

Quantitative stress radionuclide myocardial perfusion imaging can indicate significant coronary artery stenosis

Tarit Taerakul,¹ Araya Boonyaleepan,¹ Siriwan Sisai¹ and Thewarug Werawatganon²

¹Division of Nuclear Medicine, Department of Radiology, Rajavithi Hospital, College of Medicine, Rangsit University, ²Department of Anaesthesiology, Faculty of Medicine, Chulalongkorn University

Objective The objective of this study was to evaluate the effectiveness of quantitative assessment of radionuclide myocardial perfusion imaging in indicating significant coronary artery stenosis.

Methods Seven hundred and twenty patients with suspicion of coronary artery disease were retrospectively identified. All had undergone cardiac catheterization within a 6-month period after having had a one-day pharmacologic stress radionuclide myocardial perfusion scan. Important parameters analyzed included myocardial perfusion, wall motion, wall thickening severity scores of 3 coronary artery territories and left ventricular ejection fraction values. These parameters were subsequently compared with currently the gold standard for cardiac catheterization.

Results Binary logistic regression analysis found that patients who had significant coronary artery stenosis had significantly higher values in all quantitative parameters (mean severity scores in myocardial perfusion, wall motion, wall thickening in most of the 3 coronary artery territories) than those in the non-significant group ($p < 0.05$) with the exception of the wall motion severity score of the left circumflex artery. Similarly, patients with higher perfusion severity scores had a higher probability of significant coronary artery stenosis in all three coronary arteries.

Conclusion Quantitative parameters obtained from stress radionuclide myocardial perfusion imaging can indicate significant coronary artery stenosis in all three main coronary arteries at a level comparable with that of cardiac catheterization which is currently the gold standard method but it is superior to cardiac catheterization due to less invasive and less expensive. Higher perfusion severity scores indicate a higher probability of significant coronary artery stenosis. [Chiang Mai Medical Journal 2019;58\(3\):123-32.](#)

Keywords: coronary artery disease, radionuclide myocardial perfusion imaging, quantitative analysis

Introduction

Coronary artery disease (CAD) is a major cause of death and disability worldwide. At least one-third of all deaths in individuals aged over 35 are caused by CAD (1-3). Stress radionuclide myo-

cardial perfusion imaging (rMPI) is a clinically important, non-invasive alternative adjunct to exercise electrocardiography (ECG) for evaluation of patients with known or suspected CAD (4). It

Correspondence: Tarit Taerakul, MD., Department of Radiology, Division of Nuclear Medicine, Rajavithi Hospital, Bangkok 10400, Thailand
E-mail: mail: tarit.t@rsu.ac.th



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is usually used instead of exercise testing in cases of non-diagnostic stress ECG for ischemia and when patients are unable to perform an adequate exercise. rMPI allows direct assessment of rest and stress myocardial perfusion and therefore has an important role to play in the diagnosis of CAD in patients presenting with chest pain, in assessment of myocardial viability, and in evaluation of dyspnea of possible cardiac origin (5-7). An inducible perfusion abnormality indicates impaired perfusion reserve; conversely, a normal stress rMPI indicates the absence of coronary obstruction and, hence, no clinically significant disease. Significant coronary artery stenosis can be diagnosed when coronary angiography reveals more than 50% stenotic lesion in one coronary artery with evidence of moderate to severe myocardial ischemia consistent with coronary artery lesion in the stress rMPI (5). Interpretation of rMPI is usually done with qualitative analysis (visual assessment) to evaluate myocardial activity (normal, reversible, or nonreversible defects), wall motion (normal, hypokinetic, akinetic, or dyskinetic) and wall thickening (normal or abnormal) in order to diagnose CAD (8,9). Although the qualitative method is primarily used for interpretation of patients with CAD, this visual assessment is a subjective approach and may result in suboptimal reproducibility. The visual method is also particularly limited in the detection of individual coronary lesions in patients with multiple-vessel CAD (10-14) or when the degree of stenosis is not severe (10,11). Quantitative analysis is another interpretation method which is provided automatically by many commercial software suppliers. An important strength of quantitative analysis is the inherent reproducibility of its measurements (15), which have diagnostic accuracy comparable to that of visual observers in the detection of CAD (16,17).

