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The comparison of multislice computed tomography coronary angiography and invasive coronary angiography for the detection of coronary artery pathologies

Koroner arter patolojilerinin değerlendirilmesinde çok kesitli bilgisayarlı tomografi anjiografi ile invaziv koroner anjiografinin karşılaştırılması

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ABSTRACT

Objective: We aimed to compare the findings of multi-slice computed tomography (MSCT) coronary angiography and conventional coronary angiography (CCA) in the assessment of coronary artery obstructions and to identify the role of MSCT in the diagnosis of coronary artery pathologies.

Methods: 50 patients (42 males and 8 females, mean age 56±4 years) underwent MSCT followed by CCA within 4 weeks. The patients were on sinus rhythm, could hold their breaths for at least 15 second and had creatinine levels below 1.5 mg/dL. The numbers and rates of obstructions identified in the proximal, middle and distal segments of the coronary arteries with MSCT were compared to those identified with CCA. Sensitivity, specificity, positive, and negative predictive values were calculated.

Results: MSCT had sensitivity, specificity, positive, and negative predictive values for proximal segment obstructions of 95%, 92%, 92%, and 95%, respectively; for middle segment obstructions: 95%, 96%, 94%, and 97%, respectively; and for distal segment obstructions: 92%, 96%, 80%, and 98%, respectively.

Conclusion: This study shows us that MSCT is a reliable diagnostic tool in the assessment of coronary arteries, especially in the presence of proximal and middle segment obstructions. Being a non-invasive imaging modality that can be used for screening and diagnosis purposes in symptomatic or non-symptomatic coronary artery disease patients with low-to-moderate risks, MSCT is a candidate technique for more effective and widespread use thanks to the rapid developments in its technology and its continuously increasing success rates.

Keywords: Multislice computed tomography, coronary angiography, stenosis

ÖZ

Amaç: Çalışmamızda koroner arter darlıklarının değerlendirmesinde, çok kesitli bilgisayarlı tomografi anjiografi (ÇKBT) bulguları ile konvansiyonel koroner anjiografi (KKA) bulgularını karşılaştırmak ve koroner ÇKBT' nin tanıdaki yerini araştırmak amaçlanmıştır.

Yöntemler: Çalışmaya dahil edilen 50 hastaya (42 erkek ve 8 kadın; ortalama yaşları 56±4) ÇKBT ve bunu takip eden 4 hafta içerisinde KKA incelemeleri yapıldı. ÇKBT incelemesine alınan tüm hastalar sinüs ritminde ve kreatinin seviyesi 1,5 mg/dL'nin altında idi. ÇKBT' da koroner arter proksimal, orta ve distal segmentlerde tespit edilen darlık ve oranları, KKA' da tespit edilen darlık ve oranları ile karşılaştırıldı. Duyarlılık, özgüllük, pozitif ve negatif kestrim değerleri hesaplandı.

Bulgular: ÇKBT incelemesinde proksimal segment darlıklarında duyarlılık %95, özgüllük %92, pozitif kestrim değeri %92 ve negatif kestrim değeri %95; orta segment darlıklarında duyarlılık %95, özgüllük %96, pozitif kestrim değeri %94 ve negatif kestrim değeri %97; distal segment darlıklarında ise duyarlılık %92, özgüllük %96, pozitif kestrim değeri %80 ve negatif kestrim değeri %98 bulundu.

Sonuç: Çalışmamız ÇKBT'nın koroner arterlerin değerlendirilmesinde, özellikle proksimal ve orta segment darlıklarında, güvenilir bir tanısal inceleme olduğunu göstermektedir. ÇKBT, koroner arter hastalığı için düşük-orta riskli semptomatik veya asemptomatik hastalarda tarama ve tanı amacıyla non-invaziv olarak kullanılabilecek bir görüntüleme yöntemi olup teknolojisindeki hızlı gelişmeler ve devamlı artan başarı oranları sayesinde, çok daha etkin ve yaygın olarak kullanılması gereken bir tetkiktir.

Anahtar kelimeler: Çok kesitli bilgisayarlı tomografi, koroner anjiografi, stenoz

INTRODUCTION

Conventional coronary angiography (CCA) is regarded as a gold standard for the diagnosis of coronary artery disease (1). Most important advantages of CCA are high temporal and spatial resolution, and it also provides us with the opportunity to treat the pathologies identified during the procedure with revascularization techniques. The disadvantages of CCA are its invasiveness, complications, high cost and provision of limited information about plaque characterization. Evaluating the technique together with these disadvantages and considering the fact that only

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1/3 of the cases detected during diagnostic angiography require interventional procedures geared at therapy, the need for cheap and non-invasive imaging techniques for diagnostic use becomes apparent (1).

