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Rest Thallium-201/Stress Technetium-99m Sestamibi Dual-Isotope Myocardial Perfusion Single-Photon Emission Computed Tomography in Detecting of Chronic Coronary Artery Disease

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Abstract: To investigate diagnostic accuracy of 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion SPECT in chronic coronary artery disease. Sixty-seven patients with suspected CAD were enrolled in the prospective study. All patients underwent myocardial perfusion scintigraphy in SPECT with dual isotopes of Tl-201 and dipyridamole stress Tc-99m sestamibi. Rest and stress imaging protocol were performed in 2 hours by dose of 3 mCi Tl-201 and 25 mCi Tc-99m sestamibi. The acquisition parameters includes LEHR collimator, energy peak of 72 and 167 keV for Tl-201 and 140 keV for Tc-99m, 180-degree rotation from RAO to LPO, matrix size 64×64, and 25second/frame/64 frames. The 20-segment model of left ventricle was used in automatic quantitation software. Coronary angiography was used as gold standard. CAD was defined as 50% of lumen stenosis on coronary angiography. Rest Tl-201/stress tc-99m sestamibi dual-isotope SPECT demonstrated a sensitivity of 94.59% and specificity of 70%, positive predictive value of 79.54% and negative predictive value of 91.3% in detection of coronary artery disease. Sensitivity and specificity for detecting multi-vessel coronary artery disease were 82.75% and 81.57% for the left anterior descending, 77.77% and 91.83% for left circumflex and 94.11% and 82% for right coronary artery. 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion SPECT has high sensitivity, specificity, positive predictive value and negative predictive value in detecting chronic coronary artery disease with greater than 50% stenosis assessed by coronary angiography. Moreover, this imaging protocol gives high imaging quality, time-saving and convenience.

Key words: MPS (myocardial perfusion scintigarphy), SPECT (single proton emission computed tomography), CAD (coronary artery disease), CA (coronary angiography).

1. Introduction

Although there was advanced treatment for coronary artery disease, this disease is still one of main mortality causes in the world.

Therefore, continuously improved diagnostic methods for detecting early ischemic heart disease are necessary. Coronary angiography is gold standard for diagnosis of ischemic heart disease, but it is an invasive method. Now, there are many non-invasive diagnostic methods for detecting ischemic heart disease such as: stress electrocardiography, stress echocardiogram or nuclear methods such as myocardial perfusion SPECT (single photon emission computed tomography) or PET (positron emission tomography) with different isotopes. Myocardial perfusion SPECT is advantage non- invasive study that not only accessing perfusion, but also accessing heart function, viability and prognostic as well.

In recent 20 years, nuclear cardiology has been developed strongly and there are many researches about using myocardial SPECT for detecting ischemic heart disease. Routine imaging procedure of myocardial perfusion SPECT can be acquired with thallium or with any 99mTc-labeled radiopharmaceutical. In more than recent 10 years,

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dual-isotope technetium-99m and Thalium-201 imaging procedure lasted 2 hours demonstrates high diagnostic values for detecting ischemic heart disease. Dual-isotope SPECT myocardial perfusion scintigraphy was introduced in 1993 with Tl-201 at rest and Tc-99m sestamibi (MIBI) at stress. Since that time, this protocol has become widely used for the diagnosis and assessment of prognosis in patients with known or suspected CA (coronary artery) disease in a wide variety of clinical settings.

We conducted research "Rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography in detecting of chronic coronary artery disease" with purposes as followings below:

Investigate sensitivity, specificity, positive predictive value, negative predictive value of 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion SPECT in chronic coronary artery disease, and diagnose stenosed coronary artery as coronary angiographic stenosis on PTCA is gold standard (CA stenosis criteria ≥ 50%)

Investigate correlation between angiographic stenosis on PTCA and segments of myocardial perfusion defect on 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope SPECT (CA stenosis criteria ≥ 50%)

This research was the first study about role of myocardial perfusion SPECT with 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope in chronic coronary artery disease in Viet Nam.

