Myocardial Blood Flow and Flow Reserve in Proximal and Mid-to-Distal Lesions of Left Anterior Descending Artery Measured By N-13 Ammonia PET/CT

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Abstract

Purpose The purpose of this study is to compare the myocardial blood flow (MBF) and flow reserve (MFR) between proximal and mid-to-distal lesions of the left anterior descending artery (pLAD and mdLAD, respectively) using N-13 ammonia positron emission tomography/computed tomography (PET/CT).

Methods Subjects were 11 patients (six men and five women, mean age 64.5 years) with known coronary artery disease (CAD) involving LAD studied by N-13 ammonia PET/CT. They were divided into two groups by the location of stenotic lesions, i.e. pLAD versus mdLAD. Global and regional MBF and MFR were measured and compared. Characteristics of perfusion defects including the number of involved segments, basal area involvement, location, size, and shape were also compared between the two groups.

Results The regional MFR in mid-anterior segment was significantly lower in pLAD group (1.80 ± 0.35 vs 2.76 ± 1.13 for pLAD and mdLAD groups, respectively, $p=0.034$), while global MFR was not different (2.10 ± 1.10 vs 2.34 ± 0.84).

Both stress and rest MBF in LAD territories were not different in both groups. The size of the perfusion defects were significantly larger in pLAD group (44.0 ± 11.5 % vs 21.1 ± 15.8 %, $p=0.041$). Other characteristics such as location, basal area involvement, and shape were not significantly different between two groups.

Conclusions The proximal lesion makes lower MFR in the mid-anterior segment and larger perfusion defect in the LAD territory but comparable MBF compared with mdLAD lesion.

Keywords N-13 ammonia positron emission tomography · Myocardial blood flow · Myocardial flow reserve · Perfusion defect · Left anterior descending artery

Introduction

An optimal treatment of coronary arterial disease (CAD) is based on the selection of treatment strategy, invasive or medical therapy. Myocardial perfusion imaging (MPI) possesses an essential role as a gatekeeper to discriminate those lesions needed to be invasively approached, because unnecessary invasive treatment for coronary stenosis with normal perfusion may lead to unexpected adverse events [1]. In such perspective, many studies to establish the way to find the “culprit” vessel or lesion have been conducted and various assignments of vascular territory to myocardial segments have been introduced [2–5].

But the coronary tree shows a variety of anatomical variations; simple assignment of certain perfusion defect on MPI to a specific coronary branch is frequently inaccurate in clinical fields [3, 6, 7]. Therefore, to accurately predict the location of culprit lesion with MPI, profound evaluation of characteristics of the perfusion defects is needed. Discrimination between proximal and non-

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proximal stenosis in patients with CAD involving the left anterior descending artery (LAD) is of utmost importance because culprit lesion involving proximal coronary artery is related to poorer prognosis [8, 9].

Positron emission tomography (PET) with N-13 ammonia has several advantages, including absolute quantification of myocardial blood flow, repeated imaging with relatively less radiation exposure to patients and improved image quality compared with single photon emission computerized tomography (SPECT) [10–12]. In this study, we investigated the myocardial blood flow (MBF) and the image characteristics of the perfusion defects, for correct assignments of myocardial perfusion to coronary anatomy. We aimed to compare the characteristics of flow and perfusion on N-13 ammonia PET by the location of the stenosis in the LAD.

Materials and Methods

Patients

Among total 25 patients who underwent N-13 ammonia PET-computerized tomography (CT), CT coronary angiography (CTCA) and invasive coronary angiography (CAG) within 1 month of interval, 11 patients with stenosis involving LAD were selected who were six men and five women with the mean age of 64.5 ± 12.0 years old. Exclusion criteria included previous percutaneous coronary intervention (PCI) such as balloon dilation or stent insertion in LAD, contraindicated to use of vasodilator or radiocontrast, and patients with stenoses involving both the proximal and mid-to-distal LAD at the same time. They were divided into two groups by the location of stenosis: three patients with stenoses in proximal LAD (pLAD group), and eight patients with stenoses in mid-to-distal LAD (mdLAD group). The borderline of proximal and mid-to-distal LAD was the origin of the first diagonal branch, as previously suggested [5, 13]. The severity of stenosis was $>50\%$ in all cases, and anomaly of coronary arterial origin or course was not observed. One patient had ramus intermedius stenosis with mid-LAD stenosis. Characteristics of individual cases are listed in Table 1.

