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Combined quantitative analysis of attenuation corrected and non-corrected myocardial perfusion SPECT: Method development and clinical validation

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Abstract

Background—Attenuation corrected myocardial perfusion SPECT (AC-MPS) has been demonstrated to improve the specificity of detecting coronary artery disease (CAD) by visual analysis which utilizes both non-corrected (NC) and AC data. However, the combined automated quantification of NC and AC-MPS has not been previously described. We aimed to develop a combined quantitative analysis from AC and NC data to improve the accuracy of automated detection of CAD from AC-MPS.

Methods—Stress total perfusion deficit (TPD) values were generated by standard analysis for NC (NC-TPD), AC (AC-TPD) and by combined NC-AC analysis (NA-TPD), in which the hypoperfusion severity in each polar map location was defined as the average of AC and NC severity computed by comparison with separate AC and NC normal limits. Ischemic TPD was also calculated as the difference between stress TPD and rest TPD for each measure. Stress/rest Tc-99m sestamibi MPS studies in 650 patients with correlating coronary angiography and in 345 patients with a low-likelihood (LLk) of CAD were used to assess diagnostic performance of combined NC-AC analysis.

Results—NA-TPD had a higher receiver-operator-characteristic area under the curve (ROC-AUC) (0.87) than NC-TPD (0.85; $P < .01$) or AC-TPD (0.85; $P < .01$) for detection of stenosis $\geq 70\%$ in angiographic group. It also had higher specificity (75%) vs NC-TPD (65%; $P < .0001$), or AC-TPD (70%; $P = .016$). In LLk group, the normalcy rate of NA-TPD (95%) was higher than for NC-TPD (90%; $P < .01$) and similar to AC-TPD (94%; $P = \text{NS}$). NA-TPD had higher ROC-AUC than that for 17-segment expert visual scoring of stress scans in angiographic group (0.84; $P = .01$), comparable accuracy (81%) and similar normalcy rates (95% vs 97%; $P = \text{NS}$). Ischemic TPD by combined NC-AC analysis had higher ROC-AUC than that for any ischemic measure. Similar to stress NA-TPD, it also obtained the similar performance results as compared with ischemic TPD based on NC or AC and higher sensitivity (89% vs 85%; $P = .0295$) as compared with ischemic visual score in angiographic group.

Conclusion—Combined NC-AC MPS quantification using either stress or ischemic TPD shows significant improvements for ROC-AUC and specificity of MPS in the detection of CAD compared with standard NC-MPS or AC-MPS and comparable performance to expert visual scoring. This

technique may lead to an enhancement in a fully automated quantification for the perfusion analysis by AC-MPS.

Keywords

Single photon emission computed tomography; myocardial perfusion imaging; attenuation correction; total perfusion deficit

INTRODUCTION

Several studies have shown that attenuation corrected myocardial perfusion SPECT (AC-MPS) may improve the specificity and consequently the accuracy of the detection of coronary artery disease (CAD).^{1–11} Most of these studies relied primarily on visual interpretation. More recently, we have performed studies based on automated quantification of AC-MPS, in which we were unable to demonstrate significant advantage of automated quantitative AC-MPS over non-corrected (NC) MPS.^{12,13} In these previous studies, we analyzed AC and NC data separately with standard quantitative software and obtained two sets of quantitative parameters.

None of the previous quantitative analysis studies, including ours, proposed to combine AC and NC data to improve the diagnostic accuracy. However, expert readers always utilize both the AC and NC data when interpreting the AC scans visually as recommended by the ASNC guidelines.^{1–11} All previous studies demonstrating superiority of visual AC-MPS analysis over NC-MPS relied on such a reading paradigm.^{1–11} In addition, the number of subjects in previous studies evaluating quantitative AC performance was relatively small, which limited their statistical power. Therefore, the aim of this study is to develop a new automated measure based on both NC and AC study components and to validate this new approach in a large data set.