2. Patient and Methods

2.1 Patient Population

From a consecutive series of patients who underwent a study of myocardial perfusion SPECT with Rest thallium-201/stress technetium-99m sestamibi dual-isotope imaging procedure and coronary artery angiography, 67 were selected and represent the population of this study.

The criteria to enter the study were as follows: (1) suspected coronary artery disease (2) and agree to attend this research.

The criteria to exclude the study were as follows: (1) recent myocardial infarction (< 1 month), (2) unstable angina, (3) congestive heart failure occurring 1 month before the study, (4) valve heart disease, (5) arrythmiasm (block AV II or III, sinus node disfunction), (6) unstable hypertension, (7) scleroderma, (8) hyperthyroid, (9) severe fever, (10) severe underlying diseases, (11) chronic obstructive pulmonary disease. All patients were in stable hemodynamic condition over the study period.

2.2 Study Protocol

Baseline studies included 2-hour protocol of rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion SPECT and coronary angiography.

The rest study is usually performed first. 3milicuries

Table 1 Imaging parameters based on SPECT imaging's SPECT imaging of Americant Society of Nuclear Cardiology [3-6].

	Rest	Stress
Isotope dose	T1- 201: 3 mCi	Tc-99m mibi: 25 mCi
Collimator	LEHR	LEHR
Detector	400mm	400mm
Energy Window	72 KeV W: 30% 167 KeV W: 20%	140 KeV W: 15%
Turn angle	180^0 (-45^0 RAO-> 135^0 LPO)	180^0 (-45^0 RAO-> 135^0 LPO)
Picture number 2D	64 pictures and 25 second/picture	64 pictures and 25 second/picture
Matrix	64 x 64	64 x 64

of thallium was administered at rest. The acquisition can begin as soon as 15 minutes after injection. After the completion of rest study acquisition, a stress study is performed using Dipyridamole with dose 0,568 mg/kg/4 min. for stress pharmaceutical test and a technetium-labeled myocardial perfusion imaging agent with dose 25-30 milicuries of Tc-99mibi injected as soon as 7 minutes after starting of stress test by Dipyridamole. Imaging can be 30 minutes after injection of Tc-99 mibi. The images should be reviewed before the patient is released.

In all patients, calcium antagonist, digoxin and oral nitrates had been withdrawn for at least 48 hours, β-blockers for at least 72 hours, and transdermal nitrates for at least 12 hours before the protocol study. Theophylline and caffeine also had been withdrawn for at least 24 hours before the protocol study.

Informed consent was obtained form each patient before the protocol study (which was approved by the institutional ethical committee) [17-20].

2.3 Coronary Angiography

All angiograms were analysed by an investigator blinded to dual isotopes perfusion SPECT data. Coronary angiographic result was gold standard of chronic coronary artery disease.

Vessel stenosis was defined in left main, LAD (left anterior descending coronary), RCA (right coronary artery), LXC (left circumflex artery) and stenosis diameter ≥ 50% was significant stenosis and positive result. Collateral circulation was also defined dominantly in right or left circulation [2, 8, 9].

2.4 Dual Isotopes Imaging

All patients underwent rest Tl-201/stress Tc-99m sestamibi tomography as previously described. In each patient, 8 consecutive midventricular slices of 3 sections including short axis, vertical long axis, horizontal long axis for both rest and stress phage. Tomogram were then divided into 6 sectors of equal arc, representing segments such as: 1: antero (apex), 2: anteroseptal (apex), 3: posteroseptal (apex), 4: inferior (apex), 5: posterolateral (apex), 6: anterolateral (apex), 7: antero (mid), 8: anteroseptal (mid), 9: posteroseptal (mid), 10: inferior (mid), 11: posterolateral (mid), 12: anterolateral (mid), 13: antero (base), 14: anteroseptal (base), 15: posteroseptal (base), 16: inferior (base), 17: posterolateral (base), 18: anterolateral (base), 19: apex (anterior), 20: apex (posterior). Thus 20 myocardial regions were analyzed for each patient.