This study was approved by the Chonnam National University Hospital Institutional Review Board.

N-13 Ammonia PET

The patients were informed to fast more than 4 h. Methyl-xanthine derivatives, including caffeine, were abstained at least for 24 h before PET acquisition. Vasodilator medications such as nitrate, beta-blocker or calcium channel blocker were also stopped for 24 h before PET acquisition [14]. For all patients, an appropriate history and informed consent were obtained.

An intravenous line was placed in the patient's radial vein, followed by a low-dose CT scan (120 kVp, 30 mA) for attenuation correction. Then, 11 MBq/kg (0.3 mCi/kg) of N-13 ammonia was injected as a bolus within 15 s. Dynamic scan for 6 min and electrocardiogram (ECG)-gated scan for 13 min followed for rest imaging data [15]. After 1 hour, additional intravenous line was placed in radial vein of the opposite side to N-13 ammonia infusion line, and 0.14 mg/kg/min of adenosine was intravenously infused for 6 min for vasodilator stress. N-13 ammonia was injected at peak stress (3 min after the infusion had started). Then, stress imaging was done with the same dose and protocol as described above. The image acquisition was performed by a dedicated PET scanner with BGO crystal and eight-slice CT scanner (Discovery ST; GE Healthcare, USA), and image reconstruction was performed using ordered subset expectation maximization (OSEM) iterative reconstruction.

CT Coronary Angiography (CTCA)

The CT acquisitions were performed with a two-phase, contrast-enhanced, ECG-gated, multi-detector CT scanner (Sensation Cardiac 64; Siemens, Forchheim, Germany). Section thickness was 0.75 mm, gantry rotation time was 330 ms and the tube current was 800 mAs at 120 kVp. The pitch was determined as 0.2. Serial CT scanning in the axial plane was performed from the level of the left ventricular apex after a bolus injection of 60 ml nonionic contrast medium (Ultravist 370; Bayer Schering Pharma, Berlin, Germany), followed by a 60-ml saline bolus injection, both of which were injected at 4 ml/s. The axial images were reconstructed at multiple phases that covered the cardiac cycle in increments of 10 % of the RR interval between 5 and 95 %. Multiphase reconstruction was performed by using short-axis slices from the base to the apex of the heart with the use of commercially available software (Argus; Siemens Medical Systems, Erlangen, Germany).

Image Analyses

The rest and stress dynamic imaging data were transferred to Advantage Workstation 4.5 and extracted for myocardial blood flow (MBF) analysis. By using an automated software package (PMOD; PMOD Technologies, Zurich, Switzerland), myocardium was reoriented into short-axis images and segmentation was performed according to a 17-myocardial segment model [2, 16] as shown in Fig. 1. A volume of interest (VOI) was defined for each segment and a two-tissue compartment model with only two fitted tissue rate constants, where metabolic trapping of N-13 ammonia was assumed as an

Table 1 Patients characteristics

Patient no.	Age	Sex	Referral impression	Involved vessels	Stenotic site of LAD (stenosis severity)	Previous treatment
1	71	M	Unstable angina	LAD, LCX	Mid (85 %)	None
2	78	M	Unstable angina	LAD, LCX, RCA	Mid (100 %)	None
3	73	F	Unstable angina	LAD, LCX, RCA	Mid (70 %)	Stenting in LCX
4	86	M	Unstable angina	LAD, LCX	Distal (95 %)	Stenting in LCX
5	59	M	Unstable angina	LAD, RCA	Proximal (85 %)	None
6	53	F	Atypical chest pain	LAD, LCX	Distal (60 %)	None
7	72	M	Unstable angina	LAD, RCA	Mid (70 %)	None
8	60	F	Coronary stenosis on CT	LAD	Proximal (55 %)	None
9	51	F	Coronary stenosis on CT	LAD, RCA	Mid and distal (55 %)	None
10	56	M	s/p PCI	LAD, RCA	Proximal (90 %)	Ballooning in LCX
11	51	F	Unstable angina	LAD, LCX	Mid (85 %)	None

