclear. Given the potential exposure risk with the addition of CTAC, patient and clinician factors should inform decision making for use of CTAC in myocardial perfusion imaging for coronary artery disease.

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Introduction

Myocardial perfusion imaging is a non-invasive procedure that plays an integral role in the diagnosis and management of coronary artery disease (CAD). While it has been a routine procedure for more than 20 years, debate still surrounds the most appropriate acquisition and reconstruction parameters to mitigate the impact of attenuation artifacts (1). Various methods have been used to correct these artifacts. The use of transmission sources to create attenuation maps was the first attempt at attenuation correction, and became commercially available in the mid 1990's (2). Prone imaging and use of computerised tomography (CT) have also been described as appropriate methods for correcting attenuation artifacts (3, 4). Over recent years CT attenuation correction (CTAC) using hybrid systems has become the most common form of attenuation correction as described in Society of Nuclear Medicine and Molecular Imaging guidelines (5). Despite increasing popularity of CTAC, the impact of CTAC on image quality largely remains unknown.

Using CT to provide a map for attenuation correction has many benefits. CTAC does not have issues with downscatter and excessive statistical noise which is present with other transmission sources such as gadolinium line sources (2, 6). CTAC also demonstrates greater diagnostic accuracy of myocardial perfusion imaging compared to non-attenuation corrected imaging (1). A review including 5 studies of CTAC used in myocardial perfusion imaging described

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significantly greater specificity than non-corrected data with no loss in sensitivity (Diagnostic OR 20;95% CI 12 to 34) (1). Moreover, when comparing CTAC to prone imaging, CTAC reduces the number of equivocal studies (7). Despite these advantages, CTAC does have limitations .

CTAC involves additional radiation exposure to patients therefore the risk this entails must be carefully considered when deciding to perform CTAC (8). Other disadvantages such as co-registration errors and truncation artifacts have also made use of CTAC difficult (9). Advances in technology have seen the development of single photon emission computed tomography (SPECT) hybrid systems allowing for sequential acquisition of nuclear imaging with attenuation correction provided by the CT component. This has reduced the risk of misregistration as the patient does not need to be moved between emission and transmission scans. Given the benefits of CTAC for improving diagnostic accuracy compared to non-corrected data and other forms of correction, it may be assumed that CTAC is the protocol of choice for enhancing image quality.

While CTAC may improve diagnostic accuracy (1), the direct impact on image quality has not been thoroughly reviewed. Image quality can be influenced by several factors including technical parameters, patient related variables, and operator variables (10). Both technologists and physicians need to be aware of sources of possible artifacts, be able to identify them in the clinical setting and establish methods to reduce or eliminate them in order to minimise interpretation errors and enhance the overall performance of myocardial perfusion imaging (10, 11). It is imperative that acquisition protocols be optimised in order to achieve the best possible image quality so that diagnostic accuracy can be improved (12). With the use of CTAC in myocardial perfusion imaging protocols still under debate, the aim of this review was to determine the impact of CTAC on image quality in myocardial perfusion imaging for people with coronary artery disease.

Methods

This systematic review was registered with PROSPERO (registration ID: CRD42020149270) and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA statement (13).

Search Strategy

Studies to be included for review were identified through searching electronic databases Medline, Embase and CINAHL from the earliest available time until August 2019. The search strategy comprised synonyms and Medical Subject Headings (MeSH) terms of the key concepts: coronary artery disease, myocardial perfusion imaging, and attenuation correction combined with Boolean operators OR within each concept and the operator AND between concepts (Appendix I). Citation tracking was performed using Google Scholar and reference lists of all included studies were checked to supplement the search.

Study Selection

To be included, studies needed to evaluate the use of CTAC in nuclear medicine myocardial perfusion imaging and its effect on image quality. For the purpose of this review, image quality was reported as a subjective rating or objectively using assessment of the number or size of artifacts. Included studies needed to use CT for attenuation correction which was to be acquired on the same scanner, sequentially for both rest and stress scans. Comparison of attenuation corrected data to non-corrected data was also required. Studies of diagnostic accuracy were only included if data related to image quality was included. Both randomised and non-randomised designs were eligible for inclusion. Studies were excluded if external CT or other form of attenuation correction (e.g. radionuclide attenuation correction) was used. Studies using a reference standard other than non-attenuation-corrected SPECT data were also excluded (Figure1).

