의학석사 학위논문

^{13}N-Ammonia 양전자 방출 단층 촬영을 이용한 휴식기 및 부하기 침습적 생리학적 지표들의 심근 허혈 예측 능력 비교

2017 년 2 월

서울대학교 대학원

임상의과학과

황 도 연

의학석사 학위논문

^{13}N-Ammonia 양전자 방출 단층 촬영을 이용한 휴식기 및 부하기 침습적 생리학적 지표들의 심근 허혈 예측 능력 비교

2017 년 2 월

서울대학교 대학원

임상의과학과

황 도 연

A thesis of the Master's degree

Diagnostic Performance of Resting and Hyperemic Invasive Physiologic Indices to Define Myocardial Ischemia: Validation with ^{13}N-Ammonia Positron Emission Tomography

February 2017

Department of Clinical Medical Sciences
Seoul National University College of Medicine

Doyeon Hwang

^{13}N-Ammonia 양전자 방출 단층 촬영을 이용한 휴식기 및 부하기 침습적 생리학적 지표들의 심근 허혈 예측 능력 비교

지도교수 구 본 권

이 논문을 임상의과학과 석사 학위논문으로 제출함

2016 년 10 월

서울대학교 대학원

임상의과학과

황 도 연

황 도 연의 석사 학위논문을 인준함

2017 년 2 월

위 원 장	김 용 진	(인)
부 위 원 장	구 본 권	(인)
위 원	팽 진 철	(인)

Diagnostic Performance of Resting and Hyperemic Invasive Physiologic Indices to Define Myocardial Ischemia: Validation with ^{13}N-Ammonia Positron Emission Tomography

Abstract

Introductions: Diagnostic performance of invasive physiologic indices was reported to be different according to the reference to define the presence of myocardial ischemia. Therefore, we sought to compare the diagnostic performance of fractional flow reserve (FFR), instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa) using ^{13}N-ammonia positron emission tomography (PET).

Methods: A total of 115 consecutive patients with left anterior descending artery stenosis who underwent both ^{13}N-ammonia PET and invasive physiologic measurement were included. Optimal cutoff values and diagnostic performance of FFR, iFR and resting Pd/Pa were assessed using PET-derived coronary flow reserve (CFR) and relative flow reserve (RFR) as a reference. To compare discrimination and reclassification ability, each index was compared with integrated discrimination improvement (IDI) and category-free net reclassification index (NRI).

Results: All invasive physiologic indices correlated with CFR and RFR (all p values<0.001). The overall diagnostic accuracies of FFR, iFR and resting Pd/Pa were not different for CFR<2.0 (FFR 69.6%, iFR 73.9% and resting

Pd/Pa 70.4%) and RFR<0.75 (FFR 73.9%, iFR 71.3% and resting Pd/Pa 74.8%). Discrimination and reclassification abilities of invasive physiologic indices were comparable for CFR. For RFR, FFR showed better discrimination and reclassification ability than resting indices (relative IDI=1.332 and category-free NRI=0.971 for iFR; relative IDI=1.592 and category-free NRI=1.058 for resting Pd/Pa; all p values<0.001).

Conclusions: The diagnostic performance of invasive physiologic indices showed no differences in the prediction of myocardial ischemia defined by CFR. Using RFR as a reference, FFR showed a better discrimination and reclassification ability than resting indices.

Key Words: coronary artery disease; myocardial ischemia; fractional flow reserve; instantaneous wave-free ratio; ^{13}N-ammonia positron emission tomography

Student Number: 2015-22267

Contents

List of Tables

List of Figures

Abbreviations and Acronyms List

AUC = area under curve

CFR = coronary flow reserve

CI = confidence interval

FFR = fractional flow reserve

IDI = integrated discrimination improvement

iFR = instantaneous wave-free ratio

LAD = left anterior descending coronary artery

MBF = myocardial blood flow

NPV = negative predictive value

NRI = net reclassification index

Pa = aortic pressure

Pd = distal coronary artery pressure

Pd/Pa = distal coronary artery pressure/aortic pressure

PET = positron emission tomography

PPV = positive predictive value

RFR = relative flow reserve

Introduction

Previous studies demonstrated that percutaneous coronary intervention for coronary artery disease is only beneficial in patients with myocardial ischemia.(1, 2) Among invasive physiologic indices, fractional flow reserve (FFR) has been a standard invasive method to detect the lesion-specific myocardial ischemia and commonly used in daily clinical practice.(3-6) In recent years, resting indices such as instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa) were introduced as a simple invasive index to define myocardial ischemia. Three large clinical studies investigated the diagnostic performance of resting index against FFR and reported various range of diagnostic accuracy from 60% to 90%.(7-9) However, the diagnostic performance of FFR and iFR were comparable when the other reference was used to define the presence of myocardial ischemia.(10, 11)

Non-invasive myocardial perfusion imaging plays an important role in determining therapeutic plan for patients with coronary artery disease. The positron emission tomography (PET) has been considered as the most accurate non-invasive myocardial perfusion imaging to define myocardial ischemia.(12) In addition to absolute myocardial blood flow (MBF), perfusion PET scan can provide coronary flow reserve (CFR) and relative flow reserve (RFR).(13, 14) PET-derived CFR and RFR have been regarded as one of gold standard methods to define myocardial ischemia.(13-18) We performed this study to compare the diagnostic performance of FFR, iFR and resting Pd/Pa using PET-derived CFR and RFR as a reference standard.