In 1998, after 4 sectional computed tomography (CT) technology entered into use, 8 section technologies become available in 2001 and 16 sections in 2002 making it possible to obtain multiple images at the same time and resulting in the use of CT in the imaging of the heart. With the development of imaging technologies that can accompany electrocardiography (ECG) and reformat raw images to evaluate all the planes, it became easier to evaluate the coronary arteries. As the heart is a mobile organ and coronary arteries have tortuous courses with small diameters, the imaging of coronary arteries requires high temporal and spatial resolution. Furthermore, the inadequacy in imaging the distal small branches and not being able to have an ideal heart rate or long breath holding times for all patients necessitates faster devices (2-5). In 2004, with the 64 slice CT entering into use, temporal resolution (the time needed to obtain a single image) got faster and spatial resolution (the two closest points that could be separated from each other) increased, thus, thin distal branches could be detected with adequate imaging even with very short breath holding times and increased heart rates (6-9). Multi-slice CT allows for the assessment of anatomy with multiple angles and planes and shows soft tissues and neighboring anatomical structures, and the images are not projectional but three dimensional and sectional. It is possible to make plaque characterizations, and the technique is being used in the imaging of coronary arteries as a high-potential non-invasive technique (10). Together with the advances in computer technology and if the images were obtained with appropriate procedures, multi-slice computed tomography (MSCT) coronary angiography could detect coronary artery pathologies with high sensitivity (2). The effective use of MSCT coronary angiography in the imaging of the heart depends on the use of appropriate imaging techniques and correct implementation of reconstruction methods as well as adequate knowledge about the limitations of these techniques.

This study aimed to compare the results of a MSCT coronary angiography performed with 64 slice CT equipment with the findings obtained from CCA.

METHODS

This study was performed in the Gaziantep University School of Medicine Hospital after obtaining the approval of the Medical Ethics Committee with a decision number 05-2009/140 dated 21.05.2009. From May 2010 to April 2011, 57 patients who were referred to the Radiology Department with the suspicion of coronary artery disease by the Cardiology Department were prospectively included in the study group to obtain MSCT coronary angiographies. Exclusion criteria were: known contrast material allergies, renal failure (creatinine>1.5 mg/dL), unstable angina pectoris, acute myocardial infarction, pregnancy, hyperthyroidism, epilepsy, and late-stage heart failure. CCA was performed in the four weeks following the MSCT coronary angiography. The radiology specialist making the evaluations was blinded to the results of the CCA examination. The patients were provided with the information about the procedure, and their consents were obtained. Two patients for whom holding the breath required for the anticipated exam period (10-15 sec) was not possible, 1 patient who had arrhythmia and 4 patients who had heart rates of above 70 beats/min despite using ß-blockers had to be excluded from the study adding up to 7 excluded patients in total.

Of the 50 patients included in the study 84% were men (n=42) and 16% were women (n=8). The mean age was 56±4 years. The heart rate during the examination was 59±5 beats/min.

For those patients who had heart rates of higher than 70 beats/min, an oral ß-blocker (metoprolol) was administered one hour prior to the examination. If the heart rates of the patients could not be brought down under 70 beats with the use of oral ß-blockers, IV metoprolol tartrate (Beloc ampule 5 mg/mL) was used up to 3 ampules after diluting it with isotonic saline at a ratio of 1:1 with blood pressure and heart rate measurements every 5 minutes until it came down to 70.

Computed tomography examinations of all patients were performed with General Electric Brand VCT XTe Light Speed Model 64 channel device. The examination was initiated by obtaining non-contrast images under ECG monitoring for calcium scoring. For the timing of contrast material injection, the test bolus method was used. Following the administration of 15 mL of contrast material, consecutive low milliamper images were obtained to calculate the time when the highest contrast concentration was seen in the ascending aorta. Then, the exam was started. Non-ionic contrast material (80 mL) was administered at a rate of 5 ml/sec as a bolus; this was followed by 40 mL of sodiumclorur (NaCl) at a rate of 5 mL/sec. These were administered through the right antecubital vein using a Covidien LF Optivantage DH automatic injector. The parameters used for the examination were 40 mm collimation (64x0.625), 0.35 sec rotation, 0.16:1–0.24:1 pitch, 100-120 kV, and 150-600 milliamper (mA) with an X-ray tube, 25 cm scan field of view, 0.625 mm detector thickness and 0.625 mm reconstruction interval.