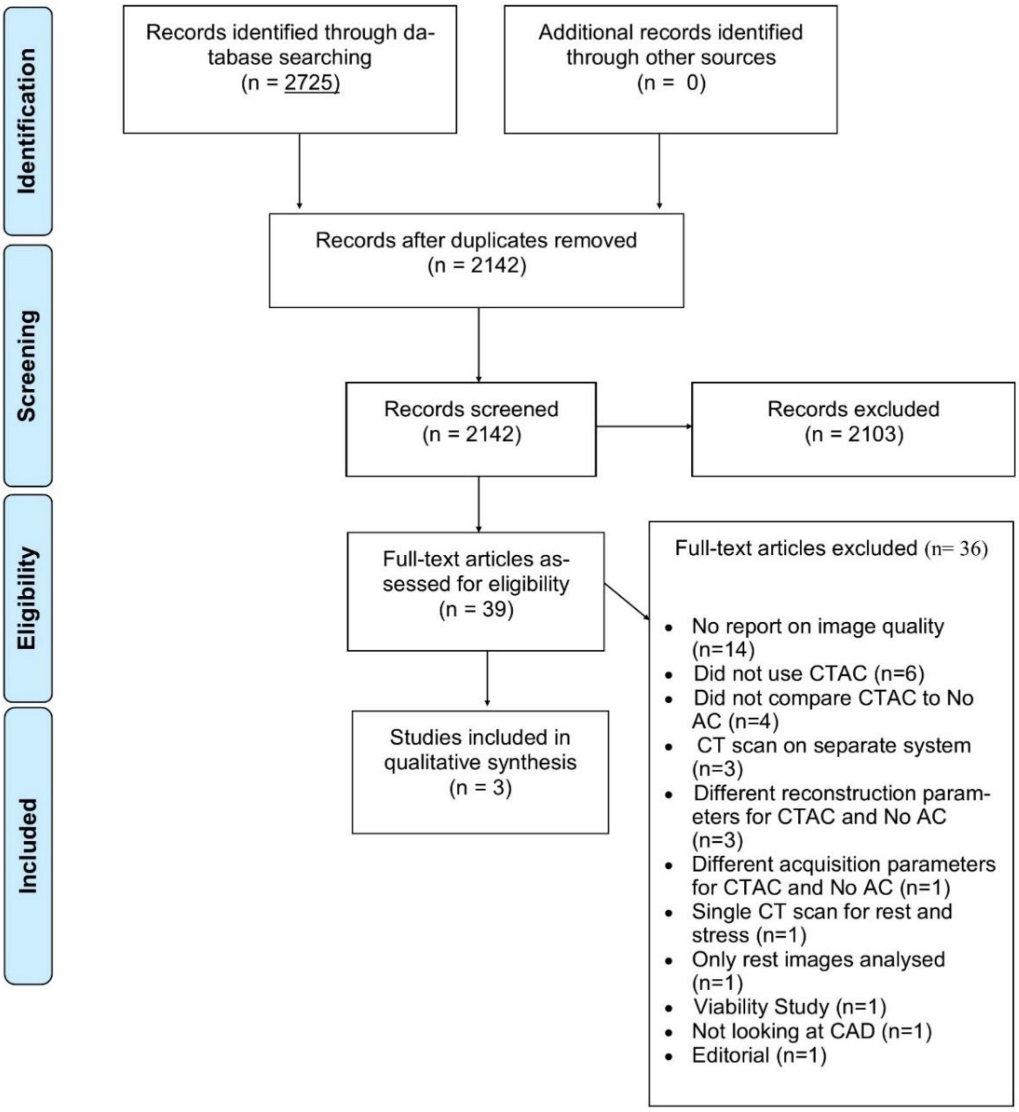

Figure 1. Flow diagram of study selection

Two researchers independently assessed the title and abstract of studies. Eligibility was evaluated upon review of title and abstract against the predefined inclusion criteria. If eligibility was unclear from the title and abstract, the full text was retrieved and screened by both researchers to determine eligibility for study inclusion. Agreement between researchers was assessed using the kappa statistic (14). A third researcher was consulted when there were discrepancies in agreement and a consensus was formed.