Of these segments, 9 segments (number 1, 2, 3, 7, 8, 13, 14, 19, 20) were assigned to the territories of the left anterior descending coronary artery, 6 segments (number 5, 6, 11, 12, 17, 18) were assigned to the territories of the left circumflex coronary artery, and 5 segments (number 4, 9, 10, 15, 16) were assigned to the territories of the right coronary artery (Fig. 1).

Alignment and analysis of the study were visually made by operator who was unaware of the echocardiography result and coronary angiography result.

5-point scoring system (0, normal uptake; 1, mild defect; 2, moderate defect; 3, severe defect; and 4, absent tracer uptake) was used to compute a summed

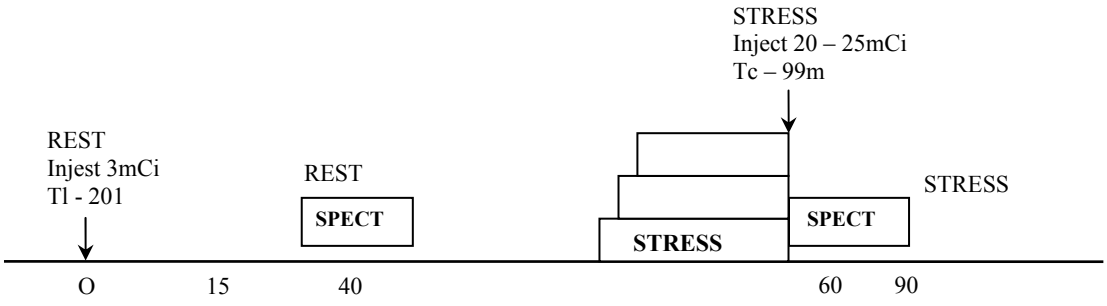


Fig. 1 Rest Tl-201/stress Tc-99m sestamibi dual-isotope study protocol.

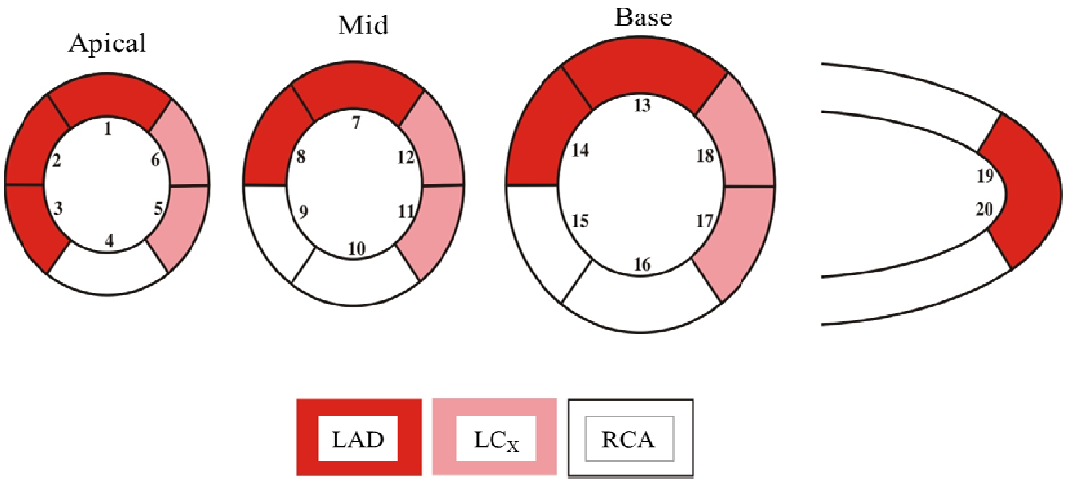


Fig. 2 Charts showing division of left ventricle into 20 segments in short axis, long vertical axis and long horizontal axis. Red segments were assigned to LAD, pink segments were assigned to LCx, white segments were assigned to RCA.

stress score, a summed rest score, and a summed difference score, as described previously. These summed scores were converted into the percentage of myocardium that was abnormal, fixed, and reversible, respectively, by use of a standard approach [11, 12, 14-16].

