Original Article
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Correlation of Morphological and Functional Cardiac Images: Fusion of Myocardial Perfusion SPECT and CT Angiography

Morfolojik ve Fonksiyonel Kardiyak Görüntülerin Korelasyonu: Miyokard Perfüzyon SPECT ve BT Anjiyografi Füzyonu

Hüseyin Şan[1], Alper Özgür Karaçalıoğlu[2], Uğur Bozlar[3], Semra İnce[2], Engin Alagöz[2], Mustafa Özdeş Emer[2], Mustafa Taşar[3], Nuri Arslan[2]

[1]University of Health Sciences Turkey, Ankara City Hospital, Clinic of Nuclear Medicine, Ankara, Turkey
[2]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Nuclear Medicine, Ankara, Turkey
[3]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Radiology, Ankara, Turkey

Abstract

Objectives: The current study evaluates the value of cardiac hybrid imaging (CHI), performed by the fusion of functional and anatomic cardiac images, in the detection of hemodynamically significant coronary stenosis in cases with multiple coronary stenosis.

Methods: A total of 36 patients (10 female, 26 male) in whom ischemia or infarction was detected on gated myocardial perfusion single photon emission computed tomography (gMPS) and multiple coronary stenosis were concomitantly detected on coronary computed tomography angiography (CCTA) and undergone invasive coronary angiography (ICA) was included in this study. Statistical analyses were performed using SPSS 22 Windows software. McNemar test was applied to show concordance between coronary CT angiography, ICA and CHI in the detection of anatomically or hemodynamically significant stenosis in three major coronary arteries. Comparison results of coronary arteries responsible for perfusion defects on CHI and gMPS are presented as percentages (%).

Results: There was total accordance between coronary arteries leading to perfusion defects detected by gMPS and CHI in 50% of patients. It was observed a partial accordance in 36.1% of the patients. Additionally, it was also detected perfusion defects originated from side branches in 25% of the patients. Between results of CCTA and ICA, no statistically significant difference was noted in the detection of anatomically significant stenoses in the left main coronary artery, left anterior descending artery (LAD), left circumflex artery (LCx) and right coronary artery (RCA) (p=1.000, 0.070, 0.549, and 1.000, respectively). In addition, no statistically significant difference was found in the detection of anatomically and hemodynamically significant stenoses in LAD, LCx and RCA by CCTA and CHI (p=0.344, 0.629, and 0.219, respectively). No statistically significant difference was observed in the detection of anatomically and hemodynamically significant stenoses in LAD, LCx and RCA by ICA and CHI (p=0.804, 1.000, and 0.344, respectively).

Conclusion: It is possible to detect hemodynamically significant coronary stenosis directly by CHI modality in patients with multiple coronary stenosis, wide perfusion defects.

Keywords: Cardiac hybrid imaging, coronary stenosis, myocardial perfusion scintigraphy, coronary CT angiography

Öz

Amaç: Bu çalışmanın amacı, fonksiyonel ve anatomik kardiyak görüntülerin füzyonu ile gerçekleştirilen kardiyak hibrid görüntülemenin (KHG), multipl koroner darlıkları ve perfüzyon defektleri olan olgularda, hemodinamik olarak ciddi koroner darlıkları saptamadaki katkısını değerlendirmektir.

Address for Correspondence: Hüseyin Şan MD, University of Health Sciences Turkey, Ankara City Hospital, Clinic of Nuclear Medicine, Ankara, Turkey
Phone: +90 312 552 60 00 **E-mail:** dr.huseyinsan@yahoo.com ORCID ID: orcid.org/0000-0002-2264-5446
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Yöntem: Çalışmaya gated miyokard perfüzyon sintigrafisi tek foton emisyonlu bilgisayarlı tomografi (gMPS) tetkikinde iskemi veya enfarkt ve koroner bilgisayarlı tomografi anjiyografi (KBTA) tetkikinde birden fazla koroner darlık saptanarak girişimsel koroner anjiyografi (GKA) yapılan toplam 36 hasta (10 kadın, 26 erkek) dahil edildi. Anatomik ve fonksiyonel görüntüler CardIQ Fusion yazılımı (GE Healthcare, IL, ABD) ile birleştirildi. İstatistiksel analizler SPSS 22 yazılımı kullanılarak yapıldı. Üç ana koroner arterde anatomik ve hemodinamik olarak ciddi koroner darlık tespitinde, KBTA, GKA ve KHG arasındaki uyumu göstermek için McNemar testi uygulandı. KHG ve gMPS'de perfüzyon defektlerinden sorumlu koroner arterlerin karşılaştırıldığı sonuçlar yüzde olarak sunuldu.

