Significant coronary artery stenosis assessment: diagnostic accuracy of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging

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การศึกษาความแม่นยำในการวินิจฉัยโรคหลอดเลือดหัวใจตีบจากการตรวจสแกนหัวใจ 4 มิติเชิงปริมาณทางเวชศาสตร์นิวเคลียร์

นายธฤต แตระกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Thesis Title	Significant coronary artery stenosis assessment: diagnostic accuracy of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging
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Field of Study	Health Development
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ธฤต แตระกุล : การศึกษาความแม่นยำในการวินิจฉัยโรคหลอดเลือดหัวใจตีบจากการตรวจสแกนหัวใจ 4 มิติเชิงปริมาณทางเวชศาสตร์นิวเคลียร์. (Significant coronary artery stenosis assessment: diagnostic accuracy of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging) อ.ที่ปรึกษาหลัก : ศ. นพ.เทวารักษ์ วีระวัฒกานนท์

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 ของบริเวณหลอดเลือดหัวใจทั้ง 3 เส้นและค่า LVEF 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

สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่อนิสิต	....
ปีการศึกษา	2561	ลายมือชื่อ อ.ที่ปรึกษาหลัก	....

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Tarit Taerakul : Significant coronary artery stenosis assessment: diagnostic accuracy of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging. Advisor: Prof. THEWARUG WERAWATGANON, M.D.

OBJECTIVES: 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 of them had undergone cardiac catheterization within the 6-month period after having one-day pharmacologic stress radionuclide myocardial perfusion scan. Important parameters were analyzed including 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 the results of gold standard cardiac catheterization.
RESULTS: Binary logistic regression analysis found that patients who had significant coronary artery stenosis had significantly higher value in all quantitative parameters (mean severity scores in myocardial perfusion, wall motion, wall thickening and left ventricular ejection fraction values in almost all 3 coronary artery territories) than those of the non-significant group (p-value <0.05) except wall motion severity score of the left circumflex artery. Similarly, higher perfusion severity scores had a greater probability of significant coronary artery stenosis in all 3 coronary arteries
CONCLUSION: Quantitative parameters obtained from stress radionuclide myocardial perfusion imaging can indicate significant coronary artery stenosis in all 3 main coronary arteries on a level comparable with that of cardiac catheterization, which is the gold standard method. Higher perfusion severity scores indicated a greater probability of significant coronary artery

Field of Study:	Health Development	Student's Signature ....
Academic Year:	2018	Advisor's Signature ....

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Tarit Taerakul

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CHAPTER 1

INTRODUCTION

Coronary artery disease (CAD) is generally used to refer to the pathologic process affecting the coronary arteries. CAD is a major cause of death and disability worldwide. At least one-third of all deaths in individuals over age 35 result from CAD.[1-3] There are many initial evaluation methods for a patient presenting with chest pain and suspected CAD — The following tests are available[4]:

1. Treadmill exercise testing
2. Stress radionuclide myocardial perfusion imaging (rMPI)
3. Stress echocardiography
4. Coronary angiography with cardiac computed tomography (cardiac CT scan)
5. Coronary artery calcium scoring
6. Cardiac magnetic resonance imaging (cardiac MRI)

Significant coronary artery stenosis is present when coronary angiography reveals at least one coronary lesion stenosis more than 50% plus one of the following criteria[5]:

1. Angina pectoris that is reasonably attributed to the lesions.
2. A stress test, including stress rMPI, showing evidence of moderate to severe myocardial ischemia consistent with coronary artery lesions.
3. Physiologic evidence at the time of cardiac catheterization supporting the finding of a significant lesion.

rMPI can evaluates rest and stress myocardial perfusion and function for diagnosis and management of known or suspected CAD patients. Resting rMPI is used for detection of presenting and extension of myocardial infarction. While stress rMPI is used together with resting images to detect regional ischemia. Indications for rMPI[5-7] are

1. Evaluation of patients with known or suspected CAD
2. Assessment of myocardial viability
3. Evaluation of dyspnea of possible cardiac origin

Moreover, rMPI is used usually instead of exercise electrocardiography (ECG) in case of

- ECG abnormalities at rest that render the stress ECG nondiagnostic for ischemia.
- Inability to exercise or exercise adequately, necessitating pharmacologic stress, which must be performed in conjunction with imaging.