2.5 Statistical Methods

Statistical analysis was performed with the SPSS 10.5 statistical package. Continuous data ware expressed as mean ± SD and categorical data as a percentage. The unpaired t-test (for continuous variables) and the χ^2 -test (for categorical variables) were used as appropriate. Value $P < 0.05$ was considered statistically significant. Sensitivity and specificity of SPECT results versus coronary angiography were calculated with the usual formulas with the associated 95% confidence intervals. Correlations between continuous variables were assessed by regression analysis.

The analysis was performed in patients who underwent myocardial perfusion scintigraphy by SPECT, percutaneous transluminal coronary angiography, in order to access sensitivity, specificity, negative predict value, positive predict value of dual isotopes SPECT as coronary angiography was defined gold standard for diagnosis of ischemic heart disease and LAD, LCx, RCA coronary artery lesion ≥ 50%.

The correlation analysis was conducted between myocardial territories assigned by LAD, LCx, RCA and culprit coronary artery.

3. Result

This study was comprised of 67 patients underwent dual isotopes myocardial perfusion scintigraphy SPECT and coronary angiography.

Table 2 Patient characteristics.

	All
Age (y)	57 (40-70)
Sex: M/F	49/18
Risk factors for CAD	
Hypercholesterolemia	59 (88,1%)
Hypertension	46 (68,7%)
Smoking	20 (29,9%)
Diabetes	15 (22,4%)
Obesity	15 (22,4%)
Familial history for CAD	21 (31,3%)
LVEF (%)	
< 50%	19 (28,4%)
≥ 50%	48 (71,6%)
Stress ECG (+)	19 (28,4%)
Stress ECG (-)	35 (52,2%)
Stress EHO (+)	31 (46,3%)
Stress ECHO (-)	23 (34,3%)
Dual-isotope SPECT (+)	44 (65,7%)
Dual-isotope SPECT (-)	23 (34,3%)
CA (+)	37 (55,2%)
CA (-)	30 (44,8%)

CA: cardial angiography; CAD, coronary artery disease; ECG, electrocardiography; ECHO, electrocardiography; LVEF, left ventricular ejection fraction; SPECT: single proton emission computed tomography.

Values represent median (25^{th}-75th percentile), frequency (N), or mean ± SD.

Table 3 Dual-isotope myocardial perfusion SPECT.

	Case number	Percent %
Perfusion defect level on SPECT		
Reversibility	8	21,6
Partial reversibility	12	32,4
Fixed	17	46

Table 4 Segments of perfusion defect on Dual-isotope myocardial perfusion SPECT scintigraphy relating to stenosed CA.

	LAD	LCx	RCA	Total number
Segments of perfusion defect	135	65	71	271

Table 5 Result of PTCA.

	All cases PTCA (+) n = 37 cases n = 67 CA	Percent %
PTCA		
PTCA (+)	37	55,2
PTCA (-)	30	44,8
1-vessel CAD	16	43,2
2-vessel CAD	13	35,1
3-vessel CAD	7	19
4-vessel CAD	1	2,7
LAD stenosis	8	21,6
LCx stenosis	4	10,8
RCA stenosis	4	10,8
LAD + LCx stenosis	6	16,2
LAD + RCA stenosis	7	18,9
LAD + LCx + RCA stenosis	5	13,5
LAD + LCx + LM stenosis	2	5,4
LAD + LCx + RCA + LM stenosis	1	2,7

LAD, left anterior descending; LCx, left circumflex artery; PTCA, percutaneous transluminal coronary angiography RCA; right coronary artery.

Table 6 CA stenosis diagnosed by PTCA.

	All CA (n = 67) (LAD, RCA, LCx, LM)	Percent %
CA stenosis ≥50% <70%	25	39,1
CA stenosis ≥ 70%	39	60,9

CA stenosis criteria ≥50%.

Table 7 Diagnostic accuracy of Dual-isotopes SPECT for CAD (CA stenosis criteria ≥ 50%).

	Sensitivity (n = 35)	Specificity (n = 21)	PPV (n = 44)	NPV (n = 23)	X^2 Value
Dual-isotope SPECT	94,59%	70%	79,54%	91,3%	30,66

(P < 0,05).

Table 8 Sensitivity of Dual-isotopes myocardial perfusion SPECT for diagnosis of CAD (CA stenosis ≥ 50% and ≥ 70% (identifying LAD, LCx, RCA).