CAG coronary angiography, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *PCI* percutaneous coronary intervention

irreversible step. The regional and global LAD territory MBF were calculated as following:

$$\frac{dC_1(t)}{dt} = K_1 C_P(t)(k_2 + k_3)C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

with K_1 corresponding to MBF. The k_3 rate constant corresponding to glutamine formation was converted into a K_1 -dependent value by the relation

$$k_3 = K_1 \left[1.65e^{(1.25/f)} - 1 \right]$$

with the V representing the distribution volume of ammonia in the C_1 compartment, which was assumed to be

constant ($V=0.8$). In contrast to Choi's method [17], this model incorporates not only a spillover from the left ventricle, but for septal regions also from the right ventricle. The operational equation is then given by

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})(C_1(t) + C_2(t)) + V_{lv}C_{lv}(t) + V_{rv}C_{rv}(t)$$

where

V_{lv} is the spill-over fraction of the blood activity in the left ventricle $C_{lv}(t)$,

V_{rv} is the spill-over fraction of the blood activity in the right ventricle $C_{rv}(t)$.

MFR was defined as the ratio of stress MBF to rest MBF with normal threshold of 2.0 [10].

The polar maps were reconstructed from gated image data, and myocardial segments were defined using the same 17-segment model described above. We analyzed the number of myocardial segments with perfusion defect (a total of seven segments in LAD territory), basal segment (segment 1 or 2) involvement, and characteristics of blacked-out perfusion defects on stress static image using Emory Cardiac Toolbox (Syntermed, Atlanta, USA). The size of perfusion defect was defined as the proportion (%) of perfusion defects to the LAD territory. The location was defined as the segment with the lowest perfusion on stress image by visual analysis. The size of perfusion defect was defined as the proportion (%) of perfusion defects to the LAD territory using Emory Cardiac Toolbox. The shape was determined by two experienced nuclear medicine physicians on polar map images with regards to their exact location and shape demonstrated on fusion images of three-dimensional PET and CTCA. For image analyses on polar map data and fusion data, CardIQ Physio and CardIQ Fusion software (GE Healthcare, USA) were used respectively. The analyses

Fig. 1 The colored areas in the 17-segment model were defined as LAD territory. Name of each segment: 1 basal anterior, 2 basal anteroseptal, 3 basal inferoseptal, 4 basal inferior, 5 basal inferolateral, 6 basal anterolateral, 7 mid-anterior, 8 mid-anteroseptal, 9 mid-inferoseptal, 10 mid-inferior, 11 mid-inferolateral, 12 mid-anterolateral, 13 apicoanterior, 14 apicoseptal, 15 apicoinferior, 16 apicolateral, 17 apex

were limited in the LAD territory. The perfusion defects involving other coronary vessel territories, such as perfusion defects in left circumflex artery (LCX) or right coronary artery (RCA) territories were not included to our analyses.

Statistical Analyses

We compared the regional and global MBF, regional and global MFR, and other characteristics of perfusion defects with dynamic and gated images between pLAD and mdLAD groups. Values are given as mean $\pm$ SD. For statistical comparison, we performed Fisher's exact test for categorical variables, and Mann–Whitney *U*-test for continuous variables. The optimal cutoff value was calculated by ROC curve analysis. For calculations, SPSS version 19.0.0 for Windows (SPSS, Chicago, IL, USA) was used. A *p* value of <0.05 was considered statistically significant.

Results

Myocardial Blood Flow and Flow Reserve

Mean global LAD territory MBF in enrolled patients was 0.98 ± 0.20 ml/min/g at rest, and 2.15 ± 0.89 ml/min/g after stress. Neither global MBF nor regional MBF of LAD territory showed significant difference between pLAD and mdLAD groups (Table 2). However, the MFR in mid-anterior segment (segment 7) was significantly lower in pLAD group compared with mdLAD group (Table 3). Otherwise, no significant difference of MFR was seen between the two groups.