MATERIALS AND METHODS

Patients

All studies were analyzed retrospectively. The subjects in this study were selected from the 9,709 patients who were referred to the Nuclear Medicine Department, Sacred Heart Medical Center, Eugene, Oregon, from March 1, 2003, to December 31, 2006, for rest and stress electrocardiography (ECG)-gated NC and AC-MPS. All patients with a prior history of CAD, cardiomyopathy, significant valve disease, left bundle branch block, and paced rhythm were excluded. MPS and coronary angiography had to be performed within 60 days without a significant intervening event. The low likelihood (LLk) studies were obtained from patients who performed an adequate treadmill stress test, did not have coronary angiography, and had <5% likelihood of CAD using the Diamond and Forrester criteria based on age, sex, symptoms, and ECG response to adequate treadmill stress testing.¹⁴ The non-LLk studies who had MPS images without coronary angiography performed or with coronary angiography performed more than 60 days after MPS scanning were also excluded. With these selection criteria, 995 sequential studies were identified to form the evaluation group. This population consisted of two subgroups of patients: 650 patients with correlative angiography as described above and 345 patients with a LLk of CAD who were classified as normal (age: 64.17 ± 11.64 vs 52.41 ± 11.07 ; $P < .0001$). Among all subjects, 432 (43.4%) patients had pharmacologic stress testing (429 adenosine or adenosine with walk, 3 dobutamine). The remaining 563 (56.6%) patients underwent treadmill stress testing, during which each patient achieved a heart rate that was $90\% \pm 5\%$ of the maximum age-predicted heart rate at the time of radiotracer injection. The clinical characteristics for all patients in this study are summarized in Table 1.

Normal database population—Gender-matched normal limits for both NC and AC acquisitions were derived from a separate group of 100 patients (50 females, 50 males) with a

LLk of CAD and visually normal scans. Patient characteristics for this population have been previously described.¹⁵

Image Acquisition and Reconstruction Protocol

The details of image acquisition and tomographic reconstruction have been previously described.¹⁵ In brief, studies were performed by using standard ^{99m}Tc-sestamibi rest/stress protocols. All subjects were imaged at 60 min after the administration of Tc-99m sestamibi at rest followed by stress images taken at 15–45 min after either radiopharmaceutical injection during treadmill testing or adenosine infusion with low-level exercise. Vertex, dual-detector scintillation cameras with low energy high-resolution collimators and the Vantage Pro attenuation correction hardware and software (Philips Medical Systems, Milpitas, CA), based on two gadolinium-153 scanning line sources, were used to acquire MPS. In this study, both stress and rest images were used for generating the perfusion measures.

Tomographic reconstruction was performed by use of the AutoSPECT and Vantage Pro programs (Philips Medical Systems). Emission images were automatically corrected for non-uniformity, radioactive decay, and motion during acquisition, and subjected to three-point spatial smoothing. The alignment of the projection data to the reconstruction matrix was applied to determine the mechanical center of rotation. Butterworth filters were applied to obtain the NC MPS with an order of 10 and cutoff of 0.50 for rest MPS, and an order of 5 and cutoff of 0.66 for stress MPS. The attenuation maps and the emission data were used to reconstruct the AC images with an iterative maximum likelihood algorithm (maximum-likelihood expectation maximization) and a uniform initial estimate. Scatter correction was also incorporated into this reconstruction, along with non-stationary, depth-dependent resolution compensation.

Coronary Angiography

Coronary angiography was performed using the standard Judkins method. All coronary angiograms were visually interpreted by experienced cardiologists. A stenosis with 70% or greater narrowing of the luminal diameter, which was considered significant, was used as a gold standard for the detection of CAD. Coronary angiographic findings are listed in Table 1.

Combined NC&AC Perfusion Quantification Analysis

In this study, a new perfusion parameter for combined NC&AC analysis was derived automatically based on the concept of total perfusion deficit (TPD).¹⁶ Standard MPS processing was first performed by the standard Quantitative Perfusion SPECT (QPS) algorithm to derive an ellipsoidal model and contours; the polar maps were then extracted based on those contours¹⁷ for AC and NC data. To obtain standard TPD, normal limits from 50 LLk patient data were defined for each gender and image type. TPD for a given patient was computed by integrating the hypoperfusion severity obtained from the maximum count profiles normal to the ellipsoidal surface and using an mean absolute deviation threshold of 3.0 as compared to normal perfusion.¹⁵ After deriving separate hypoperfusion severities for NC and AC data, combined NC-AC (NA) severity was derived at each polar map location by averaging the NA and NC severities computed separately from NC and AC normal limits. Subsequently NA-TPD was computed by integrating the average NA severities below polar map normal limits (3.0 mean absolute deviation) analogous to how standard TPD was defined.¹⁶ The final NA-TPD measure was expressed in the same units (percentage of the myocardium) as the separate NC and AC TPD measures. In addition, the ischemic TPD measures were calculated as stress—rest TPDs (iNC-TPD, iAC-TPD, and iNA-TPD).