A meta-analysis compared the test performance in patients with an intermediate pretest risk of coronary heart disease (25% to 75%) of the following tests: exercise ECG testing, planar thallium rMPI, single photon emission computed tomography (SPECT) rMPI, stress echocardiography, and positron emission tomography (PET), each of which was followed by coronary angiography if the test was positive[8]. The following values for sensitivity and specificity were noted:

- Exercise ECG testing – 68% and 77% in 132 studies
- Planar thallium rMPI – 79% and 73%in 6 studies
- SPECT rMPI – 88% and 77% in 10 studies
- Stress echocardiography – 76% and 88% in 6 studies
- PET scanning – 91% and 82% in 3 studies

Interpretation of rMPI usually use as qualitative analysis (visual assessment) evaluating myocardial activity (normal, reversible, nonreversible defects), wall motion (normal, hypokinetic, akinetic, or dyskinetic) and wall thickening (normal, abnormal) to diagnose CAD[9]. Quantitative analysis is also provided by the softwares automatically. Qualitative analysis uses visual assessment to evaluate myocardial perfusion and function. However, visual assessment is subjective and may result in suboptimal reproducibility of the results. An important strength of quantitative analysis is the inherent reproducibility of the measurements.[10] Moreover, quantitative analysis of myocardial perfusion can rival the diagnostic accuracy of visual observers in the detection of CAD.[11, 12] However, previous diagnostic accuracy studies of quantitative method usually used only myocardial perfusion data (3D myocardial perfusion scan) without other significant factors including wall motion, wall thickening or left ventricular ejection fraction (LVEF). The purpose of this study is to evaluate diagnostic accuracy of quantitative analysis using four-dimensional myocardial single photon emission computed tomography (4D-MSPECT) polar map severity scores.

CHAPTER 2

REVIEW OF RELATED LITERATURES

Searching strategies:

1. Pubmed:

Keyword and MeSH term: “coronary artery disease”[MeSH Terms] AND “myocardial perfusion imaging”[MeSH Terms] AND “single photon emission computed tomography” AND analysis AND prognosis

2. Scopus:

Syntax: “coronary artery disease” AND “myocardial perfusion imaging” AND “single photon emission computed tomography” AND analysis AND prognosis

There are 2 main types of rMPI interpretation; qualitative and quantitative analysis. A number of validated software packages for quantitative analysis of myocardial perfusion scans based on the concept of count profiles have been developed and most are commercially available, including 4D-MSPECT software. These techniques typically use a normal database that provides a reference for the expected range of relative regional uptake. A commonly used method is the 3D segmentation of left ventricle named “polar map”.[13, 14] Quantitative measures of stress, rest, and ischemic (stress-rest) defects were significantly more reproducible than the visual scores (respective repeatability coefficients 3.3%, 1.8%, 3.2% versus 4.8%, 3.8%, 4.3%, all $P<0.01$)[10, 15]. 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 demonstrate clearly the advantage of the quantitative perfusion analysis over visual segmental scoring[16]. In one study, a standard quantitative approach has been found to achieve performance better than or equivalent to clinical visual assessment in the detection of ≥ 50% stenosis as measured by the area under the receiver operator-characteristics (ROC) curve[11]. Similar results were demonstrated recently in a larger population for the blinded expert scoring with and without clinical information[12].

Leslie et al[17] used quantitative analysis for predicting cardiac death or acute myocardial infarction in a cohort. Tools for automated quantification of myocardial perfusion are available to nuclear cardiology practitioners and researchers. These methods have demonstrated superior reproducibility with comparable diagnostic and prognostic performance, when compared with segmental visual scoring by expert observers. A particularly useful application of the quantitative analysis can be in the detection of subtle changes or in precise determination of ischemia. Some challenges remain in the routine application of perfusion quantification. Multiple quantitative parameters may need to be reconciled by the expert reader for the final diagnosis. Computer analysis may be sensitive to imaging artifacts, resulting in false positive scans. Perfusion quantification may require site specific normal limits and some degree of manual interaction. New software improvements have been proposed to challenge its diagnostic accuracy.

CHAPTER 3

RESEARCH METHODOLOGY

Research question

What is the diagnostic value of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging for significant coronary artery stenosis?