Methodological quality

Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2). The tool comprises four key domains covering patient selection, index tests, reference standards and flow and timing of index tests in relation to the reference standard. The QUADAS-2 assessment was completed independently by two researchers (CF and AD) with a third researcher consulted in the event of discrepancies in agreement. As the study's primary goal was to review image quality, the reference standard was defined as the non-attenuation corrected myocardial perfusion data. The QUADAS-2 has significant improvements from the original QUADAS tool assessment (15) which has good coverage, is quick and easy to use and has good interrater agreement κ=0.66 (95% CI 0.63 to 0.67) (16). The use of QUADAS-2 was a minor deviation from protocol due to the type of studies included in this review.

Synthesis of results

Data were extracted and recorded using a predefined worksheet. Details about the study design, patient demographics, acquisition parameters, and results pertaining to image quality were extracted. Where available, details relating to diagnostic accuracy were also recorded. All data was checked by a second researcher (JP) for accuracy. Authors were contacted if there was insufficient published data for analysis. Results were summarised descriptively. Meta-analysis was planned however, due to the limited number of studies and heterogeneity of data, it was deemed not appropriate.

Results

Study Selection

A total of 2725 studies were identified through searching electronic databases. This number was reduced to 2142 after duplicates were removed. Following title and abstract screening, 39 full texts were obtained and reduced to 3 studies after assessment against inclusion criteria. No additional studies were identified from citation tracking or reference checking of included studies (Figure 1). The inter-rater agreement for study inclusion was moderate ƙ=0.43 (95% CI 0.31 to 0.56). One study responded to a data request and provided details clarifying the number of patients having stress only scans and artifacts seen in these images(9).

Risk of Bias

The QUADAS-2 identified all three studies to have an 'unclear' risk of bias and low concern regarding applicability. No study scored 'high risk' of bias in any domain. A small number of domains were judged as 'unclear'. Two studies had 'unclear' patient selection, as it was not reported whether it was a consecutive sample or if there were specific selection criteria that had to be met. One study was judged 'unclear' for reference standard as it was not disclosed whether results were interpreted without knowledge of the index test. A third study was judged 'unclear' for flow and timing because not all patients were included in analysis (Table 1). The inter-rater agreement for risk of bias assessment was moderate ƙ=0.41 (95% CI 0.13 to 0.70).

Table 1. Risk of bias assessment using the QUADAS-2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Ali et al (17)	?	☺	☺	☺	☺	☺	☺
Benkiran et al (9)	?	☺	?	☺	☺	☺	☺
Savvopoulos et al (18)	☺	☺	☺	?	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Study Characteristics

Participants

Data were collected from 1002 patients. Participants were predominantly male (61%) with mean age of 60 (SD 3) years. One study had 74 males and 26 females (17), another had 45 males and 25 females (9), the third did not specify sex of participants (18). Included participants presented with risk factors including hypertension, dyslipidaemia, diabetes, increased body mass index, end stage renal failure, peripheral arteriopathy, history of smoking, family history of coronary artery disease, personal history of previous cardiac event or known coronary artery disease (Table 2).

Table 2. Study Characteristics

Study	N =	Subjects Intervention1	Known CAD n= (%)	Suspected CAD n= (%)	Mean Age (SD)	Gender Male n= (%)	Tracer	Gating	NAC Image Quality Results	CTAC Image Quality Results	Image Quality Increase/ decrease
Ali et al. 2009 (17)	212	100[2]	105	107	57	141(66%)	Tc 99m Tetrofosmin	Yes	111/112 Excellent	111/112 Excellent	No difference
Benkiran et al 2015 (9)	70	14[3]	21	49	61	45 (64%)	Tc 99m Tetrofosmin	Yes	23 Artifacts[4]	10 Artifacts[5]	Increase
Savvopoulos et al 2013 (18)	720	720	32	688	62.5	NR	Tl-201	No	199 (28.6%) Excellent 373 (53.7%) Good 123 (17.7%) Poor but acceptable	312 (44.9%) Excellent 268 (36.8%) Good 115 (16.5%) Poor but acceptable	Increase

1 .Intervention considered as only patients that met our inclusion criteria i.e.: rest and stress studies
2.100 patients had full time scans. The rest had half time scans
3. Only 14 patients went on to have rest studies
4. Of 57 patients found to be free of CAD (from angio or echo) 23 had artifacts that lead to false positive results
5.18of the 23 artifacts were corrected for using CTAC. However, 5 additional artifacts were introduced. Total of 10 artifacts leading to false reporting