Visual Perfusion Analysis

Visual interpretation of MPS images was based on short axis and vertical long-axis tomograms divided into 17 segments. Each segment was scored by an expert observer with more than 30 years of experience in nuclear cardiology (MF) using a five-point continuous scoring system (0, normal; 1, mildly abnormal; 2, moderately abnormal; 3, severely abnormal; and 4, absence of segmental uptake). During visual scoring, no clinical information was taken into account, such as patient history. The expert was also blinded to any computer-generated myocardial perfusion quantification results and patient group information. However, all available image data including raw projections, gated stress, and resting AC and NC scans were considered during scoring. Based on the previously established threshold for visual score ($SSS \geq 3$ for abnormal study),^{15,18} the observer scored each patient. The observer could also modify the default assignment of segments to the specific vascular territory. Subsequently, summed scores for stress (SSS) were calculated by summing of respective segmental scores. Partial summed scores for each vascular territory were also obtained. Summed difference score (SDS) was also computed as the difference between SSS and summed rest score. The visual scoring was not used as a gold standard for this study but was compared to quantitative perfusion measures and angiographic results.

Statistical Analysis

Analyze-It software within Microsoft Office Excel (version 2.10) was used for all statistical computations. Receiver-operator-characteristic (ROC) curves were analyzed to evaluate the ability of TPD quantifications for forecasting $\geq 70\%$ stenoses of coronary artery. The differences between the ROC areas under the curves (ROC-AUC) were compared by Analyze-It statistical package using the Delong method.¹⁹ McNemar test was performed to compare the sensitivity, specificity, and accuracy of ROC performance based on the same threshold (3%) for all stress quantitative parameters (AC-TPD, NC-TPD, and NA-TPD) and the previously established threshold for stress visual score ($SSS \geq 3$ for abnormal study). For all ischemic measures, the same test was also implemented to compare the ROC performance based on the previously established threshold for SDS (≥ 2 for abnormal study) and inferred thresholds (2%) for quantitative ischemic parameters.

RESULTS

The ROC curves of TPD measurements for detecting CAD from NC, AC, NA, and visual analysis are shown in Figure 1. Figure 1A shows the ROC-AUC for patients with coronary angiographs ($N = 650$) and Figure 1B shows the ROC-AUC for all patients ($N = 995$). In both groups, there were no significant differences in the ROC-AUC for NC-TPD and AC-TPD; however, the ROC-AUC for NA-TPD were significantly higher than those for NC-TPD, AC-TPD, and visual SSS with one exception in the comparison between NA-TPD and AC-TPD in the overall group ($P = 0.11$). In addition, there was a marginally significant difference in the ROC-AUC for AC-TPD and visual SSS (AC-TPD vs SSS in overall group: $P = .04$). The analysis for ischemic measures also showed the similar results that the ROC-AUC for iNA-TPD were significantly higher than those for iNC, iAC, and visual SDS in both groups (Table 2; all $P < .005$). Furthermore, using the previously established abnormality threshold (3%)^{12, 13} for TPD and (≥ 3) for SSS,¹⁵ the sensitivity, specificity, and accuracy for TPD measures and visual SSS analysis were obtained and are shown in Figure 2. In the angiography group, the sensitivity of visual SSS (88%) was higher than that of any TPD measurement (83–84%); however, the specificity of NA-TPD (75%) was the highest (NA-TPD vs NC-TPD: $P = .0001$; NA-TPD vs AC-TPD: $P = .0164$; NA-TPD vs SSS: $P = .0014$). In the overall group, the specificity of NA-TPD (88%) was higher than that for NC (81%) or AC TPD (85%) and comparable to that of SSS (86%). The normalcy rate for NA-TPD (95%), AC-TPD (94%) or SSS (97%) was significantly higher than that for NC-TPD (90%) ($P = .0001$, $P = .009$, $P < .$

0001, respectively). No significant differences between the normalcy rates for NA-TPD and AC-TPD or SSS were found. The results for ischemic variables in angiography group showed similar results except that iNA-TPD had significantly higher sensitivity and marginally higher accuracy compared to that for SDS whereas stress NA-TPD showed increased specificity (sensitivity 88.8% vs 85.3%; $P = .03$; accuracy 82.9% vs 79.8%; $P = .048$).