Bulgular: Hastaların %50'sinde, gMPS ve KHG ile perfüzyon defektlerinden sorumlu olduğu düşünülen koroner arterler arasında tam bir uyum vardı. Hastaların %36,1'inde kısmi uyum gözlenirken, %13,9'unda ise gMPS ile KHG tamamen uyumsuzdu. Hastaların %25'inde, KHG sayesinde, perfüzyon defektlerinden koroner yan dallardaki darlıkların sorumlu olduğu saptandı. Sol ana koroner arter, sol ön inen arter, sol sirkumfleks arter ve sağ koroner arterde anatomik olarak ciddi darlıkların saptanmasında; KBTA ve GKA sonuçları arasında istatistiksel olarak anlamlı bir fark saptanmadı (sırasıyla; p=1,000, 0,070, 0,549 ve 1,000). Ayrıca sol ön inen arter, sol sirkumfleks arter ve sağ koroner arterde; anatomik ve hemodinamik olarak ciddi darlıkların saptanmasında, KBTA ve KHG sonuçları arasında istatistiksel olarak anlamlı fark bulunmadı (sırasıyla; p=0,344, 0,629 ve 0,219). Ayrıca sol ön inen arter, sol sirkumfleks arter ve sağ koroner arterde; anatomik ve hemodinamik olarak ciddi darlıkların saptanmasında, GKA ve KHG arasında istatistiksel olarak anlamlı bir fark gözlenmedi (sırasıyla; p=0,804, 1,000 ve 0,344).

Sonuç: Multipl koroner darlıkları ve geniş perfüzyon defektleri olan hastalarda, KHG yöntemi ile iskemiden sorumlu olan, hemodinamik olarak ciddi koroner darlıkların doğrudan tespit edilmesi mümkündür.

Anahtar kelimeler: Kardiyak hibrid görüntüleme, koroner stenoz, miyokard perfüzyon sintigrafisi, koroner BT anjiyografi

Introduction

Coronary artery diseases (CAD) are the most common causes of mortality worldwide (1,2). COURAGE and FAME studies have shown that coronary revascularization should be performed by targeting ischemia in stable CAD (3,4). Moreover, it is crucial to detect or rule out hemodynamically significant stenosis and to verify left ventricular ischemic burden using non-invasive methods to decrease risks associated with invasive interventions (5).

In patients with multiple coronary atherosclerotic plaques, history of previous percutaneous coronary intervention (PCI) and coronary artery by-pass grafting (CABG), gated myocardial perfusion scintigraphy (gMPS) usually detect perfusion defects. However, because of differences in individual coronary anatomy and the complexity of multiple coronary stenoses, detection of coronary stenosis responsible for perfusion defects that requires clinical intervention has become increasingly difficult. In such cases, cardiac hybrid imaging (CHI) is a precious approach to localize the hemodynamically significant stenosis (6). Otherwise, discrepancies between gMPS and invasive coronary angiography (ICA) may cause difficulties in patient management and usage of unnecessary and risky invasive interventions (5). CHI is a modality that fuses myocardial perfusion single photon emission computed tomography (SPECT)/positron emission tomography (PET) and coronary computed tomography angiography (CCTA) images using automatic software. CHI provides more diagnostic data compared with separately or side-by-side evaluation of these two tests (7).

Objectives

With the above background, this retrospective study investigated the potential benefits of CHI in detecting hemodynamically significant coronary stenosis in patients with a medical history of multiple coronary stenosis, CABG and PCI.