Imaging details

All participants were given specific preparation instructions. This included cessation of nitrates, calcium antagonists, beta blockers and caffeine in all studies. Imaging protocols varied across studies with one using a 99mTc-Tetrofosmin Rest/Stress protocol (17), another a 99mTc-Tetrofosmin Stress/Rest protocol (9) and the third using a Thallium-201 Stress/Rest protocol (18). One study incorporated a two day stress/rest protocol in three patients who were over 100 kg (9). All SPECT acquisitions used a 64×64 matrix with either 30 (Tc-99m studies) or 60 steps (Tl-201 study). CT scans were performed using 140kV and 1-2.5 mA. All studies performed iterative reconstruction on data using 2 iterations and 10 subsets.

Effect of CT Attenuation Correction on image quality

Two of the three studies showed an increase in image quality when using CTAC in comparison to no attenuation correction (9, 18). Of the 70 patients reported by Benkiran et al, 57 were considered free from coronary artery disease based on echo or angiogram results. When no attenuation correction was applied in this cohort of CAD free patients, 23 patients had false positives results. CTAC corrected artifacts in 18 of these 23 image datasets; however 5 patients had artifacts introduced after addition of CTAC. Another study found 312 out of 695 images (44.9%) were scored as having excellent image quality, 268 (36.8%) were scored good and 115 (16.5%) were scored as poor but acceptable image quality by two experienced Nuclear Medicine Physicians (18). In comparison, images acquired with no attenuation correction were scored as excellent in 199 patients (28.6%), good in 373 (53.7%) and poor but acceptable in 123 (17.7%) patients (18). In another study, no difference in image quality between non-attenuation corrected and CTAC data was observed, with 111 of 112 patients having excellent image quality in both cohorts (17).

Effect of CT Attenuation Correction on diagnostic accuracy and risk stratification

One study evaluated diagnostic accuracy in addition to image quality (9). This study showed the differential diagnosis was changed after viewing CTAC images in 26 (37%) patients (9). Of the 37%, 17 (24%) were correct and 9 (13%) were incorrect revisions (9). The overall diagnostic accuracy of myocardial perfusion imaging was shown to improve from 63% to 79% with the addition of CTAC (9). In another study, non-attenuation corrected myocardial perfusion imaging provided more accurate risk stratification than CTAC when assessing summed stress scores (SSS) against all-cause mortality and total event rates (18).

Discussion

This review evaluated evidence with low risk of bias about CTAC and image quality for myocardial perfusion imaging in people with coronary artery disease. Two studies found CTAC improved image quality and one found no difference between corrected and non-corrected data. While a recent review concluded attenuation correction significantly improves diagnostic accuracy of myocardial perfusion imaging by increasing specificity without loss in sensitivity (1), it remains unclear about the impact of CTAC on image quality. It is possible that other patient and clinician-related variables may be more important than image quality alone when determining the most appropriate protocols for myocardial perfusion imaging in coronary artery disease. These findings demonstrate that image quality may not be the only variable impacting diagnostic accuracy of myocardial perfusion imaging with CTAC.

While it remains unclear about the impact of CTAC for image quality, there is evidence CTAC improves diagnostic accuracy (1). This highlights accurate diagnosis is likely to be multifaceted and not just dependent on image quality. Technologist and physician training and experience are an important factor that should be considered in determining diagnostic accuracy. Greater radiologist experience has been associated with better diagnostic accuracy (19, 20). Diagnostic accuracy may also be linked to training. For example, targeted image interpretation programs increase both accuracy and confidence levels of radiographers (21, 22). This could translate to improved confidence with image interpretation and diagnostics amongst physicians when further training and expertise in use of CTAC is provided. Therefore, training and expertise in image interpretation with CTAC may be more important than improving the image quality using CTAC in myocardial perfusion imaging.