Methods

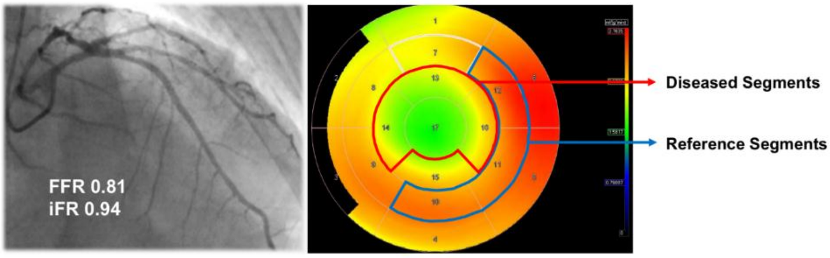
Study Population

The study population was selected from the IRIS FFR registry (NCT01366404). The IRIS FFR registry is a Korean multicenter registry enrolling consecutive patients who underwent FFR measurement for any major epicardial coronary artery. The exclusion criteria were stenosis with Thrombolysis In Myocardial Infarction flow of <3, graft vessel, depressed left ventricular systolic function (ejection fraction<30%), and stenosis that was technically not suitable for FFR evaluation. From June 2011 to September 2015, 144 consecutive patients with available ^{13}N-ammonia PET within 3 months of FFR measurement in left anterior descending coronary artery (LAD) were included in this study. Fifteen patients with poor image quality and 14 patients with unavailable iFR measurement were excluded. All patients were enrolled from Seoul National University Hospital. The study protocol was approved by the institutional review board and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment.

^{13}N-ammonia PET Protocol

The ^{13}N-ammonia PET images were acquired during resting and stress state by continuous intravenous infusion of adenosine (140 ug/kg/min). Adenosine was administered 3 min before the stress scan and low-dose computed tomographic scans were used to correct scatter and attenuation.(19) All patients were informed to refrain from any caffeine or xanthine containing products for 24 hours before scanning and vasodilating medications including nitrate, beta-blocker and calcium channel blocker were also stopped for 24 hours before PET acquisition. The 370 MBq of ^{13}N-ammonia was administrated in resting and stress state into peripheral vein and then list mode dynamic scan was performed by Siemens Biograph-40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). For image analysis and quantification of resting and stress absolute MBF in milliliters per minute per gram of tissue image acquisition, Carimas TM software (Turku PET Centre, Finland) was used.(20)

Figure 1. Representative case of PET-derived CFR and RFR measurement



$$\text{Coronary flow reserve (CFR)} = \frac{\text{Stress MBF in diseased segments}}{\text{Resting MBF in diseased segments}} = \frac{1.99}{0.99} = 1.99$$

$$\text{Relative flow reserve (RFR)} = \frac{\text{Stress MBF in diseased segments}}{\text{Stress MBF in reference segments}} = \frac{1.99}{2.81} = 0.71$$

Quantification of Absolute MBF and Physiologic Indices from ^{13}N-ammonia PET

A two-compartment model was applied to quantify absolute MBF (ml/min/g). The absolute MBF and physiologic indices of a target segment were calculated from PET scan as described previously.(21) The six basal segments in PET images were not quantified due to low counts in membranous interventricular septum and artifacts. CFR was calculated as the ratio of stress MBF to resting MBF in target segments.(13) RFR was calculated as the ratio of stress MBF in target myocardial segments to that of reference myocardial segments.(14, 15, 21) Parametric stress MBF polar maps were used to delineate defect areas in target myocardial segments and to obtain MBF values in those area.(18) The averaged stress MBF in 3 segments with the highest MBF was used as reference hyperemic MBF (Figure 1). In order to compare the diagnostic performance of invasive physiologic indices, CFR<2.0 and RFR<0.75 were used as reference standards to define the presence of myocardial ischemia.(13-15, 22)

Invasive Coronary Angiography and Measurement of Physiologic Indices

Coronary angiography was performed by standard techniques. Angiographic views were obtained following the administration of intracoronary nitrate (100 or 200ug). All angiograms were analyzed at a core laboratory (Seoul National University Hospital) in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical System, Maastricht, Netherlands). The minimal lumen diameter, reference vessel size and lesion length were measured and % diameter stenosis was calculated.

All coronary physiologic measurements were obtained after diagnostic angiography as previously described.(3) Briefly, a 5-7Fr guide catheter without side holes was used to engage the coronary artery. The pressure-temperature sensor guide wire (St. Jude Medical, St. Paul, MN, USA) was zeroed and equalized to aortic pressure and then the pressure sensor was positioned at the distal segment of a target vessel. Intracoronary nitrate (100 or 200ug) was administered before each physiologic measurement. Resting Pd/Pa was calculated as the ratio of mean distal coronary artery pressure (Pd) to mean aortic pressure (Pa) in resting state. Continuous infusion of adenosine (140ug/kg/min) was used to induce hyperemia. Hyperemic Pa and Pd were obtained during sustained hyperemia, and FFR was calculated by mean Pd/Pa during hyperemia. After measurements, the pressure wire was pulled back to the guide catheter and the presence of pressure drift was checked. All FFR readings were collected and validated at the core laboratory (Seoul National University Hospital) in a blinded fashion. iFR was calculated as the mean pressure distal to the stenosis divided by the mean aortic pressure during the diastolic wave-free period. The baseline tracing data of more than 5 heart beats were extracted and then anonymized and coded as ASCII text file. Those data were sent to the iFR core laboratory (Imperial college, London) where iFR was calculated using fully automated algorithms acting over the wave-free period over a minimum of 5 beats.(9)