	SPECT (+) (stenosed CA number)	SPECT (-) (stenosed CA number)	Sensitivity (%)
Stenosis ≥50%	54	10	84,4
Stenosis ≥70%	34	5	87,2

Table 9 Diagnostic accuracy of Dual Isotopes SPECT for CAD (stenosis CA criteria ≥ 50%).

	Sensitivity	Specificity	PPV	NPV	χ^2value	OR
LAD (n = 29)	82,8%	81,6%	77,4%	86,1%	27,39	21,26
LCx (n = 18)	77,8%	91,8%	77,8%	91,8%	29,02	39,38
RCA (n = 17)	94,1%	82%	64%	97,6%	28,26	72,89

(P value < 0,05).

Table 10 Correlation between angiographic stenosis on PTCA and segments of perfusion defect on dual-isotope SPECT (stenosis CA criteria ≥ 50%).

Segments/SPECT	LAD	LCx	RCA	LAD + LCx + RCA
Correlation (+)	79.2%	80%	64.8%	75.6%
Correlation (-)	20.8%	20%	35.2%	24.4%

4. Discussion

Our study comprised of 67 cases underwent MPI Dual Isotopes SPECT and PTCA, average age of male is 59 years old and female is 57 years old, in which male patients is majority (73,1%). And majority of patients has normal BMI, dominant CAD risk factor is dyslipidemia (88,1%), side effects are relating to dilating side effect of Dipyridamole that is usually tachycardia (62,7%). This study does not regconize correlation between Dipyridamole, LVEF and perfusion defect level of MPI SPECT [1, 2, 23]. However, dyskesinia of Echocardiography has meaningful correlation with result of MPI SPECT and PTCA.

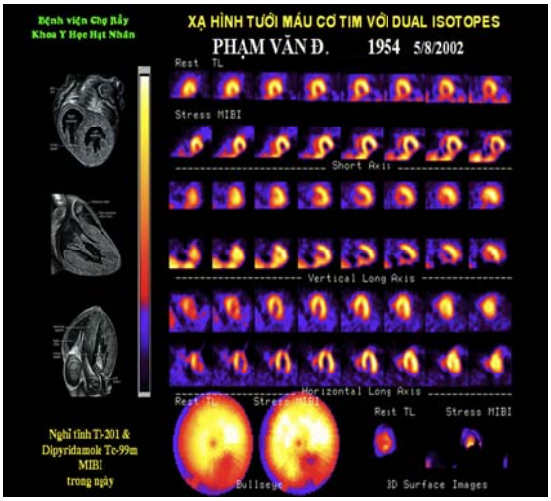
44 cases of MPI Dual Isotopes SPECT is positive (65,7%) and 23 cases is negative (34,3%), sensitivity and specificity of MPI Dual Isotopes SPECT is 94,6% and 70% respectively. Sensitivity of this study is higher than sensivitity of studies of Kiat, Iskandrian, Chae, Van Train, Rubello, Hambye, Santana Boado, Elhendy and Wackers Fran J.TH (94,59% with 93%, 82%, 71%, 89%, 93%, 82%, 87%, 91%, 76% and 88% respectively). However, sensitivity of this study is lower than sensitivity of studies of Kahn, Solot and Azzarelli (94,59% with 95%, 97%, 95% respectively). Specificity of this study is same as specificity of Wackers Fran J. TH (70%) [11, 12, 14, 15, 19, 22, 24, 25]. So that, there are many studies on sensitivity and specificity of MPI SPECT for diagnosis ischemic heart disease, difference of these values was explained by referral bias and gold standard – PTCA. Positive-stenosis level of CA assessed by gold standard - PTCA effects on sensitivity and specificity of MPI SPECT. 50% or 70% positive-stenosis of CA depends upon definition of every study.