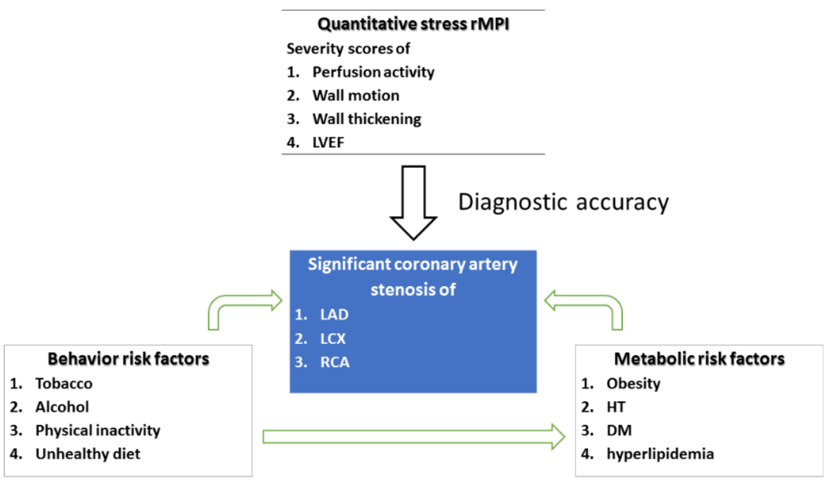
Primary objective:

To study diagnostic accuracy of quantitative 4D-MSPECT stress radionuclide myocardial perfusion imaging for significant coronary artery stenosis

Secondary objective:

To identify factors of quantitative 4D-MSPECT stress rMPI that associate with significant coronary artery stenosis

Conceptual framework:



Operational Definitions

1. Significant coronary artery stenosis is present when coronary angiography reveals one or more obstructive lesions and one of the following criteria[5]:

• Angina pectoris that is reasonably attributed to the lesion(s). Usually, the visual estimate of the severity of the stenosis is 70 percent or greater luminal narrowing.

• A stress test, with or without imaging, showing evidence of moderate to severe myocardial ischemia consistent with a proximal left anterior descending coronary artery lesion.

• Physiologic evidence at the time of cardiac catheterization supporting the finding of a significant lesion, such as an abnormal (low) fractional flow reserve.

2. Polar map is relative perfusion presenting in a 2 dimensional “bull’s-eye” display that is generated by mapping of circumferential profiles obtained from the short-axis SPECT views, with the apex at the center of the display and the base of the ventricle at the periphery[18].

3. Polar map severity maps is the polar map using a normal database providing mean and standard deviation data. Severity values are computed for each polar map sector, from

Severity = (mean-polar map)/standard deviation

The intensity of the severity values is in units of standard deviations. Positive severity values represent areas that are less than the mean (i.e. increasingly abnormal), while negative values represent areas that are greater than the mean (i.e. normal).

4. SPECT rMPI is imaging of myocardial perfusion with radiopharmaceuticals to determine the adequacy of blood flow to the myocardium, especially in conjunction with exercise or pharmacologic stress for the detection and evaluation of coronary artery disease[9].

Research design

Descriptive analytical study design

Population and Sample

Target population:

Patients suspected coronary artery disease

Study population:

Patients suspected coronary artery disease from patient's history, physical examination, ECG findings and serum cardiac enzyme by cardiologist who required further investigation at Rajavithi hospital

Inclusion criteria

1. Age 18-60 years
2. Patients suspected coronary artery disease by cardiologist
3. No previous cardiovascular disease
4. Patients had cardiac catheterization after SPECT rMPI within 6 months without clinical change because of no significant change of CAD by cardiologist opinion.

Exclusion criteria

1. Patients done either SPECT rMPI or cardiac catheterization in other indications than coronary artery disease
2. Pregnancy and breast-feeding patients

Sample size calculation

Sample size calculation for sensitivity analysis is determined by infinite calculation proportion formula[19]. The previous studies demonstrated 79% of sensitivity[20] and +/- 24% of 95% confident interval[21]. The expected sensitivity of this study is 80% with +/- 10% of 95% confident interval.

$$n = \frac{z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{d^2}$$

p = 0.8 d = 0.1 α = 0.05

n = 62

Since prevalence of coronary artery disease in intermediate risk group is 30%

Thus, sample size is 62 / 0.3 = 207 patients

Research protocol

1. A retrospective study conducts with suspected coronary artery disease patients who sent for SPECT rMPI by review medical record charts of Rajavithi hospital from 31st August 2017 retrospectively until 1st August 2015 due to estimation of 200 rMPI cases/years.

