ORIGINAL ARTICLE

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Investigation of Coronary Artery Disease by Coronary Computed Tomography Angiography and the Diagnostic Value of First-pass Myocardial Perfusion Imaging without Stress

Koroner Arter Hastalığının Koroner Bilgisayarlı Tomografi ile İncelenmesi ve Stressiz İlk Geçiş Miyokardiyal Perfüzyon Görüntülemenin Tanısal Değeri

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ABSTRACT

Aim: We aimed to investigate the diagnostic accuracy of first-pass computed tomography (CT) myocardial perfusion imaging (CT-MPI) without stress in combination with coronary CT angiography (CCTA) to detect coronary artery stenosis leading to myocardial ischemia compared to invasive coronary angiography (ICA) as the reference standard.

Materials and Methods: A total of 68 patients and 195 vessels were included in the study. We performed CCTA and first pass CT-MPI without stress on all patients. With ICA as the primary reference, the diagnostic accuracies of CCTA and CCTA plus first pass CT-MPI were expressed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of vascular territories with significant obstructive coronary artery disease (CAD).

Results: CCTA plus first pass CT-MPI without stress yielded the following results for vascular territory detection with more than 50% coronary stenosis (as determined with ICA): sensitivity, 80%; specificity, 87%; PPV, 61.5%; and NPV, 94.4%. In addition, the ability of the area under the receiver operating characteristic curve for CCTA plus first-pass CT-MPI to distinguish coronary stenosis was markedly improved compared to CCTA alone.

Conclusion: CCTA plus first-pass CT-MPI without stress does not require additional radiation or contrast agent and additionally provides information about myocardial perfusion and coronary stenosis.

Keywords: Coronary artery disease, coronary computed tomography angiography, first-pass myocardial perfusion without stress

ÖZ

Amaç: Miyokardiyal iskemiye neden olan koroner arter darlıklarını tespit etmek için koroner bilgisayarlı tomografi (BT) anjiyografi (KBTA) ile kombinasyon halinde stressiz ilk geçiş BT miyokard perfüzyon görüntülemenin (BT-perfüzyon) tanısal doğruluğunu invaziv koroner anjiyografiye (İKA) kıyasla araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamızda 68 hasta ve 198 damarı değerlendirildi. Tüm hastalara KBTA ve stressiz ilk geçiş miyokardiyal BT-perfüzyon uygulandı. Referans olarak İKA ile KBTA ve KBTA artı ile birlikte BT-perfüzyonun tanısal doğrulukları, obstrüktif koroner arter hastalığında (KAH) vasküler bölgelerin tespiti için duyarlılık, özgüllük, pozitif prediktif değer (PPD) ve negatif prediktif değer (NPD) cinsinden ifade edildi.

Bulgular: KBTA ve stressiz ilk geçiş miyokardiyal BT-perfüzyon, %50'den fazla koroner darlığı olan (İKA ile belirlenen) vasküler bölgeler için aşağıdaki sonuçları verdi: Duyarlılık; %80, özgüllük; %87, PPD; %61,5, NPD; %94,4. Ek olarak KBTA ve stressiz ilk geçiş miyokardiyal BT-perfüzyon için alıcı işletim karakteristiği eğri altında kalan alanın KAH'yi ayırt etme yeteneği, tek başına KBTA ile karşılaştırıldığında belirgin şekilde iyileşmişti.

Sonuç: KBTA ve stressiz ilk geçiş miyokardiyal BT-perfüzyon, ek radyasyon dozu ve ek kontrast madde gerektirmez ve miyokardiyal perfüzyon ve KAH hakkında ek bilgi sağlar.