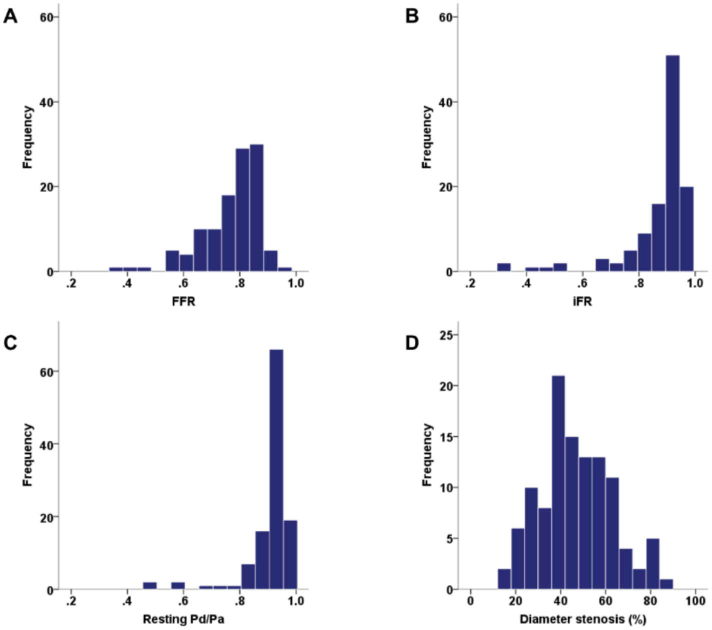
Statistical Analysis

Categorical variables were presented as numbers and relative frequencies. Continuous variables were presented as mean and standard deviation or median with interquartile range according to their distributions which were checked by the Kolmogorov-Smirnov test. Spearman correlation coefficients were calculated to estimate the correlations between invasive physiologic indices and PET-derived CFR and RFR due to the non-normal distributions of FFR, iFR and resting Pd/Pa. The differences of correlation coefficients were tested by the Fisher r-to-z transformation.

The optimal cutoff values of invasive physiologic indices for defining myocardial ischemia were calculated based on maximizing the sum of sensitivity and specificity of each index. Comparison of area under curve (AUC) from receiver operating characteristic curve analysis was performed with DeLong method.(23) Diagnostic performance of invasive physiologic indices were presented with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy. Diagnostic accuracies of FFR, iFR and resting Pd/Pa were compared using McNemar test. To compare discrimination and reclassification ability, each index was compared by absolute and relative integrated discrimination improvement (IDI) index as well as category-free net reclassification index (NRI).(24)

All probability values were two-sided and p value<0.05 was considered statistically significant. The statistical package SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) and SAS software version 9.3 (SAS Institute, Cary, North Carolina) were used for statistical analyses.

Figure 2. Distributions of FFR, iFR, resting Pd/Pa and angiographic % diameter stenosis



Results

Baseline Characteristics and Coronary Physiology Data

Table 1 shows baseline patient and lesion characteristics. The mean age was 63.6±9.0 and 103 patients (89.6%) were male. The mean diameter stenosis was 46.7±16.0% and 58.5% of the lesions had intermediate degree of stenosis. The median (interquartile range values) FFR, iFR and resting Pd/Pa values were 0.81 (0.73-0.85), 0.92 (0.87-0.94) and 0.93 (0.90-0.95), respectively. The distributions of invasive physiologic indices and angiographic lesion severity are shown in Figure 2. The mean values of CFR and RFR by PET were 2.13±0.58 and 0.77±0.09, respectively (Table 1).

Table 1. Baseline patient and lesion characteristics

Patient characteristics (N=115)	
Age, years	63.6 ± 9.0
Male	103 (89.6 %)
Body mass index, kg/m^2	24.6 ± 2.3
Hypertension	79 (68.7 %)
Diabetes mellitus	38 (33.0 %)
Hypercholesterolemia	105 (91.3 %)
Current smoker	19 (16.5 %)
Family history of coronary artery disease	20 (17.4 %)
Prior myocardial infarction	15 (13.0 %)
Left ventricular ejection fraction, %	60.1 ± 6.0
Left anterior descending artery (N=115)	
Quantitative coronary angiography	
Reference vessel diameter, mm	3.0 ± 0.4
Minimum lumen diameter, mm	1.4 ± 0.5
Diameter stenosis, %	46.7 ± 16.0
Lesion length, mm	16.0 ± 9.7
Invasive physiologic indices	
Fractional flow reserve	0.81 (0.73 - 0.85)
Instantaneous wave-free ratio	0.92 (0.87 - 0.94)
Resting Pd/Pa	0.93 (0.90 - 0.95)
PET parameters	

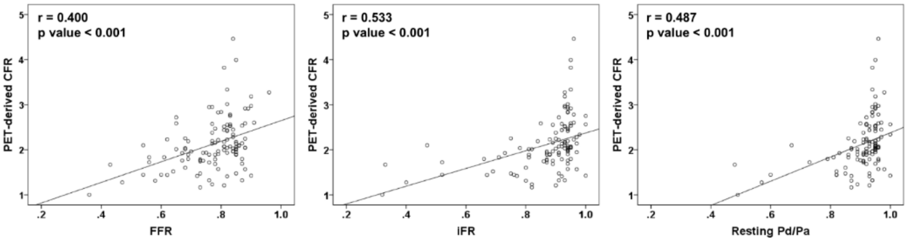
Resting myocardial blood flow, ml/min/g	0.92 ± 0.20
Stress myocardial blood flow, ml/min/g	1.80 ± 0.43
Coronary flow reserve	2.13 ± 0.58
Relative flow reserve	0.77 ± 0.09

Values are mean ± SD, median (interquartile ranges, 25^{th}-75^{th}), or n (%).