2. Select the patients who done cardiac catheterization within 6 months after SPECT rMPI study until having 207 patients.

3. All baseline patient's characteristics including age, gender, body mass index (BMI), diabetes, hypertension, dyslipidemia, chronic kidney disease are collected.

4. From the stress SPECT rMPI study; severity scores of perfusion, wall thickening, wall motion from left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA) and LVEF data are collected.

5. From cardiac catheterization results; coronary artery stenosis percentage from LAD, LCX and RCA are collected and divided into positive (≥ 50% stenosis) and negative (< 50% stenosis) categorically.

Type of data

1. Demographic data and baseline variables

- Age
- Gender
- BMI
- Diabetes
- Hypertension
- Dyslipidemia
- Chronic kidney disease

2. rMPI data

- Myocardial perfusion severity score, wall motion score and wall thickening score of LAD.
- Myocardial perfusion severity score, wall motion score and wall thickening score of LCX.
- Myocardial perfusion severity score, wall motion score and wall thickening score of RCA.
- LVEF is also collected for every coronary artery groups.

3. Cardiac catheterization data

- Percentage of coronary stenosis of LAD
- Percentage of coronary stenosis of LCX
- Percentage of coronary stenosis of RCA

Data analysis

1. For baseline characteristic analysis

   Continuous data will be reported by mean ±SD or median change.

   Categorical data will be reported by frequency.

2. For sensitivity, specificity (ROC curve) analysis

   The equations of significant coronary artery stenosis of LAD, LCX, RCA which created from rMPI data (myocardial perfusion, wall motion and wall thickening severity score, and percentage of LVEF) and regression coefficients from prediction models of logistic regression analysis[22, 23] will be analyzed by ROC curve to collect sensitivity and specificity of the best result cut off value.

3. For logistic regression analysis

3.1 Age, gender, BMI, history of diabetes, hypertension, dyslipidemia and chronic kidney disease will be analyzed with univariate analysis.

3.2 Myocardial perfusion, wall motion and wall thickening severity score of LAD, LCX, RCA and percentage of LVEF will be analyzed with binary logistic regression to create 3 prediction models of each significant LAD, LCX, RCA stenosis data (>50% coronary stenosis).

Ethical consideration

1. The research proposal must be approved by the ethical committee of Faculty of Medicine, Chulalongkorn University and Rajavithi Hospital.

2. This is a retrospective study which has no harm to patients for any condition.

3. The patient's data will be collected and recorded in an electronic database using codes to maintain patient confidentiality.

4. Results of the study will be presented in general

5. No conflict of interest of this study.

CHAPTER 4

RESULTS

Data were collected retrospectively on two hundred and seven patients who came for SPECT rMPI studies at the Nuclear Medicine Division between August 2015 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. All of whom had undergone cardiac catheterization within 6 months following SPECT rMPI were enrolled in the study. One hundred and four patients had significant LAD stenosis, 73 patients had significant LCX stenosis and 83 patients had significant RCA stenosis. 69.6% of patients were male, 38.7% had diabetes, 82.1% had hypertension, 78.7% had hypercholesterolemia, and 20.8% had chronic kidney disease. Patients' characteristics are shown in Table 1.

Table 1 Characteristics of patients included in the study. (A) characteristics of LAD patients, (B) characteristics of LCX patients, (C) characteristics of RCA patients.