Berman et al. [3-6] evaluated the sensitivity and specificity of a novel dual-isotope procedure characterized by injection of 3.5 mCi of Tl-201 at rest with image acquired 10 minutes later, followed by immediate exercise sestamibi imaging utilizing 20 to 30 mCi of tracer injected at peak exercise. This study reavealed sensitivity and specificity 91% and 75%, respectively for this technique for CAD detection (≥ 50% stenosis). These values were 96% and 82% when ≥ 70% stenosis was used as criterion for CAD detection.

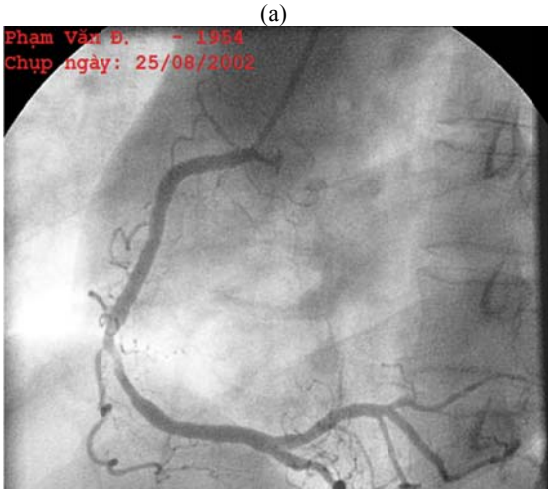
We regconized that sensitivity of our study is higher than sensitivity of Berman DS. Study (94,6% with 91%), however, specificity of our study is lower than specificity of Berman DS. study (70% with 75%). Rejection some cases with negative myocardial perfusion SPECT and subsequently without PTCA was one of causes to explain this difference, which was referral bias [10, 12, 13, 20].

Rest Tl-201 and stress Tc99m mibi myocardial perfusion SPECT study of Heo et al revealed 77% sensitivity and 65% specificity, that is lower than sensitivity and specificity in our study. Heo's study was comprised of suspected ischemic heart disease and non-significant stenosis of CA, which effected on value of sensitivity and specificity [11].

Some authors proposed value "normalcy rate"



(a)



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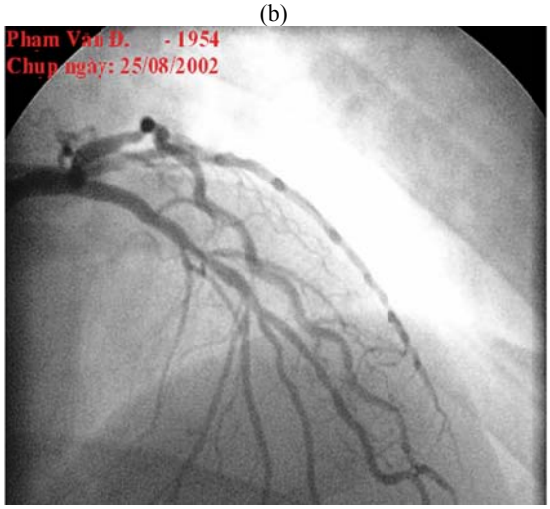

(c)

Fig. 3 A, Stress and rest myocardial perfusion Dual Isotopes SPECT images obtained with Thallium -201 and Tc mibi 99m study in a 48-year-old man with a history of hypertension and dyslipidemia demonstrating severe ischemia in the inferior wall and apex corresponding to the severe stenosis of middle LAD (B) and middle RCA (C).

calculated same as specificity but adds case numbers with negative SPECT and without PTCA, so that usually normal rate is higher that specificity.

Our study had 44 cases with positive SPECT, in which 35 cases with positive PTCA (true positive SPECT) and 9 cases with negative PTCA (false positive SPECT). In 9 cases with false positive SPECT, 5 cases have average LVEF 36% (29% to 40%) and average defect index of isotope uptake was 30.

According to author Wu Yen-Wen [26], study on twenty-nine patients with chronic failure (LVEF ≤ 40%), assessment of Tl-201 myocardial SPECT yielded modest value to distinguish nonischemic dilated cardiomyopathy from ischemic cardiomyopathy in patients with chronic heart failure. This technique could not clearly differentiate individual patients [18, 19].

Danias et al. [7] demonstrated that exercise Tc-99m mibi gated SPECT could diffentiate the two conditions by summed stress defect scores without overlap.