Materials and Methods

Patient Sample

Data of patients who underwent CCTA, Tc-99m-Sestamibi gMPS and ICA between 2011 and 2016 were reviewed from the archives of the tertiary hospital. CCTA was performed 1 month before or after gMPS. A total of 36 patients (10 female, 26 male) were enrolled in this retrospective study. The inclusion criteria of the study were as follows: (i) patients who had perfusion defects at gMPS; (ii) patients who had coronary stenosis at CCTA. Patients with valvular heart disease, morbid obesity and cardiac arrhythmias were excluded from this study.

Evaluation of gMPS imaging: For exercise imaging, cardiac vasodilatation was achieved by following the standard Bruce protocol (stepwise increments of velocity and slope every 3 min) or maximum coronary hyperemia was pharmacologically achieved by 6-min intravenous infusion of adenosine (140 mcg/kg/min). The imaging started 25±5 min after injection of 7±1 mCi (259±37 mBq) Tc-99m sestamibi (Cardio-SPECT Medi-Radiopharma, Hungary). According to the two-day protocol, the "rest-condition imaging" was performed again 24±2 h after exercise imaging by the same protocol. Before the first day of the imaging study, daily quality control of the gamma was conducted routinely. A dedicated cardiac gamma camera

(Discovery NM 530c, GE Healthcare, Haifa, Israel) was used for both the stress and rest imaging. The dedicated cardiac gamma camera was equipped with a multiple pinhole collimator and 19 stationary cadmium-zinc-telluride detectors, with each detector containing 32×32 pixel 5-mm thick (2.46×2.46 mm) elements. A window of 15% was centered on the 140 keV gamma peak and the gating was conducted with 16 frames per RR cycle. List mode files were obtained and stored. Images were reconstructed with SPECT acquisition (Xeleris II, GE Healthcare, Israel) using a dedicated iterative algorithm. A Butterworth post-processing filter (frequency 0.37, order 7) was applied to these constructed slices. The images were reconstructed without scatter or attenuation correction. All two-day evaluations were done by the automated software Quantitative Gated SPECT/Quantitative Perfusion SPECT (Cedars-SinaiMedical Center, Los Angeles, CA). The left ventricle was divided into 20 segments using an apical, mid-ventricular and basal short-axis slice as well as a mid-vertical long-axis view for visual analysis. Each segment was scored qualitatively using a 5-point scoring scale (0, normal; 1, mild; 2, moderate; 3, severe reduction in photon activity; 4, absence of photon activity). The summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores for all 20 segments and within each vascular territory [left anterior descending artery (LAD) and left circumflex artery (LCx) and right coronary artery (RCA)] for each image. The classification "reversible" was used for images with an SSS greater than the respective SRS.

Evaluation of Coronary Computed Tomography Angiography

Before the workup, pulse rates were checked and controlled with β-blocker if necessary (maximum 60/minimum). Nitroglycerin (0.4 mg) was administered sublingual 1-3 times for coronary vasodilatation and pulse rates were continuously monitored. Moreover, 70-80 mL contrast medium was infused (4.5-5 mL/s), a 320-detector CT device was used (Aquilion One, Toshiba Medical System, Japan) and imaging was performed by prospective electrocardiograph triggering with 100-120 Kvp phantom and patient-based modified tube voltage. Reconstructed images were evaluated by Vitrea FX version 6.2 (VitalImages, MN, USA) and artifacts were minimized by further investigation. Stenosis in coronary arteries and/or their branches was divided into four groups as follows: 0-24%, 25-49%, 50-74%, and >75%. Stenosis >50% was defined as "anatomically significant."

Invasive Coronary Angiography

Imaging was performed through the right femoral approach using the Judkins technique, standard 6-7 French catheters and a Siemens Axiom Artis FC device (Siemens Medical Solutions, Germany). After intubation of the left coronary artery, right anterior oblique caudal, anteroposterior axis cranial, left anterior oblique caudal and right anterior oblique caudal (spider) views were evaluated. Further investigations were performed as necessary. ICA images were evaluated retrospectively and the same stenosis classification was applied. Stenosis >50% was defined as "anatomically significant".