For the patients who had hearts rates of lower than 65 beats/min and who were cooperative for the exam, the prospective single segment protocol called snap shot pulse (axial) by the device was used. If the heart rate was 65 to 75 or if it was under 65 but the patient was not cooperating, the retrospective single segment protocol called snap shot segment by the device and tube flow modulation was applying a maximum dose at 70-80% phases and minimum dose was used in the others. During the shooting, the retrospective heart rate and ECG heart rate recordings were performed. For the snap shot pulse protocol used for patients having low heart rates, reconstruction images were obtained from the 68-83% interval with the overlapping method. For the snap shot segment protocol, in order to find the percentage segment during which at least one movement took place, reconstruction images of the coronary arteries were formed between 0-90% with 10% increments. In patients where snap shot segment protocols were used, the reconstruction percentages on the ECG recordings corresponded mostly to 40-50% intervals for the right coronary artery (RCA) and to 70-80% for left anterior descending (LAD) and left circumflex (LCX) coronary arteries. The most appropriate one was chosen, and the images to be reported were prepared from the reconstructions formed at that

Figure 1. a-d. In conventional coronary angiography (CCA), moderate level obstruction was observed in the (a) left anterior descending (LAD) proximal segment. In multislice computed tomography angiography, curved (b), three dimensional (c) and tree VR (d) images of moderate level stenosis were observed in the proximal segment of LAD immediately after diagonal 1 branch

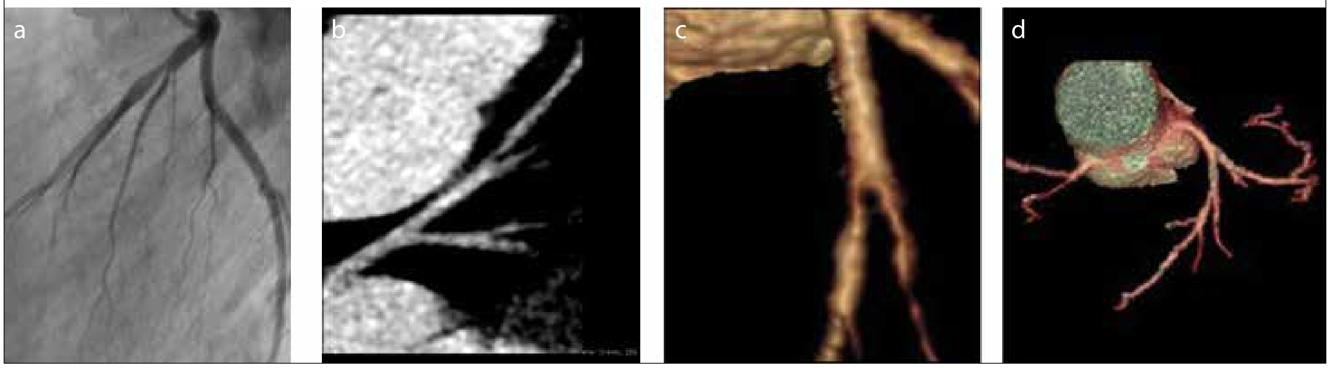

Table 1. True positive, true negative, false positive, and false negative results of MSCT in the group with the middle and proximal segments of the coronary arteries and more than 50% stenosis

Groups	TPS	TNS	FPS	FNS
Middle and proximal segments more than 50% stenosis	127	349	4	4

TPS: true positive segments; TNS: true negative segments; FPS: false positive segments; FNS: false negative segments

percentage level. The axial images where each coronary artery had the least artifact were reconstructed with multiplanar reformation (MPR), maximum intensity projection (MIP) and three dimensional volume rendering (VR) techniques to make evaluations on reconstruction images.

For the 50 patients in whom MSCT coronary angiography could be used and images fit for evaluation could be obtained from the coronary arteries, the American Heart Association (AHA) classification was used. The patients were divided into three groups as proximal segments encompassing the left main coronary artery (LMCA), proximal RCA, proximal LAD, proximal LCX; the middle segment including the middle RCA, middle LAD, middle LCX, diagonal 1-2, acute marginal 1-2, obtuse marginal 1-2; and the distal segment covering the distal LAD, distal RCA, distal LCX, posterior descending, and posterior lateral. The obstruction rate detected in each segment was compared to that detected with CCA.