Anahtar Kelimeler: Koroner arter hastalığı, koroner bilgisayarlı tomografi anjiyografi, stressiz ilk geçiş miyokardiyal perfüzyon

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INTRODUCTION

Coronary computed tomography (CT) angiography (CCTA) is a noninvasive, high-quality, cross-sectional imaging method, which is mostly preferred for detecting coronary artery disease (CAD)[1,2]. The use of CCTA to rule out acute coronary syndrome in low- and intermediate-risk populations has been described as a cost-effective and safe method with a high negative predictive value (NPV). CCTA provides both scanning of the coronary lumen and identification of high-risk plaque, such as spotty calcium and low attenuation[3]. Despite the great image quality, CCTA has some limits in cases of severely calcified coronary arteries, motion artifacts, arrhythmias, and high heart rates. CT has another limitation: while coronary artery stenosis can be quantitatively quantified, it is difficult to determine the hemodynamic importance of a particular lesion using CCTA alone[4]. The gold standard for determining the presence of coronary stenosis resulting in lesion-specific myocardial ischemia is fractional flow reserve (FFR), which is evaluated during invasive coronary angiography (ICA). According to the Fractional Flow Reserve vs. Angiography for Multivessel Evaluation research, revascularization decisions based on invasive FFR increased the patient's event-free survival compared to decisions based solely on ICA[5]. However, because of its invasive nature, high cost, and potential inaccuracy in measuring arteries with significant tortuosity and/or coronary calcification, the use of FFR is restricted[6]. Due to these restrictions, precise, noninvasive diagnostic procedures are now required to identify coronary artery stenosis resulting in myocardial ischemia.

Recent research has demonstrated that the multi-detector CT (MDCT) cardiac enhancement pattern of early defects and late enhancement permits noninvasive evaluation of myocardial viability in acute myocardial infarction[7-9]. First-pass CT imaging under pharmacological stress has recently been employed for a quantitative assessment of myocardial perfusion, as further evidenced by more recent investigations[10-12]. However, this examination requires the use of extra contrast materials and radiation. First-pass CT-myocardial perfusion imaging (MPI) without stress has recently been employed as an imaging technique that can provide crucial information about coronary artery stenosis, without the need for additional radiation exposure or contrast materials, and can be carried out concurrently with CCTA[6].

Our objective was to compare the diagnostic efficacy of first-pass CT-MPI without stress in conjunction with CCTA to ICA as the reference standard for identifying coronary artery stenosis causing myocardial ischemia.

MATERIALS AND METHODS

This retrospective study accords with the principles of the Declaration of Helsinki and was authorized by Ondokuz Mayıs University Clinical Research Ethics Committee (protocol no: B.30.2.ODM.0.20.08/819-952, date: 24.10.2019). Consent form was obtained from all patients before the CT imaging.

Patients

The population of this retrospective study consisted of patients who underwent CCTA due to suspected CAD for typical or atypical angina between January 2018 and November 2019. Within 30 days, CCTA and ICA were performed on all patients. Patients with a history of coronary artery intervention or coronary bypass surgery, iodinated contrast medium, beta-blockers, adenosine, or nitroglycerin contraindications, Q waves on resting electrocardiography (ECG), non-sinus rhythm, or previous myocardial infarction were all excluded from the study. The study was comprised of 68 participants with a possible diagnosis of CAD (21 women and 47 males).

Coronary Computed Tomography Angiography

The following CT scans were conducted using a rapid kV-switching dual-energy 64-detector MDCT scanner (GE Healthcare's Discovery CT750 HD scanner, Milwaukee, United States): Retrospective ECG gating, tube voltage of 120 kV, tube current of 450-600 mA, scan field of view of 25, gantry rotation of 0.35 s/rotation, matrix of 512512, slice width of 0.625 mm, and helical pitch range of 0.16-0.22. Based on the patient's heart rate, the pitch was selected. If the patient's heart rate was greater than 65 beats per minute before the CT scan, a single dose of metoprolol (25-100 mg) was given orally 6 hours prior to the scan. The patients were given intravenous beta blockers until the heart rate was below 60 beats per minute, if it did not drop to that level prior to scanning. The patient was in the supine posture during CCTA. A bolus injection of nonionic contrast agent was used to determine the scan delay, allowing for monitoring of the region of interest-the proximal section of the ascending aorta. Intravenous contrast material (iohexol: Omnipaque 350, GE Healthcare) was administered using a standardized weight-based dose injected at 3-5.0 cc/s, followed by a 30-cc saline flush.

We looked for the signs of significant stenosis in the right coronary artery (RCA), left anterior descending (LAD), and left circumflex (LCX) arteries. Significant stenosis was described as a narrowing of the mean luminal diameter of more than 50%.