Cardiac Hybrid Imaging Fusion Phase

All anatomic and functional images were fused by CardIQ Fusion software (Advantage Workstation 4.3, GE Healthcare, IL, USA). All axes from two separate imaging techniques were interlaced and optimized automatically. A perfusion map that was inserted into three-dimensional (3D) CCTA images of the left ventricle was assessed and discrepancies were rectified. After the exclusion of pulmonary arteries and veins, the "coronary artery tree" was created and software fused 3D images of the left ventricle and coronary artery were interlaced to create a CHI (Figure 1, 2, 3). Evaluation of gMPS and CHI results was

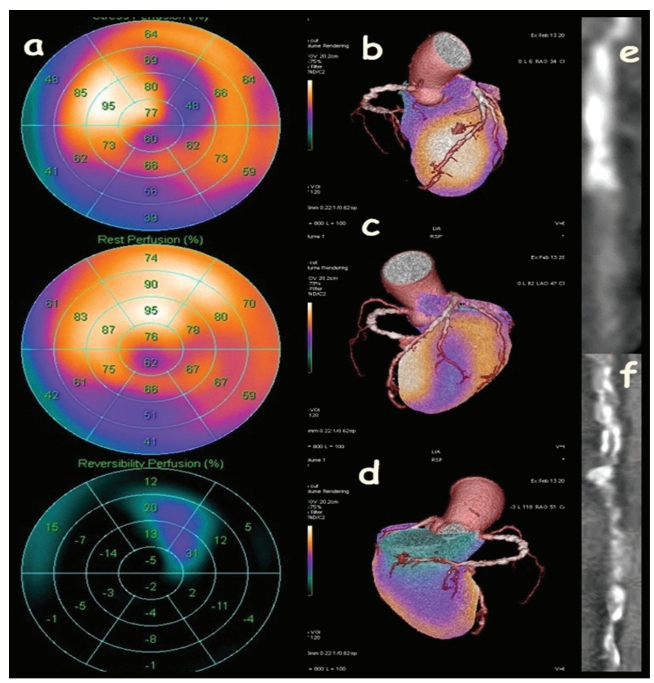

Figure 1. gMPS and CHI findings a) gMPS polar map images; top: Stress perfusion, medium: Rest perfusion, bottom: Reversibility perfusion. b) Fusion image; normal perfusion areas at LAD vascularization zone. c) Fusion image; reversible perfusion defects at diagonal artery vascularization zone. d) Fusion image; fixed perfusion defects at RCA vascularization zone. e) CCTA image; severe calcified stenosis at diagonal artery. f) CCTA image; severe calcified stenosis at main body of RCA

gMPS: Gated myocard perfusion scintigraphy, CHI: Cardiac hybrid imaging, LAD: Left anterior descending artery, RCA: Right coronary artery, CCTA: Coronary computed tomography angiography

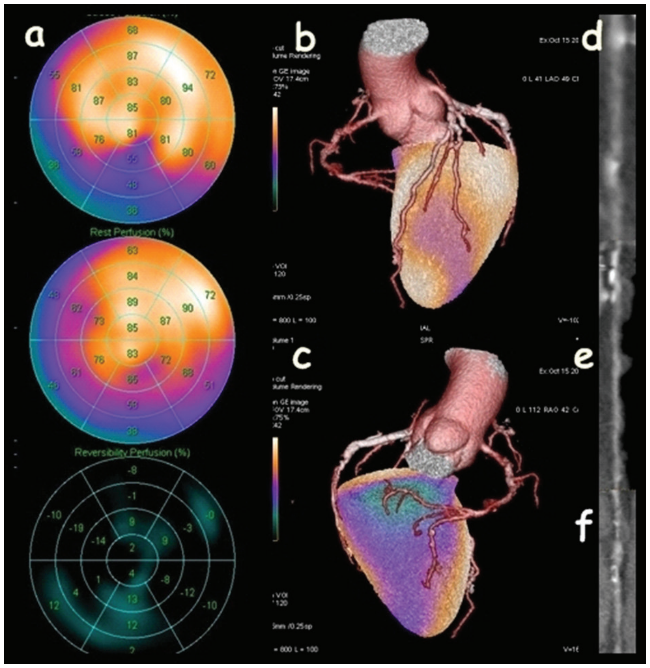

Figure 2. gMPS and CHI findings a) gMPS polar map images; top: Stress perfusion, medium: Rest perfusion, bottom: Reversibility perfusion. b) Fusion image; hypoperfusion areas at 2nd and 3rd diagonal artery vascularization zone. c) Fusion image; perfusion defects at RCA vascularization zone. d) CCTA image; severe calcified stenosis at 3rd diagonal artery. e) CCTA image; severe calcified stenosis at 2nd diagonal artery. f) CCTA image; severe calcified stenosis at main body of RCA