A Characteristic	LAD Stenosis: Number (%)	
	Yes (n=104)	No (n=103)
Age (years)[1]	64.9 (11.7)	61.6 (10.9)
Gender: male (n[%])	83.0 (79.8)	61.0 (59.2)
BMI (kg/m^2)[1]	25.4 (4.4)	26.5 (4.9)
Coronary risk factors (n[%])		
DM	51.0 (49.0)	29.0 (27.9)
HT	90.0 (86.5)	80 (76.9)
Hypercholesterolemia	89.0 (85.6)	74.0 (71.2)
CKD	25.0 (24.0)	18.0 (17.3)

B Characteristic	LCX Stenosis: Number (%)	
	Yes (n=73)	No (n=134)
Age (years)[1]	66.4 (10.7)	61.5 (11.5)
Gender: male (n[%])	59.0 (80.8)	85.0 (63.4)
BMI (kg/m^2)[1]	25.6 (4.7)	26.1 (4.7)
Coronary risk factors (n[%])		
DM	42.0 (57.5)	38.0 (28.4)
HT	67.0 (91.8)	103.0 (76.9)
Hypercholesterolemia	68.0 (93.2)	95.0 (70.9)
CKD	17.0 (23.3)	27.0 (20.2)

C Characteristic	RCA Stenosis: Number (%)	
	Yes (n=83)	No (n=124)
Age (years)[1]	65.4 (10.0)	61.8 (12.1)
Gender: male (n[%])	68.0 (81.9)	76.0 (61.3)
BMI (kg/m^2)[1]	25.9 (4.6)	26.0 (4.8)
Coronary risk factors (n[%])		
DM	38.0 (45.8)	42.0 (33.9)
HT	75.0 (90.4)	95.0 (76.6)
Hypercholesterolemia	71.0 (85.5)	92.0 (74.2)
CKD	21.0 (25.3)	22.0 (17.7)

1 Mean (SD.)

BMI, body mass index; DM, Diabetes mellitus; HT, Hypertension; CKD, Chronic kidney disease

Mean perfusion severity scores of LAD, LCX and RCA were 0.5, 1.6 and 0.3 respectively. Mean wall thickening severity scores of LAD, LCX and RCA were 0.8, 0.7 and 0.8 respectively. Mean wall motion severity scores of LAD, LCX and RCA were 0.8, 0.2 and 0.8 respectively and mean LVEF was 47.9% as showed the details in table 2. Univariable analysis revealed that the wall motion and LVEF of RCA were non-statistically ($p \geq 0.05$) associated with significant coronary artery stenosis. However, in multivariable regression analysis, all severity scores of myocardial perfusion with some severity scores of wall thickening and wall motion indicated significant coronary artery stenosis with statistical significance ($p < 0.05$), with the exception of those of severity scores of wall thickening of LAD, wall motion of LAD and RCA, and LVEF of all LAD, LCX and RCA (table 3).

Table 2 Association between coronary artery stenosis, severity scores and LVEF. (A) association of LAD, (B) association of LCX, (C) association of RCA.

A	LAD stenosis: Number		OR (95% CI)	p-value
	Yes (n= 104)	No (n=103)		
Severity score				
Perfusion[1]	1.0 (2.0)	-0.2 (0.8)		<0.001
≥ 0.15			1	
< 0.15			4.4 (2.5, 7.9)	
Wall thickening	1.0 (0.8)	0.5 (0.9)		<0.001
≥ 0.65			1	
< 0.65			3.3 (1.8, 5.8)	
Wall motion	1.2 (1.3)	0.3 (1.1)		<0.001
≥ 0.55			1	
< 0.55			3.2 (1.8, 5.7)	
LVEF	41.9 (17.1)	54.1 (15.9)		<0.001
≥ 50			1	
< 50			0.3 (0.2, 0.5)	

B	LCX stenosis: Number		OR (95% CI)	p-value
	Yes (n= 134)	No (n=73)		
Severity score				
Perfusion[1]	2.8 (2.9)	1.1 (1.4)		<0.001
≥ 0.15			1	
< 0.15			3.1 (1.7, 5.7)	
Wall thickening	1.2 (1.0)	0.5 (1.1)		<0.001
≥ 0.65			1	
< 0.65			2.5 (1.4, 4.6)	
Wall motion	0.3 (1.4)	-0.0 (1.5)		<0.05
≥ 0.55			1	
< 0.55			1.0 (0.5, 1.7)	
LVEF	41.4 (17.3)	51.3 (16.5)		<0.05
≥ 50			1	
< 50			0.4 (0.3, 0.8)	