First-pass Computed Tomography-myocardial Perfusion Imaging

For post-processing, the volume data were moved to a special workstation (AW Volumshare Workstation, GE Healthcare). With the aid of commercially available cardiac evaluation software, first-pass CT-MPI without stress was performed. In

order to reduce motion artifacts, this program was used to produce long-axis and short-axis images via reconstruction with RR intervals of 40-55% and 70-85% of the cardiac cycle. For systole and diastole, the myocardial pictures were captured at 40% and 75% of the RR interval, respectively. The slice thickness was 3 mm. The 16-segment model of the American Heart Association was utilized in the investigation to identify the segments of the left ventricle other than the apical segment[13]. Based on the CT values of the left ventricular myocardium, the first-pass CT-MPI results are displayed in color maps. Cold colors depict hypoenhanced regions with low CT values, whereas warm colors depict hyperenhanced regions with high CT values. The presence of a perfusion defect in at least one segment in any vascular territory was considered a perfusion defect[1].

Invasive Coronary Angiography

ICA was carried out utilizing the transfemoral method in accordance with industry standards. There were at least six projections of the left coronary artery and at least four of the RCA.

Statistical Analysis

Statistical Package for the Social Sciences statistics version 21 for Windows (IBM Inc., Armonk, NY, USA) was used to perform all statistical calculations. The data were expressed as the mean±standard deviation or absolute values and proportions, as appropriate.

Categorical variables, such as age, gender, height, weight, heart rate, and coronary artery risk factors, were expressed as the frequency and percentage. The sensitivity, specificity, positive predictive value (PPV), and NPV of CCTA and CCTA plus first-pass CT-MPI for the detection of vascular regions with severe obstructive coronary artery stenosis were expressed using ICA as the primary reference. The effectiveness of the diagnostic process was assessed for each patient and each vessel (RCA, LAD, and LCX arteries). The diagnosis of CCTA was reclassified depending on first-pass CT-MPI without stress (Figure 1). For every diagnostic testing strategy for which a reference standard was provided, the area under the receiver operating characteristic (ROC) curve (C statistic) was determined. Situations with a type 1 error level below 5% were considered to have a statistically significant diagnostic value while evaluating the area under the curve. A p value <p.05 was considered statistically significant in all statistical analyses.