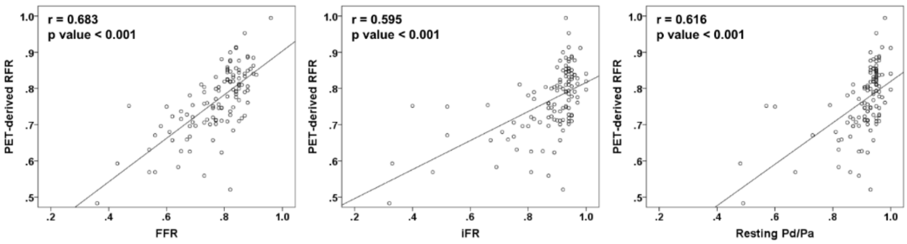
Abbreviations: PET, positron emission tomography; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 3. Correlations between invasive physiologic indices and PET-derived parameters

A. Correlations with PET-derived CFR



B. Correlations with PET-derived RFR



Correlations between Invasive Physiologic Indices and PET-derived CFR and RFR

The invasive physiologic indices showed positive correlations with both PET-derived CFR and RFR (Figure 3). The degree of correlation among the FFR, iFR and resting Pd/Pa was not different for both CFR and RFR (Table 2). The trend was the same with the relationship between stress MBF and invasive physiologic indices (Figure 4 and Table 2).

Figure 4. Correlations between invasive physiologic indices and stress MBF

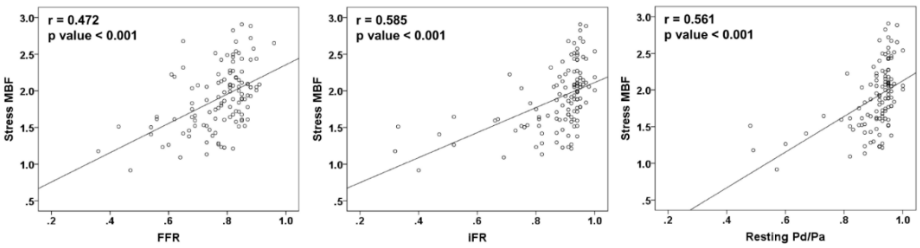


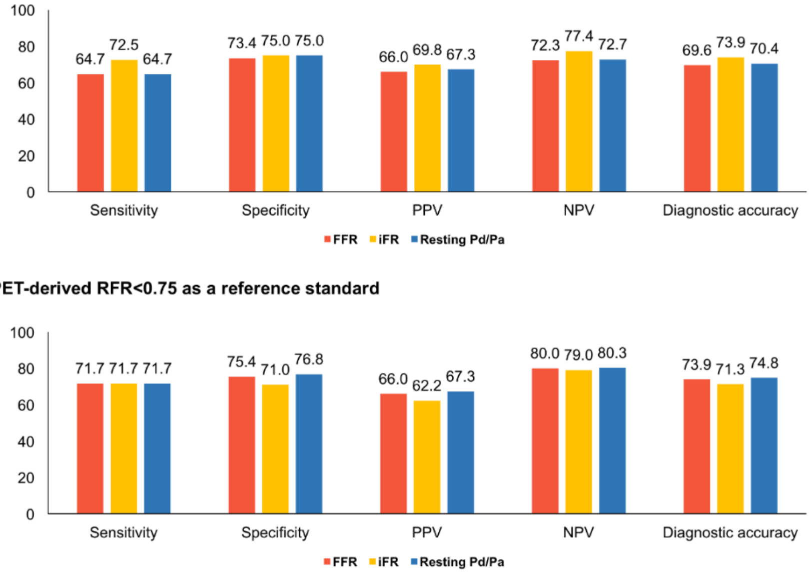
Table 2. Comparison of correlation coefficients among invasive physiologic indices with PET-derived CFR, RFR and stress MBF

	Correlation with FFR	Correlation with iFR	z score	p value
CFR	0.400	0.533	-1.28	0.201
RFR	0.683	0.595	1.12	0.263
Stress MBF	0.472	0.585	-1.18	0.238
	Correlation with FFR	**Correlation with resting Pd/Pa**	**z score**	**p value**
CFR	0.400	0.487	-0.81	0.418
RFR	0.683	0.616	0.87	0.384
Stress MBF	0.472	0.561	-0.91	0.363
	Correlation with iFR	**Correlation with resting Pd/Pa**	**z score**	**p value**
CFR	0.533	0.487	0.47	0.638
RFR	0.595	0.616	-0.25	0.803
Stress MBF	0.585	0.561	0.27	0.787

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MBF, myocardial blood flow; PET, positron emission tomography; RFR, relative flow reserve; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 5. Diagnostic performance of invasive physiologic indices

A. PET-derived CFR<2.0 as a reference standard



Optimal Cutoff Values and Diagnostic Accuracies of Invasive Physiologic Indices

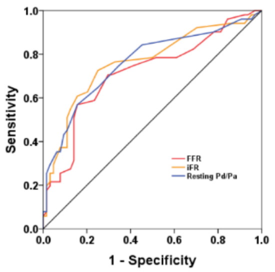
The optimal cutoff values of FFR, iFR and resting Pd/Pa for defining myocardial ischemia were calculated using CFR (<2.0) and RFR (<0.75) as reference standards. The optimal cutoff values of FFR, iFR and resting Pd/Pa were 0.79, 0.92 and 0.93 using CFR as a reference standard. The optimal cutoff values of FFR, iFR and resting Pd/Pa for RFR<0.75 were the same as CFR<2.0.