C	RCA stenosis: Number		OR (95% CI)	p-value
	Yes (n= 124)	No (n=83)		
Severity score				
Perfusion[1]	0.9 (1.7)	-0.0 (1.0)		<0.05
≥ 0.15			1	
< 0.15			3.1 (1.7, 5.4)	
Wall thickening	1.0 (0.8)	0.6 (0.9)		<0.05
≥ 0.65			1	
< 0.65			3.5 (1.9, 6.3)	
Wall motion	1.2 (1.4)	0.5 (1.4)		0.173
≥ 0.55			1	
< 0.55			3.0 (1.7, 5.4)	
LVEF	42.3 (18.0)	51.2 (16.0)		0.588
≥ 50			1	
< 50			0.4 (0.2, 0.7)	

1 Mean (SD)

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

Severity Scores and LVEF	Multi-variable analysis	
	Adjusted OR (95%CI)	P-value
LAD_ perfusion		
≥ 0.15		
< 0.15	3.1 (1.6, 1.1)	.001
LAD_wall thickening		
≥ 0.65		
< 0.65	1.2 (0.5, 2.7)	0.723
LAD_wall motion		
≥ 0.55		
< 0.55	1.8 (0.8, 4.1)	0.139
LCX_ perfusion		
≥ 1.25		
< 1.25	3.0 (1.6, 5.6)	0.001
LCX_ wall thickening		
≥ 0.65		
< 0.65	2.9 (1.1, 7.8)	0.039
LCX_ wall motion		
≥ -0.25		
< -0.25	0.3 (0.1, 0.7)	0.006
RCA_ perfusion		
≥ 0.05		
< 0.05	2.7 (1.4, 4.9)	0.002
RCA_ wall thickening		

≥ 0.65		
< 0.65	2.5 (1.1, 5.4)	0.025
RCA_ wall motion		
≥ 0.65		
< 0.65	1.9 (0.8, 4.6)	0.173
LVEF_LAD		
≥ 50.0		
< 50.0	0.8 (0.3, 1.8)	0.542
LVEF_LCX		
≥ 50.0		
< 50.0	0.5 (0.2, 1.2)	0.133
LVEF_RCA		
≥ 50.0		
< 50.0	1.3 (0.5, 3.2)	0.588

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

As many as 69.9%, 62.7% and 64.5% of non-significant LAD, LCX and RCA coronary artery stenosis cases respectively had LVEF of more than 50%, compared to only 30.1%, 37.3% and 35.5% with less than 50% LVEF. Only 41.3%, 42.5% and 42.2% of significant LAD stenosis cases had LVEF of more than 50%, while 58.7%, 57.5% and 57.8% had LVEF of lower than 50% in LAD, LCX and RCA respectively. All these data showed statistically significant difference (table 4).

Table 4 LVEF in CAG results of 3 main coronary arteries

		LVEF		P-value
		<50%	≥50%	
LAD_CAG	Non-significant	30.1%	69.9%	
	Significant	58.7%	41.3%	
Total		44.4%	55.6%	0.000
LCX_CAG	Non-significant	37.3%	62.7%	
	Significant	57.5%	42.5%	
Total		44.4%	55.6%	0.005
RCA_CAG	Non-significant	35.5%	64.5%	
	Significant	57.8%	42.2%	
Total		44.4%	55.6%	0.002