Study of Yen-Wen Wu et al. [26] used Tl-201 as the radiotracer demonstrated summed stress defect scores in patients with ischemic cardiomyopathy (mean, 27.9) significantly differed from those in patients with nonischemic cardiomyopathy (mean, 20.6). The decrepancy between the results of Danias et al. and Yen-Wen Wu et al. may be explained by the favourable imaging characteristics of Tc-99m mibi and Tl-201 and population of studies.

In our study, 5 cases of false positive dual isotopes SPECT myocardial perfusion with LVEF ≤ 40% had stress defect score > 27. So that, this result should be considered and 5 cases of positive SPECT myocardial perfusion was false or true.

The mechanisms underlying the production of perfusion defects in dilated cardiomyopathy or heart failure remain unclear. Previous studies showed that nonhomogeneous perfusion defects were associated with myocardial fibrosis.

In 9 cases of false positive SPECT myocardial perfusion, there were 4 cases of hypertension. This was

explained by abnormally blood retension of CA in hypertension patients causing perfusion defecting on SPECT as CA stenosis ≤ 50%.

Our study had 23 cases of negative SPECT myocardial perfusion, in which 2 cases is false negative SPECT myocardial perfusion and true negative SPECT myocardial perfusion. 2 cases of false negative happened on female patients with BMI ≥ 35. This was explained by obesity of patients in our study.

Furthermore, our study also demonstrated sensitivity for diagnosing stenosis of CA. The result showed 94.1% for RCA, 82.8% for LAD and 77.8% for LCx. Our study's result was differed from the result of Wacker Fran J. TH et al. [24, 25] represented that sensitivity for detecting stenosis of LAD is higher this of LCx and RCA (80%, 70% and 63% respectively). Similarly, study of Nishu et al. revealed that sensitivity for diagnosing stenosis of LAD and RCA is same (75%, CA stenosis ≥ 50%) and higher than this of LCx (60%) [21]. However, result of Van Train KF et al. showed that sensitivity for detecting stenosis of RCA is higher than this of LAD and LCx (77%, 69% and 70%, respectively) [24].

So that, majority of results showed that the sensitivity for detecting LAD stenosis was highest. The discrepancy may be explained by cases of false positive SPECT myocardial perfusion regarding to LAD, so that sensitivity for diagnosing LAD decreased subsequently.

In our study, the sensitivity for diagnosing stenosis of LCX is lowest. The detecting perfusion defect segments relating to LCx is more difficulty than these to LAD and RCA, even as using qualitative analysis. This may be explained myocardial segments perfused by LCx is posterior and far from imaging detector and artifacts caused by diaphragm and breast.

In our study, the specificity for diagnosing LCX stenosis was higher than this LAD and RCA stenosis (91.8%, 81.6% and 82%, respectively). The study of Nishu et al. on 101 patients also revealed result same as our study [22].

Sensitivity and specificity in our study were same as or higher than these in studies used mono-isotope SPECT myocardial perfusion scintigraphy [11, 12, 14, 15, 19, 22, 24, 25].

Imaging protocol of rest Tl-201 and stress Tc-99m mibi dual-isotope SPECT myocardial perfusion scintigraphy in our study was conducted among only 2 hours with optimal picture quality, which is significant for solving patient congestion at public urban hospitals in Vietnam.

5. Study Limitations

The generalizability of our findings is a potential limitation, as it is a single-site study. Refferal bias may be effect on specificity in our study. Our study was also limited because the number of patients was not too many.

6. Conclusion

Our study was the first study in Vietnam about 2-hour dual-isotope imaging protocol (rest Tl-201/stress Tc-99m mibi) myocardial perfusion SPECT in detecting of chronic coronary artery disease. The quality SPECT image, perfect imaging parameter as well as short imaging duration lasted only 2 hours is meaningful for solving overcrowded patients in Vietnam's central hospitals.

These results of our study suggest potentially complementary roles of non-invasive technique as dual-isotope myocardial perfusion SPECT scintigraphy in the detection of patients with suspected CAD.

Acknowledgment

There are no financial conflicts of interest for our study.

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