With CFR as a reference, the sensitivity, specificity, PPV, NPV and diagnostic accuracy of FFR were 64.7%, 73.4%, 66.0% 72.3% and 69.6%, respectively. Those of iFR were 72.5%, 75.0%, 69.8%, 77.4% and 73.9% and those of resting Pd/Pa were 64.7%, 75.0%, 67.3%, 72.7% and 70.4%, respectively (Figure 5A). With RFR as a reference, the diagnostic accuracies of FFR, iFR and resting Pd/Pa were 73.9%, 71.3%, and 74.8%, respectively

(Figure 5B). There was no difference in diagnostic accuracies among 3 physiologic indices for both CFR (p value=0.359 for FFR vs. iFR, p value=1.000 for FFR vs. resting Pd/Pa) and RFR (p value=0.648 for FFR vs. iFR, p value=1.000 for FFR vs. resting Pd/Pa).

Figure 6. ROC curve analysis using PET-derived parameters as reference standards

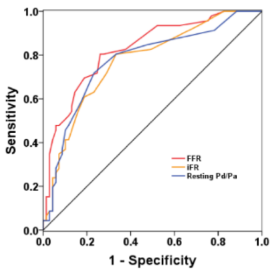
A. PET-derived CFR<2.0 as a reference standard



	AUC	95% CI	p value
FFR	0.716	0.619-0.813	<0.001
iFR	0.762	0.671-0.854	<0.001
Resting Pd/Pa	0.761	0.670-0.852	<0.001

Reference	Testing	Difference between areas	p value
iFR	FFR	0.046	0.133
Resting Pd/Pa	FFR	0.045	0.183
iFR	Resting Pd/Pa	0.001	0.932

B. PET-derived RFR<0.75 as a reference standard



	AUC	95% CI	p value
FFR	0.826	0.749-0.903	<0.001
iFR	0.771	0.684-0.858	<0.001
Resting Pd/Pa	0.774	0.684-0.864	<0.001

Reference	Testing	Difference between areas	p value
iFR	FFR	0.055	0.047
Resting Pd/Pa	FFR	0.052	0.093
Resting Pd/Pa	iFR	0.003	0.836

Discrimination and Reclassification Abilities of Invasive Physiologic Indices

There was no difference in AUC among 3 invasive indices to predict CFR<2.0 (0.716 for FFR, 0.762 for iFR and 0.761 for resting Pd/Pa) (Figure 6A). The AUC for RFR<0.75 was 0.826 (95% confidential interval [CI]: 0.749 to 0.903), 0.771 (95% CI: 0.684 to 0.858) and 0.774 (95% CI: 0.684 to 0.864) for FFR, iFR and resting Pd/Pa, respectively. The AUC of FFR was higher than that of iFR (p=0.047 for comparison) (Figure 6B).

Compared with iFR and resting Pd/Pa, FFR showed comparable discrimination and reclassification ability for determining myocardial ischemia defined by CFR<2.0 (IDI=-0.029, p value=0.138 with iFR; NRI=-0.357, p value=0.057 with iFR; IDI=-0.036, p value=0.051 with resting Pd/Pa; NRI=-0.317, p value=0.091 with resting Pd/Pa) (Table 3). As for RFR<0.75, FFR showed improvement of discrimination and reclassification ability for determining myocardial ischemia compared with resting indices (IDI=0.170, p value<0.001 with iFR; NRI=0.971, p value<0.001 with iFR; IDI=0.183, p value<0.001 with resting Pd/Pa; NRI=1.058, p value<0.001 with resting Pd/Pa) (Table 4).

Table 3. Comparison of discrimination and reclassification abilities of the invasive physiologic indices using PET-derived CFR (<2.0) as a reference standard

Model 1 (Reference)	Model 2 (Testing)	AUC			IDI			NRI (Category-free)	
		Model 1	Model 2	p value	Absolute	Relative	p value	Value	p value
Resting vs. Hyperemia									
iFR	FFR	0.762	0.716	0.133	-0.029	-0.168	0.138	-0.357	0.057
Resting Pd/Pa	FFR	0.761	0.716	0.183	-0.036	-0.201	0.051	-0.317	0.091
Resting vs. Resting									
Resting Pd/Pa	iFR	0.761	0.762	0.932	-0.007	-0.040	0.348	-0.113	0.546

Abbreviations: AUC, area under curve; CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IDI, integrated discrimination improvement; NRI, net reclassification index; PET, positron emission tomography; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Table 4. Comparison of discrimination and reclassification abilities of the invasive physiologic indices using PET-derived RFR (<0.75) as a reference standard

Model 1 (Reference)	Model 2 (Testing)	AUC			IDI			NRI (Category-free)	
		Model 1	Model 2	p value	Absolute	Relative	p value	Value	p value
Resting vs. Hyperemia									
iFR	FFR	0.771	0.826	0.047	0.170	1.332	<0.001	0.971	<0.001
Resting Pd/Pa	FFR	0.774	0.826	0.093	0.183	1.592	<0.001	1.058	<0.001
Resting vs. Resting									
Resting Pd/Pa	iFR	0.774	0.771	0.836	0.013	0.111	0.069	0.159	0.402

Abbreviations: AUC, area under curve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IDI, integrated discrimination improvement; NRI, net reclassification index; PET, positron emission tomography; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure; RFR, relative flow reserve.