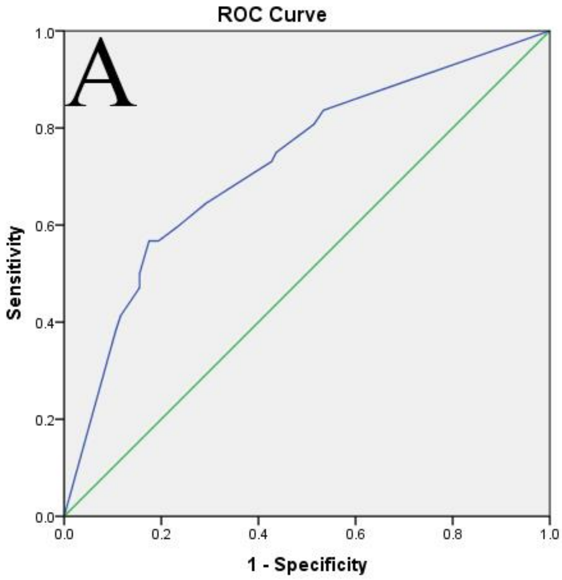
CAG, Coronary artery angiography

The equations of significant coronary artery stenosis were created from rMPI raw data of perfusion, wall thickening and wall motion severity scores, and LVEF (no categorical data were used) together with weighting factors from regression coefficients of binary logistic regression and rounding to the whole numbers (table 5). So, the equations of significant LAD, LCX, and RCA stenosis were 8.0(perfusion severity score) + 1.0(wall thickening severity score) + 4.0(wall motion severity score) + (-2.0)(LVEF), 2.0(perfusion severity score) + 2.0(wall thickening severity score) + (-2.0)(wall motion severity score) + 1.0(LVEF), and 4.0(perfusion severity score) + 4.0(wall thickening severity score) + 3.0(wall motion severity score) + 1.0(LVEF), respectively (table 5).

Table 5 Regression coefficients from logistic regression to create weighting factors in the equations of significant coronary artery stenosis

Coronary arteries	Regression coefficients (Weighting factors)			
	Perfusion	Wall thickening	Wall motion	LVEF
LAD	8.0	1.0	4.0	-2.0
LCX	2.0	2.0	-2.0	1.0
RCA	4.0	4.0	3.0	1.0

ROC curves were used to evaluate sensitivity vs specificity of the equations of significant coronary artery stenosis as shown in Figure 1. Area under the curve (AUC) of the equation of significant LAD stenosis was 0.73 (95% CI, 0.66-0.80). When result of the equation of significant LAD stenosis was 3.5; sensitivity and specificity were 75.0% and 56.3%, respectively. AUC of the equation of significant LCX stenosis was 0.71 (95% CI, 0.64-0.78). When result of the equation of significant LCX stenosis was 0.5; sensitivity and specificity were 79.5% and 48.5%, respectively. AUC of the equation of significant RCA stenosis was 0.71 (95% CI, 0.64-0.78). When result of the equation of significant RCA stenosis was 2.5; sensitivity and specificity were 90.0% and 40.0%, respectively.


ROC Curve
A
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

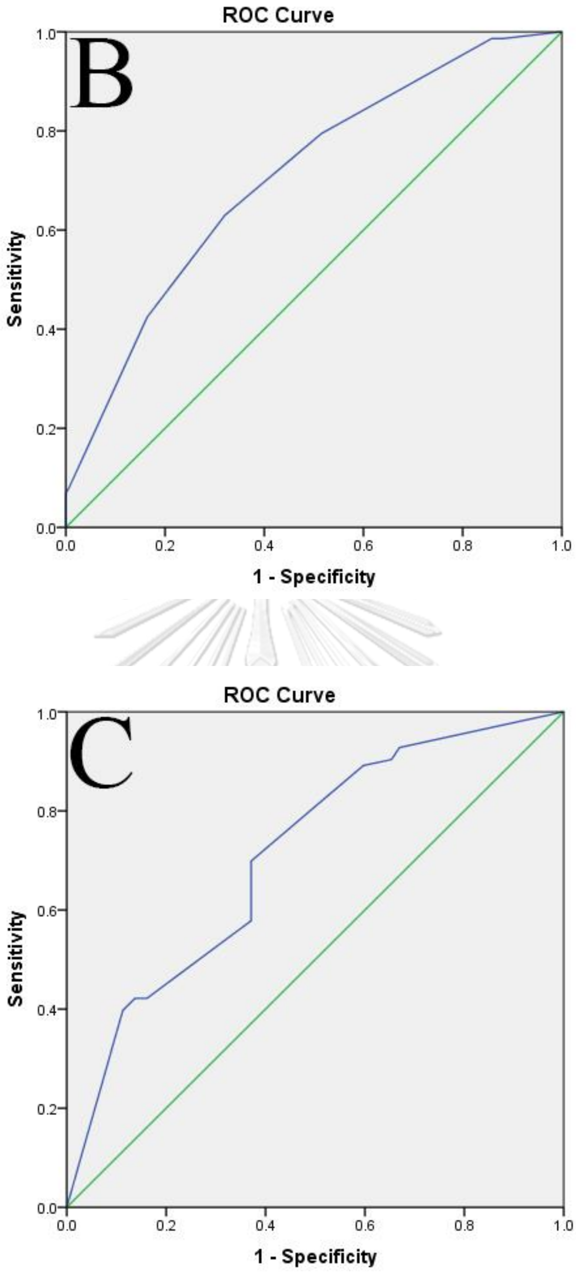


Figure 1 ROC curve discrimination of the equations of significant coronary artery stenosis. (A) ROC curve of the equation of significant LAD stenosis, (B) ROC curve of the equation of significant LCX stenosis, (C) ROC curve of the equation of significant RCA stenosis.