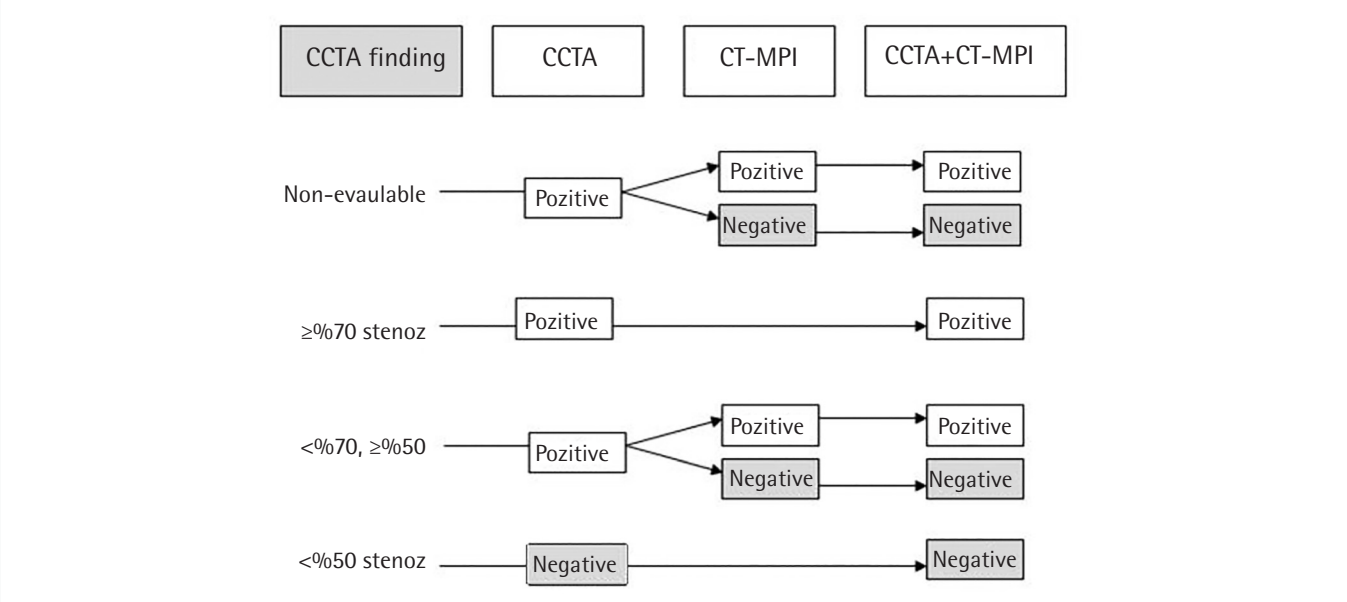

Figure 1. Reclassification criteria. Before first-pass CT-MPI analysis, nonevaluable vessels with CCTA were defined as positive for stenosis using the following criteria: those with no vessel wall definition due to marked motion artefacts, significant structural discontinuity, or heavy calcification and high image noise-related blurring that precluded the acquisition of diagnostic information. After CT-MPI analysis, nonevaluable vessels with CCTA were accepted as positive for stenosis only if they had a CT-MPI defect in the same vascular distribution. Moderate stenosis (50-70%) on CCTA was reclassified as negative if CT-MPI showed no defect in the same distribution. Stenosis with 30-50% luminal narrowing on CCTA was reclassified as positive if CT-MPI showed a defect in the same distribution. CCTA stenosis was not reclassified when no stenosis, <50% stenosis or >70% stenosis was observed on CCTA

CCTA: Coronary computed tomography angiography, CT-MPI: Computed tomography-myocardial perfusion imaging

RESULTS

Study Population

A total of 68 patients (58.7±10.8) were included in the study. There were 21 (30.9%) women (mean age: 56.3±12.3 years) and 47 (69.1%) men (mean age: 59.7±10 years). The most common risk factor was hypertension (55.9%), and other risk factors were diabetes mellitus, dyslipidemia, and smoking. The demographic findings of the patients are shown in Table 1.

Analysis of CCTA, CCTA plus First-pass CT-MPI without Stress, and ICA results

A total of 68 patients and 204 vessels (RCA and LAD and LCX arteries) were evaluated by CCTA, first-pass CT-MPI, and ICA. Of the 204 vessels, 9 had stents and were not included in the study. Six of the vessels with stents were RCAs; two were LCX arteries; and one was an LAD artery. Ultimately, 195 vessels were included in the study.

According to ICA, 24 of the 195 vessels (12%) had severe stenosis (75-100%). On a per-vessel basis, 9 (37.5%) of these were in the RCA; 10 (41.6%) were in the LAD artery; and 5 (20.8%) were in the LCX artery. A total of 16 of the 195 vessels had moderate stenosis (50-69%): 4 (25%) of them were in the RCA; 8 (50%) were in the LAD artery; and 4 (25%) were in the LCX artery. In total, significant stenosis (50-100%) was detected in 40 vessels: 18 (45%) of these 40 vessels were in the LAD artery; 13 were in the RCA (32.5%); and 9 (22.5%) were in the LCX artery. According to ICA, the most common risk factor in patients with significant stenosis was hypertension (57.6%), followed by dyslipidemia (50%).

With CCTA, greater than 70% luminal diameter narrowing was detected in 26 (13%) of the 195 vessels. In addition, 40 of the 195 vessels had moderate stenosis (between 50% and 70%). Among them, 21 vessels (11%) could not be clearly evaluated due to calcification or movement artefacts. In total, 66 (34%) vessels had obstructive stenosis (luminal narrowing greater than 50%). A proportion of 23% of these vessels were RCAs; 56% were LAD arteries; and 21% were LCX arteries. According to CCTA plus first-pass CT-MPI, 52 (27%) of the 195 vessels had obstructive stenosis (greater than 50% narrowing). A proportion of 35% of these vessels were RCAs;