Objective

The objective of this study was to evaluate the effectiveness of quantitative assessment of radionuclide myocardial perfusion imaging in indicating significant coronary artery stenosis.

Methods

Seven hundred and twenty patients (472 males, 248 females, mean age at rMPI 63.43 ± 11.4 years), who underwent an rMPI scan at Rajavithi Hospital between 1 August 2012 and 31 August 2017 were identified consecutively and retrospectively from electronic data files. All were suspected of having coronary artery disease and had undergone cardiac catheterization by a cardiologist within the 6-month period subsequent to the rMPI scan for indications of suspected coronary artery disease without any clinical change. None had started any CAD treatment. For each coronary artery, 80 patients who had been identified as having significant coronary artery stenosis by cardiac catheterization ($n=240$ from all 3 coronary arteries) and 160 cases who had non-significant coronary artery stenosis ($n=480$ from all 3 coronary arteries) were included in this study (total $n=720$). All patients underwent rMPI studies with a one-day rest-stress protocol. After the patients had fasted for 4 hours, 10 mCi of Technetium-99m labeled methoxy-isobutyl-isonitril (Tc-99m MIBI) was given at rest followed by a stress test using peripheral intravenous infusion of 140 mcg/kg/minute Adenosine over 6 minutes (total dose, 840 mcg/kg) with blood pressure and EKG monitoring. In the next step, 30 mCi of Tc-99m MIBI was injected at approximately the mid-point of the Adenosine infusion. If a patient was deemed unsuitable for the adenosine stress test for any reason, e.g., having a history of severe bronchospastic disease, dobutamine was administered via continuous intravenous infusion beginning with 5 mcg/kg/min and stepping up to a maximum of 40 mcg/kg/min to obtain the target heart rate. rMPI were acquired approximately 30-60 min after stress and 45-75 min after resting using a dual-headed SPECT gamma camera system (GE Healthcare's Infinia Hawkeye) equipped with low-energy high resolution collimators in L-mode configuration (90° angle between two detector heads). Images were gated at 8 frames per cardiac cycle in all 64 views (180°, 45° right anterior oblique, 135° left posterior oblique). No CT attenuation correction was applied. The acquired studies were then processed

and automatically evaluated with 4-dimension-myocardial single photon emission computed tomography (4D-MSPECT) software application (INVIA Medical Imaging Solutions, Ann Arbor, MI, USA), to calculate 4D-MSPECT myocardial perfusion severity score, wall motion severity score, and wall thickening severity score of the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) territories and the left ventricular ejection fraction (LVEF) together with standard qualitative myocardial perfusion and function images. Polar maps can be plotted with a color scale, known as “severity maps”, where all pixels are shown as standard deviation values (between -10.0 SD and 10.0 SD). More severe values demonstrate as higher severity score. (Figure 1) (18,19). These techniques typically use a manufacturer’s normal database of 4D-MSPECT software that provides a reference for the expected range of relative regional uptake. All of these parameters were used in developing the prediction models using the results of LAD, LCX, and RCA stenosis using the current gold standard, cardiac catheterization, which categorized scores into significant stenosis ($\geq 50\%$ stenosis) or non-significant stenosis ($<50\%$ stenosis). Coronary angiography was performed and analyzed visually by an experienced cardiologist.

Demographic data were also collected, e.g., age, sex, BMI and coronary risk factors including diabetes, hypertension, hypercholesterolemia and chronic kidney disease.

Statistical analysis

Statistical analysis was performed using the SPSS software package (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA). Sample size calculation for binary logistic regression indicated that 240 cases were required for the 4 predictor variables (perfusion severity score, wall motion severity score, wall thickening severity score, and LVEF) of 3 coronary arteries, and 480 cases were required for the control group. Median and range were calculated for all continuous variables, frequency with percentages were calculated for categorical variables. $P < 0.05$ was considered to represent statistical significance. Univariable analyses were performed using a chi-square test of association for categorical variables, while a t-test was used for continuous variables (presence of significant or non-significant coronary artery stenosis). For multivariable analysis, binary logistic regression analysis was performed using 240 significant coronary artery stenosis cases and 480 non-significant cases.