gMPS: Gated myocard perfusion scintigraphy, CHI: Cardiac hybrid imaging, LAD: Left anterior descending artery, RCA: Right coronary artery, CCTA: Coronary computed tomography angiography

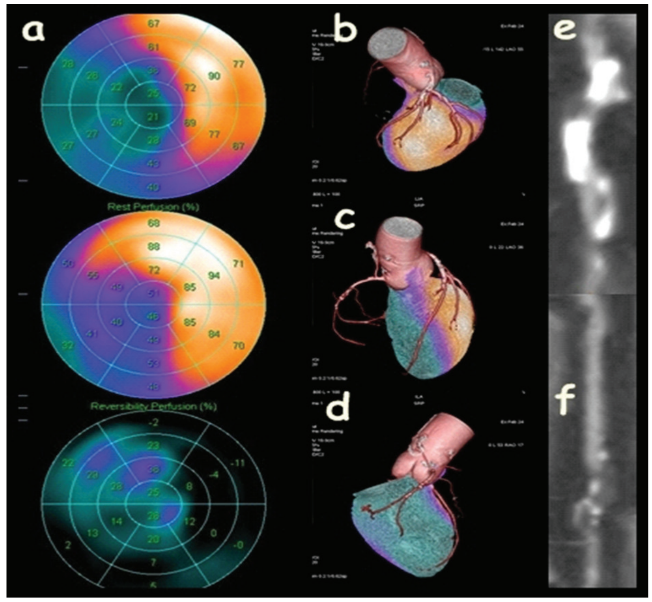

Figure 3. gMPS and CHI findings a) gMPS polar map images; top: Stress perfusion, medium: Rest perfusion, bottom: Reversibility perfusion. b) Fusion image; normal perfusion areas of diagonal branch and LCx vascularization zone. c) Fusion image; partially reversible perfusion defects at LAD vascularization zone. d) Fusion image; wide perfusion defects at RCA vascularization zone. e) CCTA image; severe calcified stenosis at LAD. f) CCTA image; severe calcified and mixed type stenosis at main body of RCA

gMPS: Gated myocard perfusion scintigraphy, CHI: Cardiac hybrid imaging, LCx: Left circumflex artery, LAD: Left anterior descending artery, RCA: Right coronary artery, CCTA: Coronary computed tomography angiography

blinded. Atherosclerotic stenosis in the coronary arteries and/or their branches with normal perfusion was defined as "hemodynamically insignificant" but perfusion defects with stenosis >50% were defined as "hemodynamically significant." Gulhane Military Medical Academy Command Local Ethics Committee granted approval for the study (approval number: 05.01.2016/25).

Statistical Analysis

Statistical consistency between CCTA, ICA and CHI results on significant anatomic and hemodynamic stenoses in three major coronary arteries were evaluated using the McNemar test. SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) was used. Comparison results of the coronary arteries responsible for the perfusion defects on CHI, gMPS and other comparisons were presented as percentages (%).

Results

The median age of the patients was 60.1±10.9 (38-82) years, 10 (27.8%) of them were female and 26 (72.2%) were male. Among the participants, thirteen patients had a history of PCI and/or CABG and twenty-three patients had native coronary arteries. Patient characteristics are presented in Table 1.