Myocardial Perfusion Defects

All the enrolled cases showed definite perfusion defects in LAD territory but in the basal anteroseptal segment

(segment 2). The number of involved segments was 4.3 ± 0.6 and 2.9 ± 1.1 in pLAD and mdLAD groups, respectively, and failed to achieve statistical significance ($p=0.072$ by Mann–Whitney *U*-test) with none exceeding five, as shown in Table 3. The mean perfusion defect size was significantly larger in pLAD group (44.0 ± 11.5 % vs 21.1 ± 15.8 % for pLAD and mdLAD group, respectively, $p=0.041$ by Mann–Whitney *U*-test). The optimal cutoff value of perfusion defect size for the prediction of pLAD lesion was 31.0 % of LAD territory with sensitivity of 100 % and specificity of 87.5 %. No correlation was found between the severity of LAD stenosis and size of perfusion defects ($r=0.246$, $p=0.466$).

The involvement of basal area was not commonly observed in both groups: only one patient with mid-LAD stenosis (patient no. 7) showed 18 %-sized perfusion defect involving basal anterior wall (segment 1).

The perfusion defect location was either segment 17 (apex) or segment 13 (apico-anterior segment) in every case. In pLAD group, all the locations were found to be segment 17. In mdLAD group, on the other hand, the locations were segment 17 in five cases, and segment 13 in the other three cases. The difference in perfusion defect locations between the two groups did not reach statistical significance ($p=0.339$) by Fisher's exact test (Table 4).

The perfusion defect shapes were classified to two different types: focal defects and defects shaped like single quotation marks ('). In pLAD group, all the cases showed quote-shaped perfusion defects as shown in Fig. 2, which was found in only two out of eight patients of mdLAD group. The difference was not of statistical significance ($p=0.061$ by Fisher's exact test). The quote-shaped perfusion defects on polar map images were observed as corresponding curvilinear defects tracking the course of LAD on the anterior myocardial wall on three-dimensional fusion images in all the five cases. The remaining six patients in mdLAD group showed focal perfusion defects on polar map images and three-dimensional fusion images as well (Fig. 3).

Table 2 Comparison of myocardial blood flow (MBF) between proximal and mid-to-distal LAD lesions

	Rest MBF (ml/min/g)				Stress MBF (ml/min/g)		
	pLAD (n=3)	mdLAD (n=8)	<i>p</i> value		pLAD (n=3)	mdLAD (n=8)	<i>p</i> value
Segment 1 (basal anterior)	0.86 ± 0.25	0.77 ± 0.14	0.480	Segment 1 (basal anterior)	2.04 ± 0.82	2.24 ± 0.55	0.480
Segment 2 (basal anteroseptal)	1.46 ± 0.70	1.05 ± 0.22	0.480	Segment 2 (basal anteroseptal)	3.14 ± 2.32	2.24 ± 0.54	1.000
Segment 7 (mid anterior)	0.99 ± 0.35	0.88 ± 0.20	0.724	Segment 7 (mid anterior)	1.85 ± 0.97	2.29 ± 0.50	0.289
Segment 8 (mid anteroseptal)	0.90 ± 0.27	0.90 ± 0.22	1.000	Segment 8 (mid anteroseptal)	2.11 ± 1.41	2.34 ± 0.34	0.480
Segment 13 (apicoanterior)	0.89 ± 0.35	0.83 ± 0.15	0.724	Segment 13 (apicoanterior)	1.70 ± 1.02	2.00 ± 0.36	0.480
Segment 14 (apicoseptal)	0.96 ± 0.40	1.08 ± 0.43	1.000	Segment 14 (apicoseptal)	1.56 ± 0.84	1.80 ± 0.22	0.480
Segment 17 (apex)	0.76 ± 0.25	1.26 ± 0.94	0.480	Segment 17 (apex)	2.50 ± 1.58	1.60 ± 0.20	0.724

Reference cut-off values of global rest and stress MBF are 0.5 and 1.5 ml/min/g, respectively in author's hospital

pLAD proximal LAD stenosis group, mdLAD mid-to-distal LAD stenosis group

Table 3 Comparison of myocardial flow reserve (MFR) between proximal and mid-to-distal LAD lesions