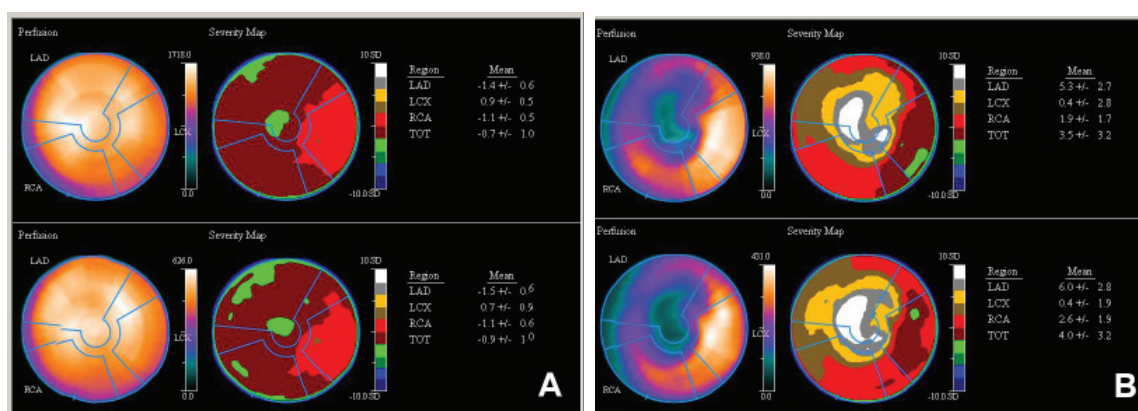


Figure 1. Severity maps of myocardial perfusion in cases of non-significant coronary artery stenosis (A) and significant LAD coronary artery stenosis (B). The left column shows polar maps of myocardial perfusion images at rest (upper row) and during stress (lower row). The middle column shows severity maps of myocardial perfusion images with colors indicating standard deviation (SD) from manufacturer’s normal database (from -10.0 SD to 10.0 SD). The right column shows regions and mean SD of severity scores

LAD; anterior descending artery, LCX; left circumflex artery, RCA; right coronary artery, TOT, total

Ethics considerations

This study was conducted after receiving approval from the Rajavithi Hospital institutional review board.

Results

Data were collected retrospectively on 2,012 patients who came for SPECT rMPI studies at the Nuclear Medicine Division between August 2012 and August 2017. Patients were excluded if they were under 18 years of age, had undergone SPECT rMPI for indications other than coronary artery disease, or had had no cardiac catheterization within the reference time (1,292 cases were

excluded). Seven hundred and twenty patients, all of whom had undergone cardiac catheterization within 6 months following SPECT rMPI, were enrolled in the study. For each coronary artery territory, 80 significant coronary artery stenosis patients were included together with 160 non-significant disease patients for prediction model analysis of all 3 main vessels separately. Initially univariable analysis was followed by binary logistic regression (Diagram 1). Patients' characteristics are shown in Table 1: 65.56% were male, 36.11% had diabetes, 82.91% had hypertension, 74.31% had hypercholesterolemia, and 21.39% had chronic kidney disease.