Discussion

In this study, we compared the diagnostic performance of FFR, iFR and resting Pd/Pa for the prediction of myocardial ischemia defined by PET-derived CFR and RFR. The main findings of this study were as follows. First, all invasive physiologic indices and PET-derived CFR and RFR showed significant correlations. Second, optimal cutoff values of FFR, iFR and resting Pd/Pa for defining myocardial ischemia defined by PET parameters were 0.79, 0.92 and 0.93, respectively. Third, there were no significant differences in diagnostic accuracies among FFR, iFR and resting Pd/Pa against CFR and RFR. Forth, discrimination and reclassification ability of FFR to define low RFR was better than that of resting indices. These findings imply that the diagnostic abilities of these physiologic indices can be different according to the reference used for the comparison.

Physiologic Indices to Define Myocardial Ischemia

The presence of myocardial ischemia is the key prognostic indicator in patients with coronary artery disease.(1, 2) As coronary angiography has several limitations to define myocardial ischemia, the use of invasive physiologic studies has become more popular.(13, 16, 17) The benefit of FFR has been validated through several clinical studies and FFR is considered as the gold standard for defining lesion-specific myocardial ischemia in daily practice.(3-5, 17) Recently, resting indices such as iFR and resting Pd/Pa which do not require hyperemia have been proposed as a simple alternative for FFR. Previous studies reported various range (60-90%) of diagnostic accuracies of iFR and resting Pd/Pa compared with FFR.(7-9) However, the diagnostic performance can be different according to the reference index used to define myocardial ischemia. Sen et al. reported comparable diagnostic agreement of FFR and iFR when hyperemic stenosis resistance was used as a reference to define myocardial ischemia.(10) Petraco et al. used coronary flow velocity reserve as a reference and showed a better diagnostic discrimination of iFR (iFR AUC, 0.82; FFR AUC, 0.72; p value < 0.001) than that of FFR.(11) In our study, PET-derived CFR and RFR were used as a reference to compare the diagnostic performance between FFR and resting indices. PET has been considered as the gold standard to measure myocardial blood flow and PET-derived CFR and RFR have been thoroughly investigated as non-invasive methods to define myocardial ischemia and prognostic indicator in patients with coronary artery disease.(13-15, 22)

Comparison Between Invasive Physiologic Indices and PET-derived Parameters

FFR, iFR and resting Pd/Pa showed significant correlations with PET-derived parameters, but showed different patterns to the CFR and RFR. With CFR, FFR demonstrated numerically lower correlation coefficient than iFR and resting Pd/Pa. This result is similar to previous study by Petraco et al. which reported a better correlation of iFR with coronary flow velocity reserve than FFR (iFR, r=0.68; FFR, r=0.50; p value for comparison<0.001).(11) Contrary to the CFR, correlation coefficient of FFR with RFR was numerically higher than those of resting indices. The degree of correlation between FFR and RFR from our study was comparable to previous study reported by Stuijfzand et al (FFR vs. RFR, r=0.54, p value<0.01).(14) Considering RFR is a hyperemic index and the concept of RFR is more similar to FFR than that of iFR and resting Pd/Pa, the better correlation between FFR and RFR seems to be natural. These different patterns of correlations with PET-derived parameters between resting and hyperemic physiologic indices suggest that the diagnostic performance of invasive physiologic indices can be different according to the reference standard used for comparison.

Diagnostic Performance of Invasive Physiologic Indices

CFR is the ratio of stress MBF and resting MBF and represents how much myocardial blood flow can be supplied in stress condition compared to that of resting condition.(13, 16) RFR is the ratio of stress MBF in diseased segments and that in normal segments and means the degree of hyperemic flow decrease due to the coronary artery stenosis.(14, 15) Although the concept of CFR and RFR are different, the prognostic value of both parameters have been thoroughly investigated. CFR is the oldest and extensively investigated physiologic index and the prognostic implication of CFR was consistently observed regardless of the methods of measurement, such as invasive flow measurement, stress echocardiography, SPECT and PET.(25-28) The clinical relevance of RFR can be inferred from the well validated FFR studies.(3-5, 15, 26)

Each physiologic index can represent different aspect of myocardial ischemia and has its own strength and weakness.(29) RFR is more epicardial stenosis-specific and CFR is influenced by resting flow condition and microvascular disease status. In this study, we compared the diagnostic performance of resting and hyperemic indices using PET-derived CFR and RFR. Like previous studies, our study results showed the different diagnostic performance of resting and hyperemic indices according to the reference.(10, 11) Although the overall diagnostic accuracy was not different, discrimination and reclassification abilities of FFR were better than resting indices when RFR was used as a reference. Our study showed that FFR, iFR and resting Pd/Pa had similar diagnostic performance when CRF was used as a reference and better discrimination ability of FFR when RFR was used as a reference. Therefore, these differences need to be appreciated when the different invasive physiologic index is used in clinical practice.