Coronary arteries responsible for perfusion defects that were detected by gMPS and CHI were totally compatible in 50% of the patients (18 of 36); however, they were partially compatible in 36.1% of the patients (13 of 36). In 46.2% (n=6/13) of partially compatible cases, additional stenoses in different coronary arteries causing the same perfusion defects were observed by CHI, apart from the coronary arteries considered responsible by gMPS. By contrast, in 53.8% (n=7/13) of the cases, CHI revealed that some coronary arterial stenosis considered responsible for the perfusion defects detected by gMPS were not the causative ones. Furthermore, 13.9% of the cases (n=5/36) were completely incompatible because the coronary arteries identified by gMPS as responsible for the perfusion defects were not actually the ones that created them because these perfusion defects were caused by different coronary arteries or branches. Moreover, in 25% (n=9) of cases, perfusion defects were actually sourced from stenosis in the side branches by CHI evaluation.

Between results of CCTA and ICA, no statistically significant difference was noted in the detection of anatomically significant stenoses in the LMCA, LAD, LCx and RCA (p=1.000, 0.070, 0.549, and 1.000, respectively). In addition, no statistically significant difference was found in the detection of anatomically and hemodynamically significant stenoses in the LAD, LCx and RCA by CCTA and CHI (p=0.344, 0.629 and 0.219, respectively). Furthermore, no statistically significant difference was observed in the detection of anatomically and hemodynamically significant stenoses in the LAD, LCx and RCA by ICA and CHI (p=0.804, 1.000, and 0.344, respectively). The distributions of anatomically and hemodynamically significant stenosis in three major coronary arteries are presented in Table 2.

Table 1. The characteristics of the participants

	Mean (SD)
Age	60.10±10.90
Ejection fraction (%) (gMPS)	58.89±2.08
Myocardial perfusion defect extent	15.22±1.93
Summed stress score	11.69±1.62
Summed rest score	5.58±0.93
Gender	**n**
Female	10
Male	26
History of treatment for coronary arteries	**n**
PCI	1
CABG	9
PCI + CABG	3
Native coronary artery	23

SD: Standard deviation, n: Number of patients, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass greft, gMPS: Gated myocardial perfusion scintigraphy

Discussion

In the last few decades, CAD has become one of the most common causes of mortality and morbidity; while diagnostic approaches have been modified according to new developments and patient populations. For diagnosis, minimally invasive methods are generally preferred, particularly when the patient has multiple comorbidities. This study focused on patients who had multiple coronary atherosclerotic plaques, history of PCI or CABG. Identification of the hemodynamically significant stenosis that causes myocardial ischemia is a challenge; thus, multidisciplinary diagnostic approaches are often preferred. CHI appears beneficial in such cases by demonstrating a hemodynamically significant stenosis directly. In this study, no statistically significant difference was noted in the detection of anatomically and hemodynamically significant stenoses in the LAD, LCx, and RCA by CCTA, ICA, and CHI. Although concepts of anatomically and hemodynamically significant stenosis are different, we suppose that most of the anatomically significant stenoses were also hemodynamically significant in our study.

In separate evaluations using gMPS and CHI, coronary arteries which were considered responsible for perfusion defects by gMPS and CHI, were completely compatible in 50%, partially compatible in 36.1% and totally incompatible in 13.9% of the patients. In partially compatible and totally incompatible groups, in addition to the coronary artery, which is thought responsible for the perfusion defects detected by gMPS, CHI revealed that perfusion defects are actually caused by stenosis in a different coronary artery and that some coronary arteries considered responsible for the perfusion defects in gMPS are not actually responsible for them. The anatomy of the coronary arteries may vary among individuals, which sometimes creates discordance with standard myocardial segmentation maps in gMPS (8). This condition suggests the superiority of CHI over separately or side-by-side evaluations performed by gMPS

Table 2. The distribution of anatomically and hemodinamically significant stenosis in three major coronary arteries

	Coronary CT angiography			Invasive coronary angiography			Cardiac hybrid imaging		
	Stenosis severity <%50	**Stenosis severity ≥%50**	**Total number of patients**	**Stenosis severity <%50**	**Stenosis severity ≥%50**	**Total number of patients**	**Hemodinamically insignificant stenosis**	**Hemodinamically significant stenosis**	**Total number of patients**
LAD	12	24	36	18	18	36	16	20	36
Cx	11	25	36	14	22	36	14	22	36
RCA	16	20	36	16	20	36	20	16	36

LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery and CCTA. CHI enables direct 3D observation of coronary arteries that cause perfusion defects (7). Javadi et al. (9) reported that this discordance was observed between PET and CHI for at least one segmentation in 72% of the patients, with a total discordance rate of 9% (n=112/1207 segmentations). In the "EVINCI" study of Liga et al. (8), 25% (n=146/1004) of the perfusion defects detected by gMPS and PET did not show actual concordance with individual anatomical evaluations performed by CHI. By CHI, 18% of the perfusion defects were detected to originate in a totally different coronary artery; thus, diagnoses in 42% of the cases were modified (8).