CHAPTER 5

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 observers 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%, 3.2% versus 4.8%, 3.8%, 4.3%, all $P<0.01$) [10, 15]. These comparisons clearly demonstrate the advantage of quantitative perfusion analysis over visual segmental scoring. In one study, a standard quantitative approach was found to achieve performance that was equivalent to, or better than, clinical visual assessment in the detection of ≥ 50% stenosis, as measured by the area under the receiver operator characteristics (ROC) curve[11]. Similar results were demonstrated recently in a larger population with blinded expert scoring with and without clinical information[12].

In identifying its effectiveness for indicating significant coronary artery stenosis from many important parameters of this quantitative rMPI method, this study showed that patients with significant coronary artery stenosis had significantly higher mean severity scores compared with the non-significant group in almost all myocardial perfusion, wall motion, and wall thickening except wall motion of LCX and had significantly lower mean LVEF in all 3 coronary arteries (p-value <0.05) (table 2). Only wall motion of LCX were also not associated with significant coronary artery stenosis in univariate analysis ($p > 0.05$) (table 3). In multivariate analysis, there were many parameters that also indicated significant coronary artery stenosis, including severity scores of myocardial perfusion of all arteries, wall thickening of LCX and RCA, and wall motion of LCX. Although some parameters showed non-significant for coronary stenosis which could be due to other factors that affect the severity score such as radiation attenuation defects from breast, bowel or diaphragmatic activity, or caused by other types of cardiac disease beside CAD. For every 1 score increment in almost all severity scores, the likelihood of significant coronary artery stenosis increases (adjusted OR > 1) and perfusion severity scores were the most indicative parameters for all significant coronary artery stenosis (adjusted OR of LAD, LCX and RCA were 3.13, 2.97 and 2.66, respectively). However, parameters of wall motion of LCX and LVEF of LAD, and LCX had adjusted OR < 1. Similarly, when LVEF was stratified into 2 groups (LVEF <50% and LVEF ≥50%), there was also a significant difference in significant stenosis of all 3 coronary arteries ($p \leq 0.05$) (table 4) but LVEF regression coefficients of LAD and LCX still showed negative numbers (table 5) which might be due to some non-significant stenosis subjects also had low LVEF from the other cardiac diseases. All these results showed that in addition to the strength of quantitative analysis in terms of its reproducibility, this quantitative method can also be used with confidence in evaluating CAD.

The equations of significant coronary stenosis of each coronary artery were created to evaluate diagnostic accuracy of this quantitative method. The results showed that the sensitivity of all 3 coronary arteries were close to 79% sensitivity of the previous qualitative method but had a lower specificity than the original technique (76% specificity)[19]. This results represent as the previous studies that showed equivalent diagnostic accuracy. However, by this quantitative technique, radiologists can put numbers of severity scores and LVEF in the equation of each coronary artery to get the probability to be coronary artery stenosis and can reproduce the same result in every interpretation. The reasons that the latest 4D imaging and processing technique used in this study still showed the same diagnostic accuracy as the old technique may be due to the difference of study design to evaluate diagnostic accuracy of the equations in each coronary artery one by one which is not include all 3 coronary arteries in the same analysis as the other studies. A limitation may be due to 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 processing 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 myocardial perfusion obtained from the same cases using different software packages including 4D-MSPECT[18, 24]. Using additional available software would yield benefits in terms of the generalizability of the research. Increase the sample size collection with higher sensitivity expectation could be the other aspect to be done in further study.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

Quantitative 4D-MSPECT stress rMPI can evaluate significant coronary artery stenosis of all three main coronary arteries with sensitivity close to the qualitative technique even though it has a lower specificity and the severity scores of myocardial perfusion had the most association with significant coronary artery stenosis of all coronary arteries.

REFERENCES

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