	Mean regional MFR ^a		
	pLAD (n=3)	mdLAD (n=8)	p value
Segment 1 (basal anterior)	2.34±0.48	3.03±1.18	0.289
Segment 2 (basal anteroseptal)	2.62±2.28	2.17±0.52	0.724
Segment 7 (mid anterior)	1.80±0.35	2.76±1.13	0.034*
Segment 8 (mid anteroseptal)	2.18±0.84	2.71±0.74	0.289
Segment 13 (apicoanterior)	1.83±0.47	2.45±0.62	0.289
Segment 14 (apicoseptal)	1.61±0.15	1.94±0.70	0.480
Segment 17 (apex)	2.85±2.25	1.81±1.00	0.724
Mean global LAD territory MFR			
	pLAD (n=3)	mdLAD (n=8)	p value
	2.10±1.10	2.34±0.84	0.480

Reference cut-off value of regional and global MFR is 2.0 [10]

* $p < 0.05$

^aMFR was defined as the ratio of stress myocardial blood flow to rest myocardial blood flow

Other clinical factors, such as age, sex, and obstruction severity, were not significantly different between the two groups.

Discussion

This study showed that N-13 ammonia PET could discriminate culprit proximal from mid-to-distal lesion of LAD by using regional MFR as well as size of perfusion defect. A culprit lesion is not able to make sufficient blood flow to myocardium and a deranged regional flow reserve, which can be defined as the ability of coronary vessel to adjust its flow volume for the oxygen and energy demands of myocardium. A deranged regional flow reserve can be defined as inability of coronary vessel to adjust its flow volume for the oxygen and energy demands of myocardium. However, the diagnostic value of regional MFR has been a topic of debate for a long time; only few papers demonstrated the diagnostic value of regional MFR [18, 19]. Yoshinaga et al. [18] reported that regional hyperemic MBF and regional MFR were decreased in myocardial segments with ischemia. The difference was even more significant when compared with

MFR; it was useful in discrimination of both ischemic versus non-ischemic myocardium and CAD patients versus normal subjects, while MBF itself was not useful in discrimination of ischemic versus non-ischemic myocardial segment. Discrimination of proximal and mid-to-distal LAD stenosis was also a topic in a previous study [19] in which the authors used Doppler wave for measurement of MFR. Similarly to our work, pLAD stenosis showed relatively lower MFR which was measured in LAD and coronary sinus. Interestingly pLAD group showed the lowest MFR in apicoseptal segment (segment 14) but the lowest relative uptake in apex. This discrepancy results from the correction of myocardial blood flow of a specific myocardial segment by the mass of myocardium ("ml/min/g"). While the thinnest wall of apex leads to lowest uptake by partial volume effect on polar maps.

The number of involved segments has been used as the size of perfusion defects in several studies [20, 21], but it may account simply for an overlapped position of perfusion defect on border of adjacent myocardial segments. For that reason, the perfusion defect size per se can be different from the number of segments involved. We also performed the

Table 4 Comparison of characteristics between patient groups with proximal and mid-to-distal LAD lesions

	pLAD (n=3)		mdLAD (n=8)		p value
Age (years)	58.3±2.1		66.9±13.5		0.539
Sex (M:F)	2:1		4:4		0.576
Involved segments	4.3±0.6		2.9±1.1		0.072
Perfusion defect size ^a	44.0±11.5 %		21.1±15.8 %		0.041*
Basal area involvement	0/3 (0 %)		1/8 (12.5 %)		0.727
Perfusion defect location (n) ^b	Segment 17	3	Segment 17	5	0.339
	Segment 13	0	Segment 13	3	
Quote-shaped perfusion defect	3/3 (100 %)		2/8 (25 %)		0.061
Stenosis severity	75.0±21.8 %		76.9±17.3 %		0.918

^aSize was defined as the proportion of pixels with perfusion defect to total LAD territory pixels

^bThe location was defined as the segment showing the lowest perfusion on stress image

Fig. 2 Coronary angiography (a) of a 59-year-old man shows 85 % stenosis of proximal LAD. A quote-shaped perfusion defect with size of 43 % of LAD territory is noted on polar map image (b). Perfusion defect along the anterior wall on three-dimensional PET (c) follows the path of LAD, which is also illustrated on the fusion images of PET and coronary CT angiography (d)

analysis of proportion of perfusion defect to LAD territory by automated quantitative perfusion defect size analysis and concluded that the sizes of the perfusion defects of pLAD

lesions were significantly larger than those of mdLAD lesions, while the number of involved segments was not significantly different between two groups.