To further evaluate the improvement of NA-TPD, additional tests for quantitative measures were performed according to obesity: 426 patients who had body mass index (BMI) values of 30 kg/m^2 or greater and 569 patients who had BMI values of $<30 \text{ kg/m}^2$. The results are shown in Table 3. The comparison between AC-TPD and NC-TPD shows that the significant improvements of the specificity and accuracy for AC-TPD were found only in the high-BMI group. However, the comparison between NA-TPD and NC-TPD shows that the significant enhancements of the specificity and accuracy for NA-TPD were found in both BMI groups. In addition, the ROC-AUC for NA-TPD (0.920) was significantly higher than that for NC-TPD (0.895) in the high-BMI group ($P = .0001$). However, no significant improvement of the ROC-AUC for AC-TPD compared with NC-TPD were found in the high-BMI group ($P = .07$). Moreover, the specificity of NA-TPD was significantly higher than that of AC-TPD in the low-BMI group (91% vs 87%; $P = .0495$). No significant difference in the sensitivity between any two quantitative measures was found.

To demonstrate the improvement of specificity of NA-TPD, two examples of NC and AC images in two patients (A: female, age = 73; B: male, age = 74) are shown together with the NC, AC, and combined NA-TPD analysis results in polar map format in Figure 3. Both panels show that differences exist between NC and AC images. The reasons of those differences are not only due to attenuation correction, but also due to other corrections, such as scatter and geometric response correction. Figure 3A contains images from a patient with normal coronary angiography who had significant septal and anterior wall defects by AC quantification and by visual analysis (SSS = 6), which are not seen when NC or NA quantification is performed. Figure 3B shows images of another patient who has normal coronary angiography result but has apparent septal and lateral wall defects seen by NC-TPD quantification and with no significant defect detected by AC or NA-TPD quantification or visual analysis (SSS = 0). These two cases also show that NC-TPD and AC-TPD analysis have a complementary ability to detect CAD. In the overall population, the total number of correctly classified (true positive or true negative) cases by NC-TPD but not by AC-TPD is 49 including 23 true positives; on the other hand, there are also 82 cases (including 32 true positive cases) correctly classified by AC-TPD but not by NC-TPD. We could not identify any significant pattern for the cases correctly classified by only one of the scans, which could be used for some automatic selection of the correct data set.

For angiographic population, we tested the performance in the detection of coronary artery stenosis using the previously established threshold ($\geq 2\%$ for TPD measurements and ≥ 2 for SSS)^{18,20} for quantitative and visual measurements in each coronary artery territory (Table 4). There were no significant differences between sensitivity for most of the quantitative measures; however, the specificity of NA-TPD was significantly higher as compared with NC-TPD in left anterior descending artery (LAD): $P = .05$; left circumflex artery (LCX): $P = .048$; right coronary artery (RCA): $P = .016$. Moreover, the specificity of NA-TPD in LAD and LCX was significantly higher than that of AC-TPD (LAD: $P < .0001$; LCX: $P = .0124$). In general, the sensitivity of visual SSS was higher than the quantitative measures including NA-TPD, but the specificity and accuracy were lower than these of NA-TPD for all vessels.

DISCUSSION

To our knowledge, this is the first study that has used a combined quantitative parameter derived from AC and NC MPS. Combined NC and AC analysis is always used in visual interpretation of AC but to date it has not been applied in automated quantification of MPS. We demonstrate that there are incremental, but nevertheless significant improvements in the diagnostic performance measured both by the area under ROC curves and specificity and accuracy when using the combined parameter as compared to using NC data or AC data alone. Although there was a trend for better performance for AC analysis compared with NC analysis, no significant differences between them could be demonstrated despite using a large number of studies. NA analysis, however, demonstrates significantly improved stress and ischemic results. Compared with other quantitative studies (Table 5), it should be noted that the sample size of our study ($n = 995$) is the largest to date.

Similar to Grossman's study,¹⁰ our study obtained significant improvement in specificity and accuracy for AC-TPD as compared with NC-TPD only in the high-BMI group. However, our new combined quantification not only strengthens the above result, but also significantly improves the specificity and accuracy in the low-BMI group as compared with NC-TPD. In addition, this new measure shows significant enhancement in the ROC-AUC as compared with NC-TPD in the high-BMI group and in the specificity as compared with AC-TPD in the low-BMI group.