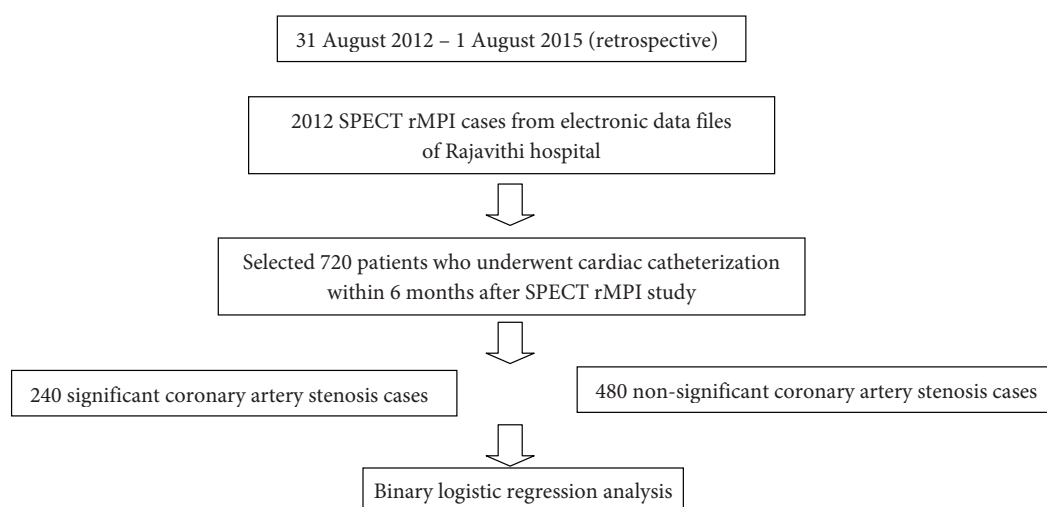


Diagram 1. Study design and source of data in the study

Table 1. Characteristics of patients included in the study

Characteristic	Significant stenosis	Non-significant stenosis
Age (mean $\pm$ SD)	66.1 $\pm$ 10.6 years	62.1 $\pm$ 10.1 years
Gender (male/female (n[%]))	192 [80.0] / 48 [20]	280 [58.3] / 200 [41.7]
BMI (mean $\pm$ SD)	25.5 $\pm$ 4.6	26.1 $\pm$ 5.1
Coronary risk factors (n[%])		
Diabetes mellitus	136 [56.7]	124 [25.8]
Hypertension	226 [94.2]	371 [77.3]
Hypercholesterolemia	208 [86.7]	327 [68.1]
Chronic kidney disease	66 [27.5]	88 [18.3]
Location of significant coronary artery stenosis (n[%])		
Left anterior descending	80 [11.1]	160 [22.2]
Left circumflex	80 [11.1]	160 [22.2]
Right coronary artery	80 [11.1]	160 [22.2]

BMI; body mass index

Mean perfusion severity scores of LAD, LCX and RCA were 0.26, 1.55 and 0.3, respectively. Mean wall thickening severity scores of LAD, LCX and RCA were 0.66, 0.62 and 0.64, respec-

tively. Mean wall motion severity scores of LAD, LCX and RCA were 0.69, -0.1 and 0.75, respectively, and mean LVEF was 48.45% (Table 2).

Table 2. Severity scores of perfusion, wall thickening and wall motion in LAD (A), LCX (B), RCA (C) and LVEF (D)

A	Severity scores					
	Significant stenosis			Non-significant stenosis		
	LAD_ perfusion	LAD_ wall thickening	LAD_ wall motion	LAD_ perfusion	LAD_ Wall thickening	LAD_ wall motion
Mean	1.03	1.04	1.15	-0.21	0.48	0.38
Std. Deviation	2.02	0.84	1.26	0.78	0.95	1.10
Minimum	-2.0	-0.8	-1.9	-1.8	-1.1	-1.5
Maximum	7.1	2.5	3.5	1.7	2.3	3.1

B	Significant stenosis			Non-significant stenosis		
	LCX_ Perfusion	LCX_ wall thickening	LCX_ wall motion	LCX_ Perfusion	LCX_ wall thickening	LCX_ wall motion
Mean	2.75	1.18	0.27	1.05	0.24	-3.4
Std. Deviation	2.87	0.98	1.36	1.26	1.03	1.41
Minimum	-1.1	-1.0	-2.0	-1.7	-2.1	-3.7
Maximum	8.9	2.7	3.2	6.5	2.8	3.0

C	Significant stenosis			Non-significant stenosis		
	RCA_ Perfusion	RCA_ wall thickening	RCA_ wall motion	RCA_ Perfusion	RCA_ wall thickening	RCA_ wall motion
Mean	0.90	0.95	1.23	-0.3	0.55	0.51
Std. Deviation	1.70	0.80	1.40	1.01	0.88	1.43
Minimum	-1.7	-0.8	-3.1	-2.5	-1.1	-3.7
Maximum	6.2	2.1	4.0	3.0	2.4	3.5