Fig. 3 Coronary angiography (a) of a 51-year-old woman shows 70 % stenosis of mid-LAD. A focal perfusion defect with size of 22 % involving apical wall is shown on polar map image (b). It is also shown as a focal defect on three-dimensional PET (c) and fusion image of PET and CT coronary angiography (d)

The relation between stenosis location and perfusion defect size was also demonstrated in a previous study conducted by Mahmarian et al. [22], and it is consistent with our results. They analyzed the results of CAG and TI-201 myocardial SPECT in 158 patients with single-vessel disease and a considerable range of severity of stenosis. They found that the perfusion defect size was larger in pLAD than mdLAD stenosis, where the size was defined as percent abnormal perfusion area to total left ventricle, similar to our methods. They also reported that perfusion defects were larger in severe stenosis than in moderate stenosis, but the correlation between perfusion defect size and stenosis severity was very weak ($r=0.38$). They suggested heterogeneity in perfusion defect size was considered to be the reason for weak correlation. The heterogeneity of perfusion defect size was also observed in our study showing no correlation between severity of coronary stenosis and perfusion defect size.

The pLAD group showed no involvement of basal areas despite of significantly larger sizes of their perfusion defects. Considering the report by Donato et al. [2], which emphasized an exclusive predominance (>95 %) by LAD in basal segments of anterior and antero-septal wall, the normal perfusion in basal segments in the pLAD group might have been resulted from preserved perfusion from left main branch. The perfusion defect in the lateral portion of basal anterior segment in a patient with mid-LAD stenosis can be associated with combined stenosis of the first diagonal branch (Supplementary Fig. 4).

The shape of perfusion defect tended to be different between pLAD and mdLAD groups. The negative predictive value was 100 % when the single quotation mark shape was applied as a criterion for predicting proximal LAD lesion. In terms of shape of perfusion defects, polar map analysis has a limitation because the three-dimensional myocardial volume is deviated to be fitted in a circular map without regards to individual variation in heart size and shape. With those concerns, hybrid imaging strategies of radionuclide imaging with CT or magnetic resonance imaging are getting more attention from researchers [3, 23, 24]. Also in this study, we were able to more accurately specify the shape and location of perfusion defects by comparing them on both polar map images and three-dimensional fusion images.

There are several limitations in this study. First, the sample size is small. But our observation well matches with the previous works with myocardial SPECT [22, 25]. More sophisticated evaluation of MBF and perfusion defects will be possible in a large-scaled study in the future. Second, most of the enrolled patients were diagnosed with multi-vessel disease. Our data from multi-vessel disease patients were directly compared with other studies derived from subjects with single-vessel diseases. But we chose the LAD territory because it was demonstrated to be LAD-dominant in several

studies [2, 26]. Hemodynamic change can still be a problem because multi-vessel disease induces coronary steal phenomenon via collateral circulation [27], which was not definitely observed in our patients. However, the exact effects of hemodynamic change in multi-vessel disease on findings of MPI are yet to be completely known and should be studied in the future. The MBF heterogeneity might affect the regional MFR we investigated as concerned by some reports [10, 28]. In this study the regional MFR was generally lower in pLAD stenosis throughout the LAD territory compared with mdLAD stenosis with two exceptions (segments 2 and 17), indicating its diagnostic implication in CAD.

In conclusion, the proximal lesion makes lower MFR in the mid-anterior segment and larger perfusion defect, while making comparable MBF to the LAD territory compared with mdLAD lesion. N-13 ammonia PET/CT is a useful tool to evaluate regional myocardial flow disturbance of each coronary lesion and can guide the treatment of CAD properly by clarifying the location of stenosis by proximal versus mid-to-distal LAD.

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