Although it is beyond the scope of this study, the demonstration of prognostic implication is the most important aspect in the evaluation of clinical relevance of any diagnostic test. The benefit of FFR-guided revascularization strategy has been well-demonstrated by several clinical studies.(3-5) Ongoing clinical studies which compare the clinical outcomes of FFR-guided and iFR-guided strategies (DEFINE-FLAIR NCT02053038, SWEDEHEART NCT02166736) will provide additional information on the prognostic implication of iFR.

Limitations

This study had several limitations. First, reference standards used in this study are also the surrogate for myocardial ischemia. With the lack of clinically available true gold standard, this limitation can be applied to all clinical studies. Second, PET segmentation by vascular territory can be influenced by individual variations in coronary anatomy. Although the quantification of myocardial blood flow by PET is known to have low intra- and inter- observer variability, myocardial segmentation of target vascular territory in PET image could be different by observers. Third, our study used ^{13}N-ammonia as a PET tracer and the absolute myocardial blood flow measured by different tracers could be different. However, the flow ratio such as CFR or RFR was reported to be relatively constant among different tracers.(30)

Conclusions

The diagnostic performance of invasive physiologic indices showed no difference in the prediction of myocardial ischemia defined by CFR. Using RFR as a reference standard, FFR showed higher discrimination and reclassification ability than iFR or resting Pd/Pa. The user needs to understand this difference while applying an invasive physiologic index in clinical practice.

References

1. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA. 2007;297(18):1985-91.

2. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation. 2008;117(10):1283-91.

3. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49(21):2105-11.

4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.

5. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.

6. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. EuroIntervention. 2015;10(9):1024-94.

7. Jeremias A, Maehara A, Genereux P, Asrress KN, Berry C, De Bruyne B, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol. 2014;63(13):1253-61.

8. Berry C, van 't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol. 2013;61(13):1421-7.

9. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012;59(15):1392-402.

10. Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration. Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). J Am Coll Cardiol. 2013;61(13):1409-20.

11. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic

Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). Circ Cardiovasc Interv. 2014;7(4):492-502.

12. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012. 2012;59(19):1719-28.

13. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. J Am Coll Cardiol 2012. 2013;62(18):1639-53.

14. Stuijfzand WJ, Uusitalo V, Kero T, Danad I, Rijnierse MT, Saraste A, et al. Relative flow reserve derived from quantitative perfusion imaging may not outperform stress myocardial blood flow for identification of hemodynamically significant coronary artery disease. Circ Cardiovasc Imaging 2015, http://dx.doi.org/ 10.1161/circimaging.114.002400.

15. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation. 1994;89(3):1013-22.

16. Naya M, Tamaki N, Tsutsui H. Coronary flow reserve estimated by positron emission tomography to diagnose significant coronary artery disease and predict cardiac events. Circ J. 2015;79(1):15-23.

17. Berry C, Corcoran D, Hennigan B, Watkins S, Layland J, Oldroyd KG. Fractional flow reserve-guided management in stable coronary disease and acute myocardial infarction: recent developments. Eur Heart J. 2015;36(45):3155-64.

18. Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA, et al. Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: cutoff values and diagnostic accuracy of quantitative [(15)O]H2O PET imaging. J Am Coll Cardiol. 2014;64(14):1464-75.

19. Lubberink M, Harms HJ, Halbmeijer R, de Haan S, Knaapen P, Lammertsma AA. Low-dose quantitative myocardial blood flow imaging using 15O-water and PET without attenuation correction. J Nucl Med. 2010;51(4):575-80.

20. El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82)Rb PET: comparison with (13)N-ammonia PET. J Nucl Med. 2009;50(7):1062-71.

21. Lee JM, Kim CH, Koo BK, Hwang D, Park J, Zhang J, et al. Integrated Myocardial Perfusion Imaging Diagnostics Improve Detection of Functionally Significant Coronary Artery Stenosis by 13N-ammonia Positron

Emission Tomography. Circ Cardiovasc Imaging 2016, http://dx.doi.org/10.1161/circimaging.116.004768.

22. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334(26):1703-8.

23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.

24. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27(2):157-72.

25. Chamuleau SA, Tio RA, de Cock CC, de Muinck ED, Pijls NH, van Eck-Smit BL, et al. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol. 2002;39(5):852-8.

26. Marques KM, Knaapen P, Boellaard R, Lammertsma AA, Westerhof N, Visser FC. Microvascular function in viable myocardium after chronic infarction does not influence fractional flow reserve measurements. J Nucl Med. 2007;48(12):1987-92.

27. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM, et al. Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol. 2009;54(2):150-6.

28. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Molinaro S, Picano E, et al. Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. JACC Cardiovasc Imaging. 2012;5(11):1079-85.

29. Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? JACC Cardiovascular Imaging. 2012;5(2):193-202.

30. Tahari AK, Lee A, Rajaram M, Fukushima K, Lodge MA, Lee BC, et al. Absolute myocardial flow quantification with (82)Rb PET/CT: comparison of different software packages and methods. Eur J Nucl Med Mol Imaging. 2014;41(1):126-35.

Figure Legends

Figure 1. Representative case of PET-derived CFR and RFR measurement

The patient had a stenosis in LAD and iFR and FFR were 0.94 and 0.81, respectively. For PET parameters, parametric stress MBF polar map was used to delineate defect areas and obtain MBF values in target myocardial segments (Red line). The averaged stress MBF in 3 segments with the highest MBF was used as reference MBF (Blue line). In this patient, PET-derived CFR and RFR were 1.99 and 0.71, respectively.