D	LVEF					
	LAD		LCX		RCA	
	Significant stenosis	Non-significant stenosis	Significant stenosis	Non-significant stenosis	Significant stenosis	Non-significant stenosis
Mean	41.90	53.59	41.44	55.45	42.28	51.17
Std. Deviation	17.06	15.46	17.33	14.76	17.98	15.96
Minimum	11.00	14.00	11.00	14.00	11.00	18.00
Maximum	75.00	80.00	75.00	79.00	80.00	79.00

Univariable analysis revealed that only wall motion of LCX was not statistically ($p \geq 0.05$) associated with significant coronary artery stenosis (Table 3). Similarly, in multivariable regression analysis almost all severity scores of myocardial perfusion, wall thickening and wall motion, and LVEF indicated significant coronary artery stenosis were statistically significant ($p < 0.05$), with the exception of wall motion of LCX.

Table 3. Analysis of severity scores and LVEF of 3 main coronary arteries to indicate significant coronary artery stenosis

Severity scores And LVEF	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
LAD_ perfusion			1.721 (1.179, 2.513)	.000
≥ 0.15	1			
< 0.15	4.358 (2.465, 7.707)	0.000		
LAD_wall thickening			1.242 (.616, 2.505)	.001
≥ 0.65	1			
< 0.65	3.283 (1.865, 5.780)	0.000		
LAD_wall motion			1.159 (.695, 1.933)	.001
≥ 0.55	1			
< 0.55	3.186 (1.815, 5.592)	0.000		
LCX_ perfusion			1.388 (1.072, 1.798)	.000
≥ 1.25	1			
< 1.25	3.070 (1.663, 5.670)	0.000		
LCX_ wall thickening			2.479 (1.264, 4.863)	.000
≥ 0.65	1			
< 0.65	3.355 (1.787, 6.299)	0.000		
LCX_ wall motion			.702 (.457, 1.078)	.376
≥ -0.25	1			
< -0.25	1.031 (0.568, 1.873)	0.919		
RCA_ perfusion			1.766 (1.218, 2.559)	.000
≥ 0.05	1			
< 0.05	3.272 (1.863, 5.746)	0.000		
RCA_ wall thickening			1.122 (.563, 2.236)	.005
≥ 0.65	1			
< 0.65	3.646 (2.070, 6.420)	0.000		
RCA_ wall motion			1.230 (.828, 1.828)	.003
≥ 0.65	1			
< 0.65	3.917 (2.195, 6.991)	0.000		
LVEF_LAD			1.605 (1.088, 2.367)	.017
≥ 50.0	1			
< 50.0	0.316 (0.181, 0.552)	0.000		
LVEF_LCX			1.394 (1.066, 1.824)	.015
≥ 50.0	1			
< 50.0	0.311 (0.168, 0.575)	0.000		
LVEF_RCA			1.736 (1.184, 2.546)	.005
≥ 50.0	1			
< 50.0	0.378 (0.217, 0.660)	0.001		

LAD; left anterior descending artery, LCX; left circumflex artery, RCA; right coronary artery, LVEF; left ventricular ejection fraction, OR; adjusted odd ratio

There were 160 cases of non-significant stenosis out of a total of 240 cases (66.7%) and 80 cases of significant stenosis (33.3%) of each coronary artery territory. Of the non-significant LAD, LCX and RCA coronary artery stenosis cases, 66.2%,

76.5% and 73.6%, respectively, had LVEF of more than 50%, compared to only 36%, 52.0% and 46.0% of cases with less than 50% LVEF. Only 33.8%, 23.5% and 26.4% of significant LAD stenosis cases had LVEF of more than 50%, while

64.0%, 48.0% and 54.0% had LVEF of lower than 50% in LAD, LCX and RCA, respectively. All these data showed statistically significant difference (Table 4).