The results for CCA and MSCT coronary angiography were reported as normal, 1-49% obstruction, 50-74% obstruction, 75-99% obstruction and occlusion (100%).

None of the patients developed complications during the MSCT coronary angiography examination.

Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic value were calculated and analisis was performed by using Statistical Package for the Social Sciences SPSS for Windows version 22.0 (IBM Corp.; Armonk, NY, USA)

RESULTS

In the group where proximal parts of the coronary arteries were evaluated, a total of 200 images (LMCA, RCA, LAD, and LCX) were evaluated. CCA identified obstructions of different degrees in 107 of these images. In 93 of these, the MSCT coronary angiography results were in correlation with those of CCA in terms of detectability and obstruction rates (true positive results) (Figure 1-5). In the remaining 14 segments, the MSCT coronary angiography results did not correlate with CCA for the detectability of the lesion (5 segments) and obstruction rates (9 segments) (false positive results). Of the 5 patients for whom MSCT coronary angiography could not detect any lesions, 2 were identified to have 50% obstructions at the RCA ostium with CCA. When the CCA images of these two patients were reevaluated, the obstructions observed at RCA ostia were due to the vasospasm inflicted by the catheter, and they were not real obstructions. In the remaining 3 cases, CCA detected obstructions of less than 50% in the LAD proximal segment. For the 9 proximal segments (2 LMCA, 3 RCA, 1 LAD, 2 LCX), the MSCT coronary angiography obstruction rates did not correlate with CCA. In 2 cases, CCA identified 50-74% obstruction in LMCA while MSCT identified 1-49% obstruction. For 3 cases, CCA identified 50-74% obstruction in RCA while MSCT detected this as 1-49%. For 1 patient, CCA identified 1-49% obstruction in LAD while MSCT identified it as 50-74%. In 1 patient, CCA identified 50-74% of an obstruction in LCX while MSCT identified this as 1-49%. In 1 other case, CCA identified 1-49% of stenosis whereas MSCT reported it as 50-74%.

While CCA evaluated 93 proximal coronary artery segments as normal, 92.5% (n=86) of these were normal on MSCT coronary angiography (true negative results). In 7 proximal coronary artery segments evaluated as normal with CCA, MSCT detected obstructions (false positive results). In 2 of these, there were discrete calcified plaques resulting in 1-49% obstruction in proximal RCA and in three 1-49% obstruction in proximal LMCA. Discrete mixed plaques obstructed one of the proximal RCAs by 50-74% and one LCMA with 50-74% as well. Two discrete mixed plaques that resulted in 50-74% obstruction in MSCT coronary angiography showed extensions to the aorta lumen from RCA and LMCA, which might have been the reason for not being detected by CCA. The sensitivity of MSCT in detecting proximal segment obstructions was 95%, its specificity was 92%, positive predictive value was 92% and negative predictive value was 95% (Table 1, 2).

Figure 2. a-f. In CCA, (a) LAD is occluded starting from its proximal part. In MSCT coronary angiography, tree VR (b), curved (c), axial (d) and three dimensional (e, f) images show that LAD is occluded starting from the proximal