In 995 cases, we found that 49 cases (23 true positive cases) were correctly classified by NC-TPD not by AC-TPD; on the other hand, 82 cases (32 true positive cases) could be correctly classified by AC-TPD not by NC-TPD. If the algorithm required, the severity to fall below normal limits at both locations, similar to the principle for combining prone and supine MPS,¹⁶ it would inadvertently reduce the sensitivity of the test. We found that AC and NC scans have complementary abilities to detect CAD. Therefore, a simple but general method of averaging hypoperfusion severities after the comparison to respective AC and NC normal limits was chosen to generate the combined TPD values. This approach demonstrated significant improvements in accuracy and specificity when compared with the standard TPD from NC or as well as AC-MPS. When this approach was applied to calculate ischemic parameter, it not only showed a similar significant improvement to the comparison obtained in stress scans but also presented significant enhancement in sensitivity as compared with the visual ischemic score. One of the possible reasons for this enhancement might be that the additional information provided by rest images increased the potential to identify the mild change so that more true positive cases were diagnosed.

This study has several limitations. Coronary angiography, used as a gold standard in this study, might not be related to the physiologic significance of abnormal myocardial perfusion. However, the present study was performed in a fully automated mode with visual interpretation only for additional comparison and patients with LLk of CAD were included to evaluate the new measure performance. It is, therefore, reasonable to assume that the side-by-side comparison of each TPD measure and visual assessment will provide a valid test of performance. Moreover, only static perfusion data were considered in the quantitative analysis, without taking advantage of the additional information provided by gated images, which is used in the visual analysis. Therefore the quantitative analysis could be considered to be at a disadvantage to the visual analysis. New CT attenuation correction methods²¹ could have an impact on the performance or our approach and remain to be validated in this context. In the current study, we excluded patients with a prior history of CAD, cardiomyopathy, significant valve disease, left bundle branch block, and paced rhythm. Additional studies including these patients should be performed to validate our new quantification in these patients. Finally, this

study did not consider the influence of the AC artifacts or combined contour definition for both AC and NC data with the use of automatic quality control flags.²²

CONCLUSION

A new automatic quantification based on combined AC and NC MPS analysis has been developed for the detection of CAD. The application of this new combined measure objectively demonstrates a significant improvement in the specificity of the detection of CAD and is comparable to expert visual analysis of combined AC and NC data. This technique may allow further performance improvement of fully automated quantification of myocardial perfusion by taking advantage of the additional information from AC-MPS.

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Figure 1.

ROC curves for the detection of CAD by TPD and SSS measures. Panel A shows the results in the angiography group (N = 650) and B shows the results in the overall data set (N = 995) where LLk patients are classified as normal. Significant differences between ROC-AUCs in angiography group: NA vs NC: $P = .009$; NA vs AC: $P = .006$; NA vs SSS: $P = .01$. Significant differences between ROC-AUCs in overall group: NA vs NC: $P = .0001$; NA vs SSS: $P = .0058$; AC vs SSS: $P = .04$.

Figure 2. Comparison of sensitivity, specificity and accuracy in the detection of CAD obtained with NC-TPD, AC-TPD, NA-TPD and SSS analysis in angiographic population (A) and in the overall population (B). * $P < .05$ vs NC-TPD. # $P < .05$ vs AC-TPD. † $P < .05$ vs NA-TPD. ‡ $P < .05$ vs SSS.

Figure 3.

Two examples of NC and AC-MPS studies. In each panel, the first row includes NC images (from left to right, three left images are in short-axis orientation, the fourth one is in horizontal axis orientation, the last one is in vertical axis orientation); the second row includes AC images with the same organization of NC images; the last row includes three polar maps with TPD measures in NC, AC and a combined perfusion information. Panel A shows a false-positive TPD value in the AC image; panel B shows a false-positive TPD value for the NC image. In both cases, the NA analysis provides correct classification.

Table 1

Characteristics of the patients

	Number of patients	% of n
Total number (<i>n</i>)	995	
Males	504	51
Females	491	49
BMI < 30 kg/m ²	569	57
BMI ≥ 30 kg/m ²	426	43
1 day protocol	811	82
2 day protocol	184	18
Angio-no CAD	160	16
Angio-CAD (stenosis ≥ 50%)	490	49
Angio-CAD (stenosis ≥ 70%)	463	47
LAD (stenosis ≥ 70%)	296	30
LCX (stenosis ≥ 70%)	182	18
RCA (stenosis ≥ 70%)	254	26
LLK	345	35
Diabetes	178	18
Hypertension	546	55
Hypercholesteremia	467	47
Typical angina	207	21
Atypical angina/no angina	526	53
Dyspnea	95	10
Smoking	204	21

	Average	STD
Age	60.1	12.7
BMI	30.0	6.4

Table 2

ROC-AUC values and Performance for ischemic variables

	ROC-AUC (N = 650)	ROC-AUC (N = 995)	Performance (N = 650) (sen/spe/acc)%
iNC-TPD	0.848 [‡]	0.905 [‡]	87/62/80
iAC-TPD	0.840 [‡]	0.910 [‡]	87/58/79
iNA-TPD	0.871	0.924	89 [‡] /68 ^{*#} / 83
Visual SDS	0.807	0.882	85/66 [#] /80

Sen, Sensitivity; *spe*, specificity; *acc*, accuracy.