It is also possible CTAC is more beneficial for improving imaging quality based on different clinical groups such as gender. It is widely acknowledged men and women often exhibit different patterns of attenuation on myocardial perfusion images. Men are more likely to have diaphragmatic attenuation artifacts in the inferior wall, while women are more likely to have breast attenuation artifacts in the anterior wall (10, 23, 24). One study of over 300 participants found CTAC is more beneficial in correcting attenuation artifacts seen in the inferior wall compared with the anterior wall (7). This finding is supported by several smaller studies with one demonstrating more obvious reduction in defect size in the inferior wall in men than women due to use of CTAC (p=0.027) (25). Another study concluded sex was the only physiological determinant for likelihood of attenuation artifact correction (9). They reported 15 (33%) artifact corrections in males with 2 (8%) observed in females (9). Given this preliminary evidence that CTAC may be more beneficial in males or patients with inferior wall artifacts, CTAC could be limited to this patient cohort in order to avoid unnecessary radiation exposures to people from other populations.

The advantages of CTAC should be weighed against the risk of increased radiation exposure. The risk to individual organs should be taken into consideration when deciding to perform CTAC, in particular the radiosensitivity of breast tissue, especially in younger patients (8). Justification of use of CTAC against other methods of determining true nature of defects may also be necessary. Prone imaging can be used in conjunction with supine imaging to determine if perfusion defects are true or artifact, particularly those located in the inferior wall (7). While prone imaging requires no additional radiation exposure, not all patients are capable of lying prone and it can be time consuming when additional acquisitions are required. In this instance, CTAC may be preferred to correct for attenuation artifacts. CTAC could also offer another means of assessing attenuation artifacts when electrocardiogram (ECG) gating is not feasible. Assessment of regional wall motion from ECG gating has previously been found to be more beneficial than CTAC in differentiating between artifacts and true perfusion abnormalities (9). However, patients should be screened for suitability for gated SPECT and non-gated acquisitions may be necessary in patients with severe arrhythmias (10). Cardiac arrhythmias may lead to inaccurate assessment of wall motion, wall thickening and ejection fraction (10). Rejected beats that fall outside the acceptance window, will also lead to low counts and possible errors in assessment of perfusion defects (10). It is suggested CTAC should be applied if results are inconclusive after analysing gated data (9). While some concern remains about the safety and efficacy of CTAC in myocardial perfusion imaging, when appropriate acquisition parameters are used in conjunction with adequate justification process, CTAC is a valid tool for attenuation correction (8). Appropriate screening of patients and assessment of available resources should help identify the most appropriate imaging protocol in people with coronary artery disease.

Guidelines are required to assist clinicians and nuclear medicine technologists in selecting the most appropriate imaging protocol for patients with coronary artery disease. Currently guidelines suggest three methods of performing CT scans for use in hybrid imaging: an unenhanced, non-gated, free tidal breathing CT for attenuation correction; an unenhanced, gated, breath hold CT for coronary artery calcium scoring; and a contrast-enhanced, gated, breath hold CT for coronary CT angiography (5). With various methods of generating attenuation maps available, it is necessary to be aware of factors that may influence the quality of the attenuation map (26). In terms of attenuation correction, hybrid SPECT/CT systems and stand-alone SPECT and CT scanners are both recognised methods of performing CTAC, the latter using image fusion software to merge external datasets (27). While separate CT scans are often required for rest and stress studies (5), more recent literature has proven both methods to produce the same level of accuracy (28). This demonstrates the need to consider various CT acquisition protocols and their feasibility for the desired outcome (5).

Strengths and limitations

To our knowledge, this is the first review to directly compare use of CTAC with non-attenuation correction on the impact of image quality. This review was reported in accordance with PRISMA guidelines and prospectively registered. Overall, studies were not at high risk bias.

There were some limitations to this review. Given the small number of studies included and data heterogeneity, a meta-analysis could not be performed. A small number of studies were identified with limited data available for review limiting the generalisability of the results. Another possible limitation is the use of the QUADAS-2 tool for quality assessment as this tool is primarily used for diagnostic studies. Despite this, the QUADAS was able to be applied to the selected studies, with no studies demonstrating high risk of bias and low concerns with applicability. We did not investigate the benefit of CT data in terms of the anatomical information it can provide, nor did we consider the impact visible calcium may have on final diagnosis or risk stratification. Other benefits CT may provide such as incidental findings were not considered in this review. Use of CTAC in dedicated cardiac solid state (CZT) detectors was also not evaluated.

Conclusion

The benefits of using CTAC for improving image quality remain unclear. Patient and clinician factors need to be considered when deciding whether to perform CTAC. Screening of patients and further development of guidelines may assist decision making relating to protocol selection for myocardial perfusion imaging. Further research in the use of CTAC with a focus on select patient cohorts is needed.

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