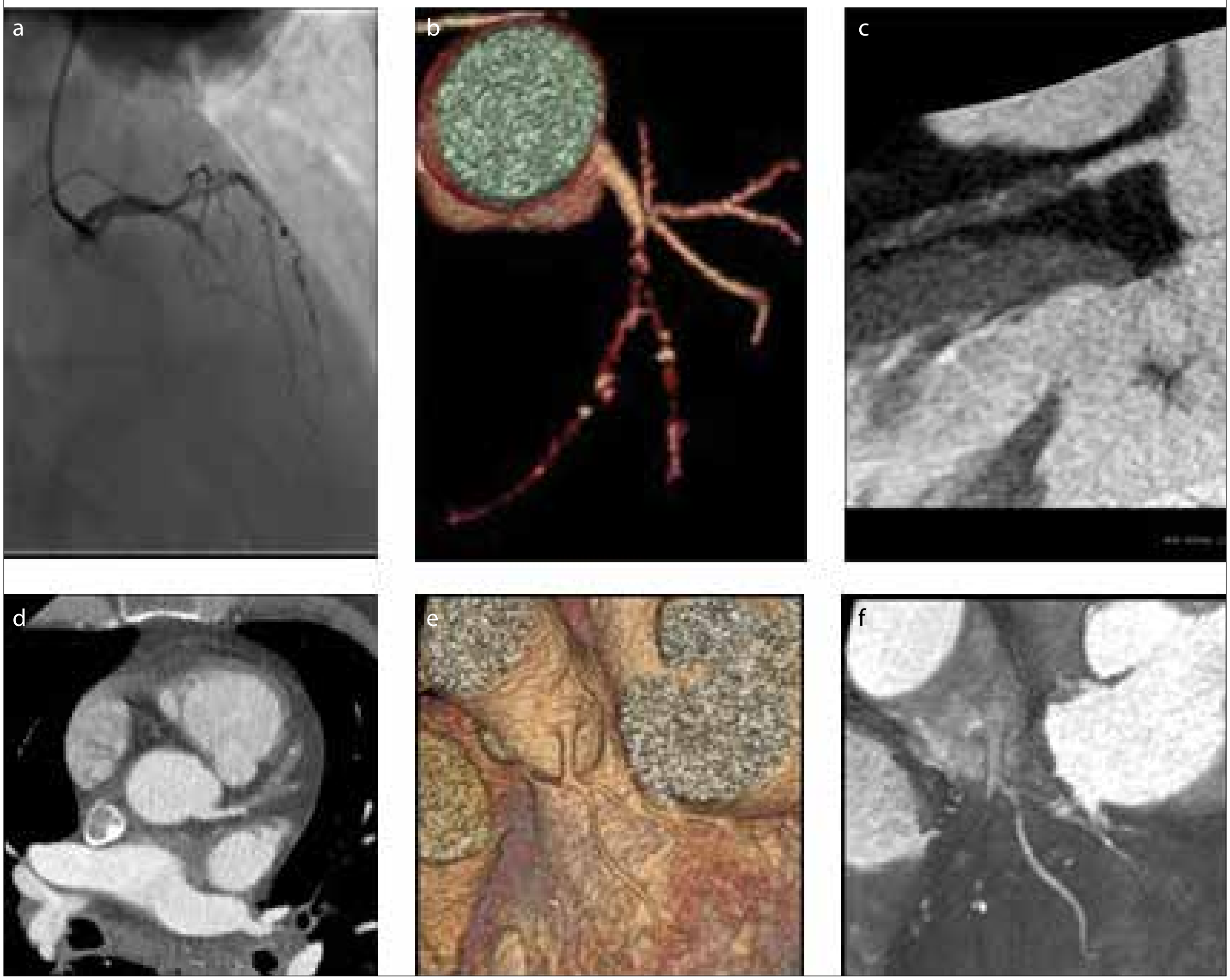

Figure 3. a-d. In CCA, (a) obstructions were observed in the proximal and middle segments of LAD. In MSCT coronary angiography, IVUS (b), curved (c) and three dimensional VRT images (d) show calcified plaques that result in moderate level obstructions in the proximal and middle segments of LAD

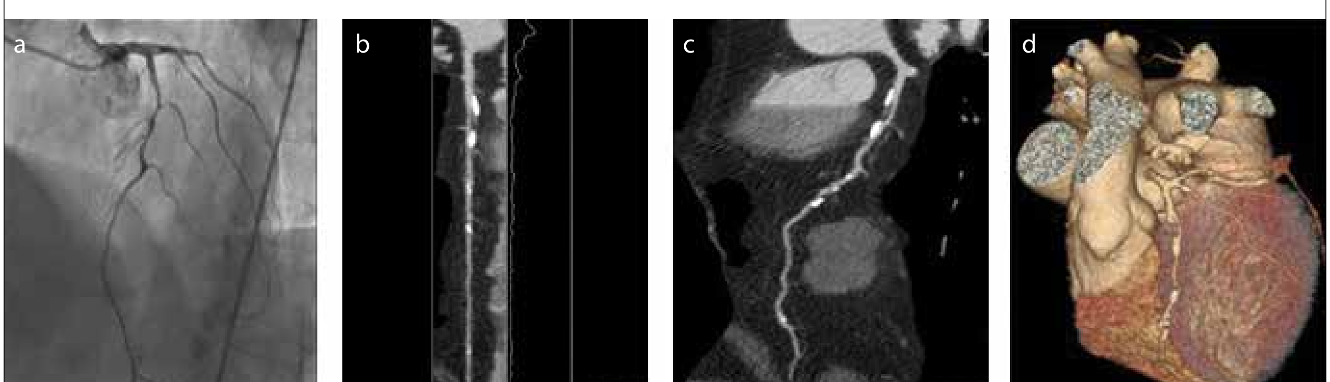

Figure 4. a-d. In CCA, (a) moderate to severe stenosis were seen in the proximal segment of LAD. In MSCT coronary angiography, curved (b), IVUS (c) and three dimensional (d) images show calcified plaques resulting in moderate-severe obstructions in the proximal LAD segment