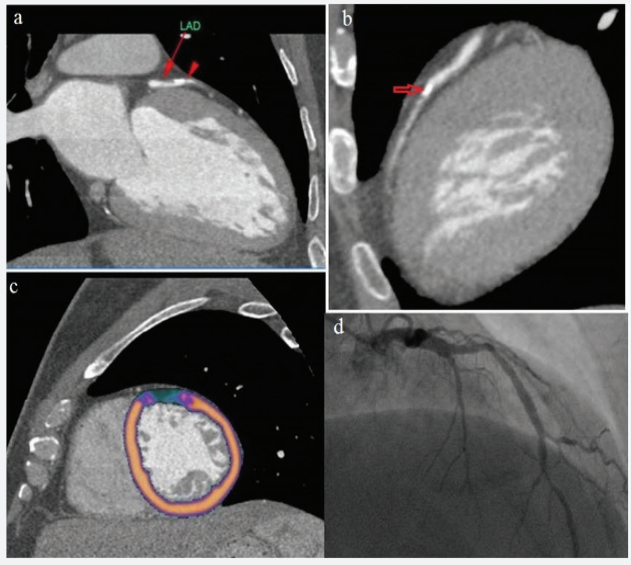

Figure 2. a, b) CCTA showed a calcified plaque in the proximal segment of the LAD artery and greater than 50% luminal narrowing in the distal segment of the LAD artery due to mixed plaque. c) First-pass CT-MPI without stress revealed a perfusion defect in the mid-anterior segment of the left ventricle. d) Invasive angiography shows greater than 50% luminal narrowing in the distal segment of the LAD artery

LAD: Left anterior descending, CCTA: Coronary computed tomography angiography, CT-MPI: Computed tomography-myocardial perfusion imaging

Table 1. Demographic findings of the patients (n=68)

Variable	Mean±SD	
Age (years)	58.7±10.8	
Hypertension (n=38)	Systolic blood pressure (mmHg)	137.17±20.09
	Diastolic blood pressure (mmHg)	84.92±9.89
Serum lipid biomarkers (n=28)	Total cholesterol (mg/dL)	181.11±46.85
	LDL cholesterol (mg/dL)	102.20±39.89
	HDL cholesterol (mg/dL)	44.73±15.86
	Serum triglycerides (mg/dL)	174.82±89.23
	Serum creatine (mg/dL)	0.88±0.19
Variable	**Number (%)**	
Smoker (n)	29 (42.6%)	
Patients with stent placement (n)	9	
Diabetes mellitus (n)	29 (42.6%)	

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation

48% were LAD arteries (Figure 2); and 17% were LCX arteries (Figure 3).

CCTA yielded the following results for vascular territory detection with more than 50% coronary stenosis (as determined with ICA): sensitivity, 92.5%; specificity, 70.9%; PPV, 45.1%; and NPV, 97.3%.

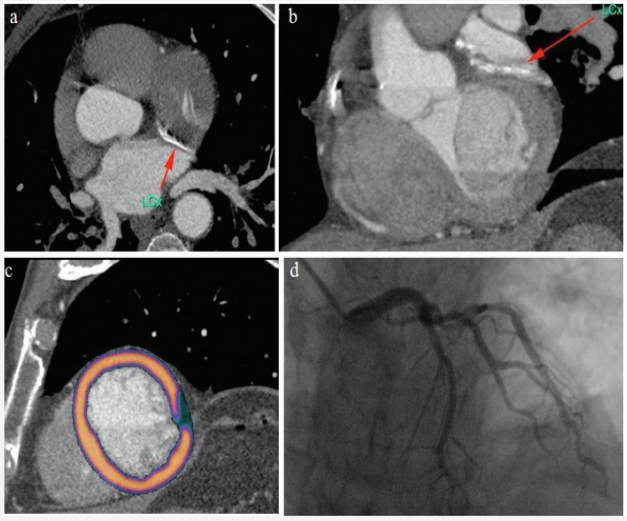

Figure 3. a, b) CCTA shows a calcified plaque and an irregularity in the LCX artery wall. The LCX artery also has motion artefacts. c) First-pass computed tomography myocardial perfusion imaging (CT-MPI) without stress revealed a perfusion defect in the left ventricular mid-anterolateral segment. d) Invasive angiography showed greater than 50% luminal narrowing in the LCX artery

LCX: Left circumflex coronary, CCTA: Coronary computed tomography angiography, CT-MPI: Computed tomography-myocardial perfusion imaging

For vascular territory detection with higher than 50% coronary stenosis (as measured by ICA), CCTA plus first-pass CT-MPI without stress produced the following results: sensitivity, 87%; specificity, 87%; PPV, 61.5%; and NPV, 94.4% (Table 2).