Discussion

SPECT rMPI studies play an important role in the diagnosis, prognosis, risk assessment and management of coronary artery disease. In current practice, rest and stress planar images are interpreted together with gated imaging to evaluate myocardial perfusion and function. The quantification of perfusion and function is relative in image counts. An important strength of quantitative analysis is the inherent reproducibility of its measurements which rival the diagnostic accuracy of visual observation in the detection of CAD. Quantitative measures of stress, rest, and ischemic (stress-rest) defects have been found to be significantly more reproducible than visual scores (respective repeatability coefficients of 3.3%, 1.8%, and 3.2% versus 4.8%, 3.8%, and 4.3%, all $p < 0.01$) (15,20). Repeatability coefficients were 6.1%, 6.4%, and 5.7% for the quantitative analysis of stress, rest, and ischemic total perfusion deficit versus 10.1%, 11.8%, and 9.0% for the visual scoring of the percentage abnormal myocardium. These comparisons clearly demonstrate the advantage of quantitative perfusion analysis over visual segmental scoring (21). In one study, a standard quantitative approach was found to achieve per-

formance that was equivalent to, or better than, clinical visual assessment in the detection of $\geq 50\%$ stenosis, as measured by the area under the receiver operator characteristics (ROC) curve (16). Similar results were demonstrated recently in a larger population with blinded expert scoring both with and without clinical information (17).

In evaluating the effectiveness for indicating significant coronary artery stenosis from many important parameters of a quantitative rMPI method, this study showed that only wall motion of LCX was not associated with significant coronary artery stenosis in univariable analysis ($p > 0.05$) (Table 3). However, when LVEF was stratified into 2 groups (LVEF $< 50\%$ and LVEF $\geq 50\%$), there was a significant difference in significant coronary artery stenosis as well ($p \leq 0.05$) (Table 4). In multivariate analysis, almost all parameters were associated with significant coronary artery stenosis ($p \leq 0.05$) with the exception of severity score of wall motion of LCX. This indicates that quantitative rMPI methods can be used to evaluate CAD using all of its parameters including severity scores of myocardial perfusion, wall motion, and wall thickening together with LVEF. Leslie et al, (22) used quantitative analysis to identify cardiac death or acute myocardial infarction in a cohort. Tools for automated quantification of myocardial perfusion are readily available to nuclear cardiology practitioners and researchers. These methods have demonstrated superior

Table 4. LVEF in CAG results of 3 main coronary arteries

		LVEF		Total	p-value
		<50%	$\geq 50\%$		
LAD_CAG	Non-significant	36.0%	66.2%	66.7%	0.001
	Significant	64.0%	33.8%	33.3%	
Total		100.0%	100.0%	100.0%	
LCX_CAG	Non-significant	52.0%	76.5%	66.7%	0.006
	Significant	48.0%	23.5%	33.3%	
Total		100%	100%	100%	
RCA_CAG	Non-significant	46.0%	73.6%	66.7%	0.002
	Significant	54.0%	26.4%	33.3%	
Total		100%	100%	100%	

CAG; coronary artery angiography

reproducibility with comparable diagnostic and prognostic performance to segmental visual scoring by expert observers. A potentially particularly useful application of quantitative analysis is in the detection of subtle changes in blood supply or in precise determination of ischemia. In this study, for every 1 point increment in severity scores of LAD, LCX, RCA perfusion, wall motion, wall thickening or LVEF, the likelihood of significant coronary artery stenosis increased (adjusted OR > 1) with the exception of LCX wall motion (adjusted OR=0.702) (Table 3). Perfusion severity score and LVEF were the two most indicative parameters for significant LAD and RCA coronary artery stenosis (adjusted OR>1.6), while wall thickening severity score was the most indicative factor for significant LCX coronary artery stenosis (adjusted OR=2.479) (Table 3). Similarly, patients with significant coronary artery stenosis had significantly higher mean severity scores for myocardial perfusion, wall motion, wall thickening and LVEF compared with the non-significant group in all 3 coronary arteries ($p<0.05$) with the exception of wall motion severity score of the left circumflex artery ($p=0.479$). These results indicate that in addition to the strength of quantitative analysis in terms of its reproducibility, it can also be used with confidence in interpreting CAD.

As our objective was to evaluate important factors from quantitative analysis of rMPI, a limitation of this study was the lack of inclusion of other clinical factors, e.g., underlying non-communicable diseases, a history of smoking, and other characteristics (age, sex, BMI) of patients included in this study. Another limitation is related to the software used in this study, as only 4D-MSPECT was used. Future research should employ prospective cohort study designs that take into account important clinical factors and should employ a variety of commercial software: there have been few studies comparing the results of LVEF or wall motion obtained from the same cases using different software packages including 4D-MSPECT (23). A logistic regression model should be created for further potential clinical use. Using additional available software would

yield benefits in terms of the generalizability of the research.