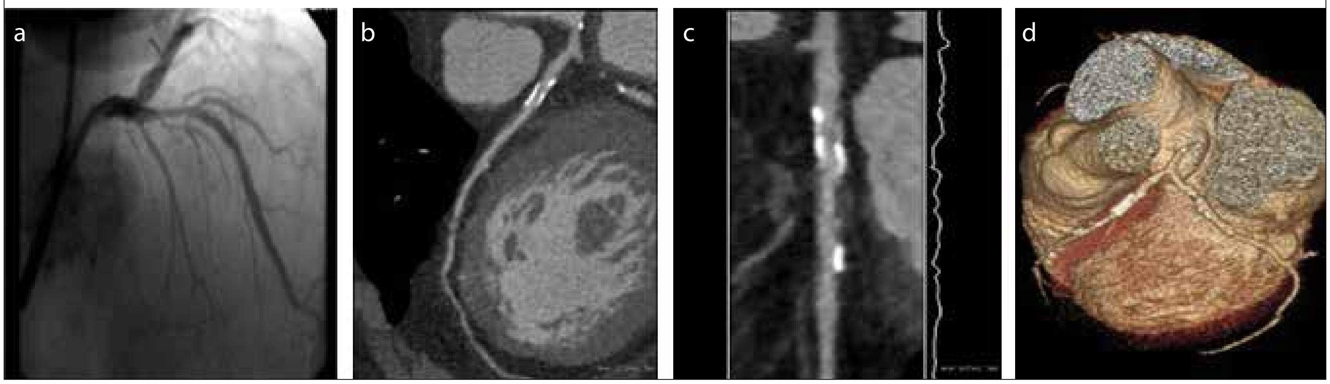

Figure 5. a-e. In CCA, (a) LAD was seen to be occluded from the proximal segment onwards. In the MSCT coronary angiography, curved (b), IVUS (c) and three dimensional VRT (d, e) images show that LAD is occluded from the level it gives its D1 branch

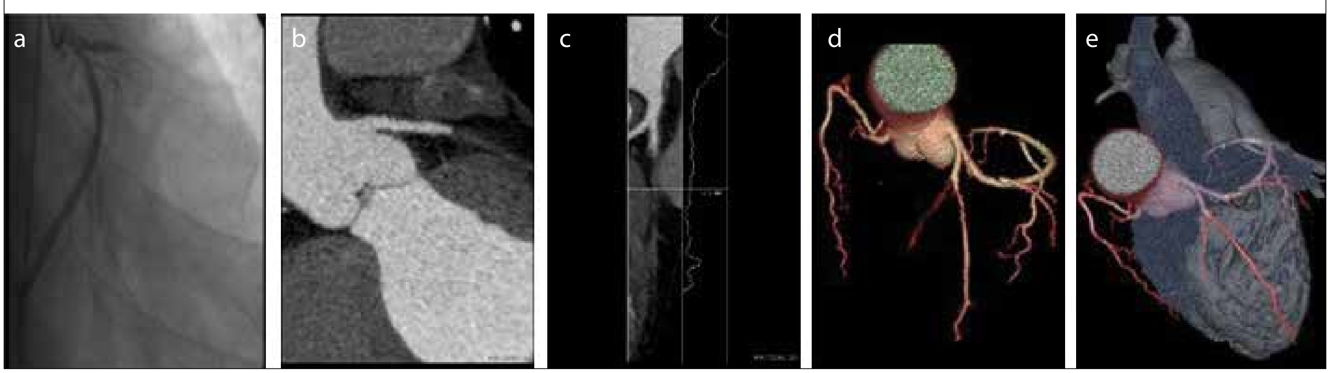

Table 2. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic value of MSCT in the group with the middle and proximal segments of the coronary arteries and more than 50% stenosis

Groups	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Diagnostic value %
Middle and proximal segments more than 50% stenosis	96.9	98.9	96.9	98.9	98.3

Table 3. True positive, true negative, false positive, and false negative results of MSCT in the group with the middle and distal segments of the coronary arteries

Groups	TPS	TNS	FPS	FNS
Middle	98	174	6	5
Distal	24	161	6	2

TPS: true positive segments; TNS: true negative segments; FPS: false positive segments; FNS: false negative segments