When compared to CCTA alone, the area under the ROC curve with CCTA plus first-pass CT-MPI was significantly better in differentiating stenotic coronary arteries, increasing from 0.817 to 0.835 in the per-vessel analysis.

DISCUSSION

In this study, we found that CCTA plus first-pass CT-MPI was more useful in defining stenotic coronary arteries that might cause myocardial ischemia than CCTA alone in patients without a history of CAD. Myocardial vascular volume may have been reduced as a result of substantial epicardial coronary artery stenosis, according to a decrease in myocardial signal intensity during diastole. We proved the diagnostic utility of first-pass CT-MPI conducted with CCTA to assess substantial coronary artery stenosis in patients without myocardial infarction based on this assumption.

Coronary capillaries are primarily responsible for intramyocardial perfusion. The ideal coronary blood flow is disturbed by stenotic epicardial coronary flow. Due to the need to preserve capillary hydrostatic pressure, capillary resistance rises, which reduces myocardial blood volume and attenuates perfusion[14]. The main cause for decreasing the blood flow in coronary artery stenoses, which is more than 75%, is deterioration in the capillary vessels rather than stenosis itself[1]. It has also been shown that myocardial perfusion is affected by coronary artery stenosis without stress[14]. Hydrostatic blood pressure is controlled by coronary capillary microvessels to preserve equilibrium. Epicardial coronary pressure is maintained constant in moderate coronary artery

Table 2. Diagnostic accuracy of CCTA and CCTA plus CT-MPI without stress for the detection of significantly stenotic coronary arteries in 195 vessels

	CCTA Per vessel (n=195)	CCTA+ first pass CT-MPI Per vessel (n=195)
No of results		
True positive	37	32
True negative	110	135
False positive	45	20
False negative	3	8
Statistical analysis		
Sensitivity	92.5	80
Specificity	70.9	87
Positive predictive value	45.1	61.5
Negative predictive value	97.3	94.4
C statics	0.817	0.835

CCTA: Coronary computed tomography angiography, CT-MPI: Computed tomography-myocardial perfusion imaging

stenosis by rising capillary resistance. However, in patients with severe coronary artery stenosis without myocardial infarction, reducing myocardial blood volume becomes more evident. These actions can be seen as a reduction in myocardial perfusion in first-pass CT-MPI[1,6].

Myocardial ischemia is not necessarily brought on by the morphological luminal constriction of the coronary artery. It is not easy to decide whether moderate coronary artery narrowing causes myocardial ischemia. According to recent research, CCTA combined with adenosine stress CT-MPI is a useful imaging technique for identifying coronary artery stenosis. However, this imaging technique needs additional contrast agent, and radiation is one of the important disadvantages[15]. First-pass CT-MPI without stress is a simultaneous imaging method with CCTA that does not need additional radiation or contrast agent to evaluate coronary arteries, especially those with severe calcification or intermediate stenosis. Evaluating first-pass CT-MPI together with CCTA can help show coronary artery stenosis leading to ischemia[6].

Matsuoka et al.[16] used 64-slice MDCT at rest to analyze 75 patients with probable CAD in order to find myocardial ischemia, which is often shown by myocardial perfusion scintigraphy (MPS). They claimed that using pharmacological MPS as the reference standard, first-pass CT-MPI at systole alone exhibited good performance in diagnosing CAD patients with a sensitivity of 90%, a specificity of 83%, a PPV of 86%, and an NPV of 88%[16]. They reported that rest perfusion abnormalities, which occur in systole, provided very similar information to that of adenosine stress studies. In this study, the degree of stenosis assessed with CCTA could not be clearly evaluated due to severe calcifications in 15% of patients. However, first-pass CT-MPI was used to provide information on the ischemia and perfusion status in the region of a severely calcified coronary artery. Therefore, they reported that first-pass CT-MPI at rest, a noninvasive method, showed the typical ischemia enhancement pattern. In addition, it overcomes the limitations of CCTA and provides the significant advantage of increasing the diagnostic accuracy for CAD.