Bold: Significantly different than all others.

* $P < .05$ vs iNC-TPD;

$P < .05$ vs iAC-TPD;

† $P < .05$ vs iNA-TPD;

‡ $P < .05$ vs SDS.

Table 3

Performance of standard TPD analysis (NC and AC), NA-TPD and visual score in high and low BMI groups

	H-BMI (N = 426) (sen/spe/acc) %	L-BMI (N = 569) (sen/spe/acc) %
NC-TPD	84/74/79	82/86/84
AC-TPD	86/82 [*] /84 [*]	83/88/86
NA-TPD	85/84 ^{*†} /85 [*]	82/91 ^{*#} /87 [*]
Visual SSS	90 ^{*†} /77 ^{*†} /84 [*]	86/92 ^{*#} /89 ^{*#}

H-BMI, High BMI group; *L-BMI*, low BMI group; *sen*, sensitivity; *spe*, specificity; *acc*, accuracy.

Bold: Significantly different than all others.

^{*} $P < .05$ vs NC-TPD;

[#] $P < .05$ vs AC-TPD;

[†] $P < .05$ vs NA-TPD;

^{*†} $P < .05$ vs SSS.

Table 4

Performance of standard TPD analysis (NC and AC), NA-TPD and visual score for the detection of individual coronary artery stenosis ($N = 650$)

	LAD ($N = 296$) (sen/spe/acc) %	LCX ($N = 182$) (sen/spe/acc) %	RCA ($N = 254$) (sen/spe/acc) %
NC-TPD	73/78 [‡] /76 [‡]	56/75 [‡] /69	70 ^{#†} /78 [‡] /75 [‡]
AC-TPD	78 ^{*†} /73 [‡] /75 [‡]	58/74 [‡] /70	62/81 ^{*‡} /73
NA-TPD	75/ 81/78	57/ 77 /71 [‡]	65/81 ^{*‡} /74 [‡]
Visual SSS	87 /57/74	64 /68/67	74 ^{#†} /67/70

LAD, Left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; sen, sensitivity; spe, specificity; acc, accuracy.

Bold: significantly different than all others.

* $P < .05$ vs NC-TPD;

$P < .05$ vs AC-TPD;

† $P < .05$ vs NA-TPD;

‡ $P < .05$ vs SSS.

Table 5

The comparison of published studies to date and current report on quantitative evaluation of CAD by NC and AC perfusion images

Author	Angio (normal)	LLK	Known CAD	Sensitivity/specificity/normalcy (%)	
				NC	AC
Bateman et al ²³	92 (27)	18	Y	77/67/94	83/71/100
Ficaro et al ⁴	35 (16)	59	N	95/67/76 ^{‡∞}	95/93/95
Grossman et al ¹⁰	74 (35)	21	Y	97 [‡] /29 ^{‡∞} /52 ^{‡∞}	90/57 [∞] /90
Hendel et al ^{7*}	112 (16)	88	Y	76/44 [∞] /86 [∞]	78/50 [∞] /97
Kluge et al ^{5*}	25 (0)	25 [‡]	Y	84/uA/uA	100 [∞] /uA/uA
Masood et al ¹	118 (41)	37	Y	72 ^{‡∞} /61/100 [‡]	81/78/100
Shotwell et al ⁹	49 (0)	29	Y	71 ^{‡∞} /uA/76 ^{‡∞}	90/uA/69 [∞]
Slomka et al ¹⁵	174 (44)	141	N	89/73/91	87/80/95
Wolak et al ¹²	114 (45)	134	N	80/73/93	81/73/93
Xu et al [this study]	650 (187)	345	N	83/65 [∞] /90 [∞]	84/75/95

UA, Unavailable.

Bold is the automatic combined analysis result.

[‡] LLK for CAD in the study was defined as <10%; in all others, it is defined as <5%.

* Stenosis with ≥50% narrowing of luminal diameter was considered as a diagnostic cutoff; in all other studies ≥70% threshold was used.

[‡] P < .05 as compared to our NC results.

[∞] P < .05 as compared to our NA results.