In the group where the obstructions of the middle coronary segments were evaluated, a total of 283 segments were evaluated. In 98% of these lesions, MSCT coronary angiography results were in correlation with CCA in regards to the detectability of the lesion (true positive results) (Table 3). However, in 11 segments, although the detectability of the lesions was in correlation with the MSCT and CCA, the degrees of obstructions were different. For 5 segments, CCA showed obstructions, whereas MSCT did not identify any lesions (false negative results) (Table 3). In 174 segments, neither MSCT nor CCA identified lesions (true negative results) (Table 3). In 6 segments where MSCT coronary angiography identified obstructions, CCA did not identify any obstructions (false positive results) (Table 3). In the group where the middle segments of the coronary arteries were evaluated, the sensitivity of the MSCT was 95, its specificity was 96%, positive predictive value was 94% and negative predictive value was 97% (Table 4).

For the group where the distal segments of the coronary arteries were evaluated, 193 segments were evaluated. In 24 of these segments, the MSCT results were in correlation with CCA for the detectability of the lesions (true positive results) (Table 3). In 3 seg-

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic value of MSCT in the group with the middle and distal segments of the coronary arteries

Groups	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Diagnostic value %
Middle	95.1	96.7	94.2	97.2	96.1
Distal	92.3	96.4	80	98.8	95.8

ments, the lesion detectability of MSCT and CCA were in correlation, but the obstruction rates were different. In 2 segments, CCA identified stenosis, but MSCT did not (false negative results) (Table 3). In 161 segments, neither MSCT nor CCA identified lesions (true negative results) (Table 3). For 6 segments where MSCT coronary angiography detected obstructions, CCA did not identify any obstructions (false negative results) (Table 3). In the group where the distal segments of the coronary arteries were evaluated, MSCT had a sensitivity of 92%, specificity of 96%, positive predictive value of 80% and negative predictive value of 98% (Table 4).

DISCUSSION

The development of atherosclerotic plaques on the arterial walls starts before the obstructions within the lumen start and goes together with compensatory vascular enlargement (positive remodeling). That is why as a technique that can detect both luminal diameter changes and plaque characterizations in coronary arteries, MSCT coronary angiography has a special place in the recognition of coronary artery disease during its early stages as well as in prevention of its progression and complications (10-11). The use of ECG synchronized imaging and reconstruction techniques in MSCT coronary angiography, the ability to perform faster volume screening, and high spatial and temporal resolution made it possible to detect coronary artery pathologies with high sensitivity in patients with low heart rate when appropriate procedures were used

In the studies, it was shown that the appropriate contrast level that would allow for the evaluation of the arterial lumen and the identification of the potential lesions on the arterial wall could be obtained by administering the contrast agent at a rate of 5 mL/sec for 64 slice CT (12). As the number of detectors increased, the required contrast material decreased. In the exams performed with the 64 slice equipment, 80 mL of contrast would be sufficient, while 100 mL contrast would be required for 16 slice CT (12). In this study, 80 mL of contrast material was administered at a rate of 5 mL/sec to achieve an appropriate level of contrast that would allow for the visualization of both the arterial wall and the potential lesions on the wall.

Good patient preparation constitutes half of what needs to be covered in the MSCT coronary angiography examination. As the heart rate increases, the systole gets longer, and the end diastolic interval shortens. Even in the presence of high temporal resolution of MSCT, this necessitated bringing the heart rate to the most appropriate level. In a study by Giesler et al. (13) when the heart rate was below 70 beats/min, 13% of the arteries had deteriorated image quality; when the heart rate was above 70, this rate was 33%. In the same study, the sensitivity of MSCT coronary angiography for coronary arteries was 62% for patients with slow heart rates whereas it was 33% for patients with fast heart rates. Nieman et al. (14) concluded that obstruction sensitivity was 82% in patients with low heart rates, while it was 32% for patients having heart rates of above 80 beats/min. In our study, when the heart rate was below 65 beats/min, vessel trackability was better. Quality images might not be obtained due to severe calcifications, cardiac and respiratory movements, ECG incompatibility as well as inadequacies in the timing of the contrast and shooting technique.

In a study by Heuschmid et al. (15) images of adequate quality that would allow for evaluation could be obtained in 70-98% of the patients who had undergone MSCT coronary angiography. In our study, of the 58 patients having undergone the MSCT coronary angiography examination, 86.2% (n=50) had images of interpretable quality.