Yoshida et al.[17] evaluated 70 patients with single-vessel disease, who underwent CCTA followed by ICA. The signal densities at diastole were measured to assess cardiac enhancement. According to their findings, segment-based analysis using 64-MDCT of major stenoses revealed sensitivity, specificity, and accuracy for segments without calcified lesions of 92%, 100%, and 99.7%, respectively, and those for calcified lesions of 95.2%, 50%, and 77.1%, respectively. They calculated the percentage drop in the signal densities to account for cardiac enhancement, and they reported the values as 95.2%, 85.7%, and 91.4%, respectively, for segments with calcified lesions. As a result, they observed that first-pass CT-MPI provided new diagnostic information about severe coronary artery stenosis, particularly in the presence of calcified plaque. It does this by identifying the diminished myocardial enhancement of the lateral ventricle wall in diastole[17].

Osawa et al.[1] evaluated 45 patients with suspected CAD with CCTA and CCTA plus first-pass CT-MPI without stress. As color maps, they assessed the signal concentrations during diastole. Comparing diagnostic accuracy to ICA allowed for evaluation. In comparison to CCTA alone, they found that CCTA + first-pass CT-MPI improved diagnostic performance. Per-vessel analysis showed a rise in the sensitivity, specificity, PPV, and NPV from 81% to 85%, 87% to 94%, 63% to 79%, and 95% to 96%, respectively. Additionally, the area under the ROC curve for detecting CAD increased from 0.84 to 0.89 ($p=0.02$)[1]. They reported that first-pass CT-MPI could be particularly useful in the evaluation of coronary artery segments with severe calcification and motion artefacts. Particularly in patients with extensive calcification or motion artifacts, it can contribute to the diagnostic value of identifying coronary artery stenosis. They reported that CCTA with CT-MPI performed more effectively as a diagnostic tool than CCTA alone[1]. In our study, CCTA plus first-pass CT-MPI had a sensitivity of 80%, specificity of 87%, PPV of 61.5%, and NPV of 94.4%. In addition, the area under the ROC curve for detecting CAD was 0.835 likely as the other studies in literature. In our study, the number of patients with a false positive decreased, and accordingly, the PPV increased.

There are benefits to first-pass CT-MPI. It can provide information about myocardial perfusion without the use of drugs. It is not necessary to increase the radiation dose or contrast agent for first-pass CT-MPI compared to stress CT-MPI performed with pharmacological agents[1]. However, first-pass CT-MPI has some disadvantages. Due to poor filtration of the contrast medium in the myocardium, it has a significant false-positive rate. Furthermore, first-pass CT-MPI is unable to distinguish between reversible and irreversible myocardial ischemia. Although there are many studies in the literature that compare CCTA to ICA, few studies have evaluated CAD with CCTA plus first-pass CT-MPI.

Study Limitations

The limitations of our study include the small number of patients and the lack of interobserver variability among radiologists in this study. Studies with large sample sizes can contribute to the literature on the contribution of first-pass CT-MPI to CAD diagnosis.

CONCLUSION

In conclusion, our study has shown that CCTA plus first-pass CT-MPI is superior to CCTA alone in the diagnosis of obstructive

CAD. As a result, in cases of suspected coronary artery stenosis, first-pass CCTA plus CT-MPI can provide significant additional information in terms of severe coronary artery stenosis and as a complement to CCTA in clinical practice without the need for additional radiation doses or additional contrast agent. It can also provide information about myocardial perfusion and ischemia.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University, and it complies with the principles of the Declaration of Helsinki (protocol no: B.30.2.ODM.0.20.08/819-952, date: 24.10.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.D., A.T.S., Ç.Ç., Design: S.D., A.T.S., Ç.Ç., Data Collection or Processing: S.D., Analysis or Interpretation: S.D., Ç.Ç., Literature Search: S.D., A.T.S., Ç.Ç., Writing: S.D., A.T.S.

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