Conclusions

Quantitative severity scores of stress radio-nuclide myocardial perfusion imaging and LVEF are effective in evaluation of CAD in all 3 main coronary arteries. Higher severity scores and lower LVEF indicate a greater chance of significant coronary artery stenosis.

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การศึกษาความสามารถและปัจจัยในการบ่งบอกโรคหลอดเลือดหัวใจตีบจากการตรวจสแกนหัวใจ 4 มิติ เชิงปริมาณทางเวชศาสตร์นิวเคลียร์

ธฤต แตระกุล,¹ อารยา บุญยะสิทธิ์พรหม,¹ ศิริวรรณ ศรีใส¹ และ เทวรักษ์ วีระวัฒนกันนธ์²

¹งานเวชศาสตร์นิวเคลียร์ กลุ่มงานรังสีวิทยา โรงพยาบาลราชวิถี วิทยาลัยแพทยศาสตร์ มหาวิทยาลัยรังสิต,

²ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

วัตถุประสงค์ การวิจัยนี้มีเป้าหมายเพื่อศึกษาความสามารถและปัจจัยในการบ่งบอกโรคหลอดเลือดหัวใจตีบจากการตรวจสแกนหัวใจ 4 มิติ เชิงปริมาณทางเวชศาสตร์นิวเคลียร์ในผู้ป่วยที่สงสัยเป็นโรคหลอดเลือดหัวใจ

วิธีการ ทำการศึกษาย้อนหลังในผู้ป่วยที่ได้รับการสงสัยว่าเป็นโรคหลอดเลือดหัวใจและได้รับการตรวจสแกนหัวใจทางเวชศาสตร์นิวเคลียร์ร่วมกับการสวนหัวใจ (CAG) ภายใน 6 เดือน จำนวน 720 ราย ปัจจัยที่สำคัญจากการตรวจสแกนหัวใจ 4 มิติ เชิงปริมาณถูกนำมาวิเคราะห์ ได้แก่ ค่า myocardial perfusion, wall motion และ wall thickening severity scores ของบริเวณหลอดเลือดหัวใจทั้ง 3 เส้น ได้แก่ LAD, LCX, RCA รวมทั้งค่า LVEF โดยเปรียบเทียบกับผลการสวนหัวใจเพื่อบ่งบอกการเป็นโรคหลอดเลือดหัวใจ

ผลการศึกษา ผู้ป่วยที่มีหลอดเลือดหัวใจตีบเส้นใดเส้นหนึ่งอย่างมีนัยสำคัญ มีค่าเฉลี่ยของค่า myocardial perfusion, wall motion, wall thickening severity scores บริเวณหลอดเลือดหัวใจทั้ง 3 เส้น สูงกว่าผู้ป่วยที่ไม่เป็นโรคอย่างมีนัยสำคัญ ยกเว้นค่า wall motion severity score ของหลอดเลือดหัวใจ left circumflex artery ในทำนองเดียวกันผู้ป่วยที่มีค่า myocardial perfusion severity scores ที่มากกว่า มีโอกาสที่จะมีหลอดเลือดหัวใจตีบได้มากกว่าเช่นกัน

สรุป การตรวจสแกนหัวใจ 4 มิติ เชิงปริมาณทางเวชศาสตร์นิวเคลียร์สามารถบ่งบอกโรคหลอดเลือดหัวใจตีบจากหลอดเลือดหัวใจทั้ง 3 เส้นหลัก เมื่อเปรียบเทียบกับผลการสวนหัวใจที่เป็นวิธีตรวจมาตรฐาน ค่า myocardial perfusion severity scores ที่สูงขึ้น บ่งบอกถึงโอกาสที่จะเป็นโรคหลอดเลือดหัวใจตีบได้มากขึ้น **เชียงใหม่ เวชสาร 2562;58(3):123-32.**

คำสำคัญ: โรคหลอดเลือดหัวใจ การตรวจสแกนหัวใจ 4 มิติ เชิงปริมาณทางเวชศาสตร์นิวเคลียร์