In MSCT, as the vascular diameters of the proximal and middle segments are larger and the movement artifact is less, it is easier to detect the obstructions and to evaluate the vascular wall structure compared to the distal segment. Ehara et al. (16) evaluated 884 segments in their study and reported the sensitivity as 90%, specificity as 94%, positive predictive value as 89% and negative predictive value as 95% in the identification of the obstruction. In another study performed on 80 patients, the sensitivity was 96%, the specificity was 98%, the positive predictive value was 91% and the negative predictive value was 99% when evaluating the proximal segments (17). In our study, in the evaluation of proximal segment obstructions, the MSCT coronary angiography had sensitivity, specificity, positive predictive value, and negative predictive values of 95%, 92%, 92%, and 95%, respectively. For the middle segment obstructions of the coronary arteries, these values were 95%, 96%, 94%, and 97%, respectively, and for distal segment obstructions, they were 92%, 96%, 80%, and 98%, respectively. In correlation with the literature, the MSCT was more successful in identifying the lesions in proximal and middle segments compared to distal segments, and the different aspect was that the middle segment results were as successful as the proximal ones.

Especially in the evaluation of coronary artery ostia, the reliability of MSCT is higher than CCA. That is because of the technique and application related limitations of the CCA examination, the catheterization related spasm at the coronary ostium might result in diagnostic mistakes (18). In 2 cases in this study, CCA and MSCT yielded different results due to catheterization related spasm. In these patients, MSCT clearly demonstrated that there were no plaques or obstructions at the level of the ostia. When these cases were reevaluated by cardiology specialists, these appearances were thought to be spasm related.

Currently, especially in low to moderate risk symptomatic patients, cardiac MSCT is being used for the exclusion of coronary artery disease. This indication is specifically being supported by wide scientific circles because of its high negative predictive value in obstructive coronary artery disease (19). In the analysis of three large scale multicenter trials by Miller et al. (20) although the negative predictive value was high, the positive predictive value was lower. For segments that were reported as normal in CCA, the fact that MSCT can identify obstructions could be explained by the presence of suboptimal image quality due to technical problems and movement artifacts. MSCT cannot detect the coronary artery obstructions that are present in CCA as these lesions are mostly located in small coronary artery segments and bifurcations (21). The presence of intensively calcified plaques is one of the reasons why the lumen obstructions can be misinterpreted. When the calcification is severe, there can be an exaggerated appearance once the contrast fills the lumen. In the analysis of the study named CorE-64, Vavere et al. (22) demonstrated that the diagnostic quality decreased in cases with multiple coronary artery calcifications. In our study, especially in distal segments and in cases identified to have severe calcifications, MSCT identified different rates of obstruction compared to CCA.

Another reason why the positive predictive value was not as high as the negative predictive value and why the obstruction rates in MSCT are higher than CCA is because the parameters these techniques use for coronary artery obstructions are different. To detect the coronary artery lumen obstructions, CCA most often uses the diametric obstruction measurement of the lumen, whereas MSCT mostly prefers areal obstruction measurements. Arbab-Zadeh and Hoe (23) also reported an opinion that is parallel to ours. When it was correlated with hemodynamic parameters (coronary flow, myocardial perfusion), diametric measurement was found to be better than areal measurement (24). Furthermore, in cases with irregular lumens and multiple plaques, the measurement of diametric obstruction yields erroneous results in terms of real luminal obstructions in several cases. The selection of a normal reference area by proportioning with the narrowest measured diameter also results in mistakes. In a study performed by making a comparison with a 64 slice CT and intravascular ultrasonography, a high correlation was reported between areal obstruction measurements (25). In order to obtain more precise and reliable results in the evaluation of coronary segments, we believe that studies comparing CCA and MSCT coronary angiography should be performed on larger patient groups by standardizing these parameters.

CONCLUSION

In conclusion, this study shows that in the evaluation of coronary arteries, MSCT coronary angiography is a reliable diagnostic tool especially for proximal and middle segment obstructions. For low to moderate risk asymptomatic or symptomatic coronary artery disease patients, MSCT coronary angiography can be used for screening and diagnosis as a non-invasive imaging technique. It is eligible for more effective and widespread use thanks to rapid advances in its technology and continuously increasing success rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine Hospital Medical Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - M.M.B.; Design - F.G.Y.; Supervision - M.M.B.; Resource - F.G.Y.; Materials - F.G.Y.; Data Collection and/or Processing - F.G.Y.; Analysis and/or Interpretation - F.G.Y.; Literature Search - F.G.Y.; Writing - F.G.Y.; Critical Reviews - M.M.B.

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