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; LAD, left anterior descending artery; MBF, myocardial blood flow; PET, positron emission tomography; RFR, relative flow reserve.

Figure 2. Distributions of FFR, iFR, resting Pd/Pa and angiographic % diameter stenosis

Histograms of distributions of FFR (A), iFR (B), resting Pd/Pa (C) and diameter stenosis (D) are shown.

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 3. Correlations between invasive physiologic indices and PET-derived parameters

Scatter plots show that CFR has significant correlations with FFR, iFR and resting Pd/Pa (A). And also, for RFR, there are significant correlations with FFR, iFR and resting Pd/Pa (B).

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; PET, positron emission tomography; RFR, relative flow reserve; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 4. Correlations between invasive physiologic indices and stress MBF

Scatter plots show that stress MBF has significant correlations with FFR, iFR and resting Pd/Pa.

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MBF, myocardial blood flow; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 5. Diagnostic performance of invasive physiologic indices

Diagnostic performance of FFR, iFR and resting Pd/Pa were compared using CFR (A) and RFR (B) as reference standards for predicting myocardial ischemia.

Abbreviations: CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NPV, negative predicted value; PPV, positive predictive value; RFR, relative flow reserve; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

Figure 6. ROC curve analysis using PET-derived parameters as reference standards

Comparison of ROC curves of FFR, iFR and resting Pd/Pa to predict CFR<2.0 is shown and AUCs are presented (A). Also, with RFR<0.75 as a reference standard to predict myocardial ischemia, ROC curves of FFR, iFR and resting Pd/Pa are compared (B).

Abbreviations: AUC, area under curve; CI, confidential interval; CFR, coronary flow reserve; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, relative flow reserve; ROC, receiver operator characteristic; resting Pd/Pa, resting distal coronary artery pressure/aortic pressure.

^{13}N-Ammonia 양전자 방출 단층 촬영을 이용한 휴식기 및 부하기 침습적 생리학적 지표들의 심근 허혈 예측 능력 비교

국문 초록

서론: 심근 허혈을 진단하는 침습적 생리학적 지표들의 진단 능력은 심근 허혈의 기준을 무엇으로 하느냐에 따라 다르게 보고되고 있다. 따라서 본 연구에서는 ^{13}N-Ammonia 양전자 방출 단층 촬영을 이용하여 심근 허혈을 진단하는 침습적 생리학적 지표로 잘 알려진 fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), 그리고 resting distal coronary artery pressure/aortic pressure (resting Pd/Pa) 들의 심근 허혈을 진단하는 능력을 비교하고자 한다.

방법: 본 연구에서는 좌전하행동맥에 협착이 있는 환자들 중 ^{13}N-Ammonia 양전자 방출 단층 촬영과 침습적 생리학적 검사를 시행한 115 명의 환자를 대상으로 하였다. FFR, iFR 그리고 resting Pd/Pa 의 심근 허혈을 진단하는 능력은 양전자 방출 단층 촬영을 통해 구할 수 있는 coronary flow reserve (CFR) 과 relative flow reserve (RFR) 을 각각 이용하여 평가하였다. 심근 허혈을 감별하는 능력과 재분류하는 능력을 종합적으로 비교하기 위해 integrated discrimination improvement index (IDI) 와 net reclassification index (NRI) 라는 통계적인 방법을 사용하였다.

결과: 심근 허혈을 진단하는 침습적 생리학적인 지표들은 모두 CFR 과 RFR 과 유의한 양의 상관관계를 보였다 (all p values<0.001). FFR, iFR 그리고 resting Pd/Pa 간의 심근 허혈에 대한 진단 정확도는 CFR<2.0 을 심근 허혈의 기준으로 할 때와 (FFR 69.6%, iFR 73.9% and resting Pd/Pa 70.4%) RFR<0.75 를 심근 허혈의 기준으로 할 때 (FFR 73.9%, iFR 71.3% and resting Pd/Pa 74.8%) 모두 유의한 차이를 보이지

않았다. 심근 허혈을 감별하는 능력과 재분류하는 능력은 CFR 을 심근 허혈의 기준으로 하였을 때는 침습적 생리학적인 지표들 간에 차이를 보이지 않았으나, RFR 을 심근 허혈의 기준으로 하였을 때는 FFR 이 휴식기 침습적 생리학적 지표인 iFR 과 resting Pd/Pa 보다 개선된 능력을 보여주었다 (relative IDI=1.332 and category-free NRI=0.971 for iFR; relative IDI=1.592 and category-free NRI=1.058 for resting Pd/Pa; all p values<0.001).

결론: 침습적 생리학적 지표들 간에 심근 허혈을 진단하는 능력은 CFR 을 심근 허혈의 기준을 할 때는 유의한 차이를 부이지 않아다. 하지만 RFR 을 심근 허혈을 기준으로 정의하였을 때는 FFR 이 휴식기 지표들에 비해 개선된 심근 허혈을 감별하고 재분류하는 능력을 보였다. 이러한 차이를 이해하는 것은 임상에서 침습적 생리학적인 지표를 적용하는데 있어 필요하다.

주요어: 관상 동맥 질환, 심근 허혈, fractional flow reserve, instantaneous wave-free ratio, 양전자 방출 단층 촬영

학 번: 2015-22267