Studies have indicated that CHI plays a major role in patients with intermediate to high risk of CAD who have unclear gMPS and CCTA findings (7,10,11). In a prospective study, Schaap et al. (10) found that CHI had a positive predictive value of 91% [95% confidence interval (CI): 72-98] and negative predictive value of 90% (95% CI: 60-98) in cases with non-conclusive gMPS and CCTA findings. Researchers claimed that the fusion of functional and anatomical imaging data provides a "synergistic" approach to compensate for their own weaknesses, especially potential false-positive results by CCTA and false-negative results by gMPS (10). In our study, CCTA was reported as suboptimal due to intense coronary calcifications and motion artifacts in one patient. CHI revealed that stenosis at the LAD and the third obtuse marginali branch of the LCx were responsible for perfusion defects; however, stenoses at the first diagonal branch of the LAD and RCA were hemodynamically insignificant in this patient. Another patient had a perfusion defect at inferior cardiac wall that was suspected as a potentially false-positive result at gMPS, due to the gastrointestinal activity. False-positive result at gMPS was confirmed by CHI since there was no coronary stenosis in the RCA. In addition, perfusion defects that are not accompanied by coronary stenosis might have resulted from a microvascular disease or endothelial dysfunction. Certain diagnosis of these diseases can be made by quantitative evaluation of regional absolute myocardial blood flow with Rb-82, N-13-ammonium, and O-15 PET radionuclides (12). By this modality, anatomically insignificant but with impaired blood flow CAD, such as a microvascular disease or endothelial dysfunction may be also detected (12).

In this study, with CHI, 25% (n=9) of the detected perfusion defects were caused by hemodynamically significant stenosis at the side branches. It is impossible to specify and differentiate whether the major coronary arteries or the side branch is responsible for perfusion defects detected by gMPS, particularly when there are multiple stenosis. CHI can guide targeted revascularization by direct observation of hemodynamically significant stenosis at the side branches responsible for ischemia (13).

Study Limitations

The retrospective design, lack of routine measurement of fractional flow reserve during the gold standard ICA and absence of a statistical design for the correlation between CCTA and gMPS are the limitations of our study.

Conclusion

In patients with high risk of CAD, multiple coronary stenoses, history of PCI or CABG and wide perfusion defects, specifying the location of hemodynamically significant stenosis becomes challenging. In such cases, CHI appears beneficial by providing fused data of the 3D coronary anatomy and myocardial perfusion map with high spatial accuracy, which enables direct observation of hemodynamically significant stenosis. CHI can guide ischemia-targeted revascularization procedures. In addition, CHI can prevent unnecessary interventions to hemodynamically insignificant stenosis.

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Ethics

Ethics Committee Approval: Gulhane Military Medical Academy Command Local Ethics Committee granted approval for the study (approval number: 05.01.2016/25).

Informed Consent: Since the study had been designed as a "retrospective study"; no informed consent was required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ş., A.Ö.K., U.B., S.İ., E.A., M.Ö.E., Concept: H.Ş. A.Ö.K., U.B., M.T., N.A., Design: H.Ş., A.Ö.K., U.B., M.T., N.A., Data Collection or Processing: H.Ş., A.Ö.K., U.B., S.İ., E.A., M.Ö.E., M.T., N.A., Analysis or Interpretation: H.Ş., A.Ö.K., A.Ö.K., U.B., Literature Search: H.Ş., S.İ., E.A., M.Ö.E., A.Ö.K., U.B., Writing: H.Ş., A.Ö.K., U.B.

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