

# Relationship between reversibility score on corresponding left ventricular segments and fractional flow reserve in coronary artery disease

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## ABSTRACT

**Objective:** The objective of this study was to find the correlation between the severity of perfusion abnormality detected by scintigraphy and the FFR value, as well as the localization of a particular coronary lesion. On the basis of FFR values and the corresponding left ventricular segments, we proposed a combined index to aim for better correlation with myocardial ischemia than the FFR parameter alone.

**Methods:** Twenty-eight patients (male: 22, female: 6, age  $62 \pm 7.62$ ) having FFR measurements and myocardial perfusion SPECT studies were enrolled in our retrospective analysis. FFR measurements on 36 vessels (20 LAD, 6 LCx, 10 RCA) with intermediate stenosis (40%-60%) were compared to the Tc-99m SestaMIBI myocardial perfusion SPECT studies. SPECT studies were performed before the invasive procedure in all cases. We introduced a new ischemic index, the left ventricular ischemic index (LVli), by combining FFR values with the number of corresponding myocardial segments (N) [ $LVli = N \times (1 - FFR)$ ]. This index correlated with the regional myocardial perfusion defects identified on the scintigrams. A perfusion reversibility score of 2 or above was considered indicative of active ischemia (regional difference score: rDSc). For the statistical analysis, we used linear regression analysis and receiver operating characteristic (ROC) curve analysis to compare the different parameters.

**Results:** A close linear relationship was found between the LVli and rDSc values ( $p < 0.001$ ) with linear regression analysis. When analyzing all FFR values independently of the localization of the lesions, they also correlated significantly to the rDSc, but this relation was not as close. LVli predicted active ischemia ( $\geq 2$  rDSc) on myocardial scintigraphy with 78% sensitivity and 94% specificity when the cutoff value was set to 0.96. FFR alone predicted ischemia on scintigraphy with 72% sensitivity and 94% specificity at the best 0.8 cut-off value. The area under the ROC curve was significantly higher for LVli than FFR (0.94 vs. 0.87;  $p < 0.05$ ).

**Conclusion:** The scintigraphic data indicate that an LVli  $> 0.96$  implies a clinically relevant stenotic lesion. In our opinion, FFR values, weighted with the corresponding left ventricular segments, should be taken into consideration for the best clinical decision-making.

(*Anatol J Cardiol* 2015; 15: 469-74)

**Keywords:** FFR, Technetium-99m SestaMIBI, myocardial SPECT, LVli

## Introduction

For years, one of the most sensitive diagnostic modalities for diagnosing coronary artery disease (CAD) was myocardial perfusion imaging (MPI). MPI is a well-established method for obtaining functional information of the myocardium. Furthermore, it is well known that stable angina patients with normal MPI study have a low risk of fatal cardiovascular events (1, 2).

The perfusion imaging technique detects relative myocardial perfusion. The myocardial distribution of the isotope is proportional to the perfusion and can be summarized on the polar map display of the entire left ventricle.

In 1994, invasive coronary pressure measurements were validated with positron emission tomography (PET) (3). This method suggested that the manipulation of the wire into the coronary tree is easy and safe (3). Pijls et al. (4) presented that the determination of fractional flow reserve (FFR) was comparable with standard non-invasive tests for myocardial ischemia. An FFR value  $< 0.75$  implied significance and correlated strongly with non-invasive ischemia in further publications (5-8). The latest studies confirm the clinical relevance of FFR values in single-vessel (DEFER study) (9) and multivessel disease (FAME study) (10).

FFR can be calculated from actual measured flow (in the stenotic vessel) and achievable maximal flow (in a normal ves-

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**Accepted Date:** 11.06.2014 **Available Online Date:** 11.07.2014

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DOI:10.5152/akd.2014.5500



sel) in the relevant coronary artery. At maximal arteriolar vasodilatation, a close linear relationship can be found between coronary flow and pressure. The invasively measured FFR value, calculated as a pressure ratio of the distal and proximal pressure (Pa/Pd), shows the fraction of achievable flow through the stenotic coronary artery, indicating the functional severity of the coronary lesion. The translesional pressure gradient must be evaluated at maximal hyperemia by a wire with a pressure sensor at the tip during FFR measurements (11).

When non-invasive stress imaging is unavailable, the measurement of FFR on coronary lesions with intermediate severity is helpful. According to the current ESC guidelines, the indication of percutaneous coronary interventions is based on the determination of FFR when functional information of moderate coronary stenosis is lacking (12). It is a simple, reliable, and reproducible method (13), but the FFR value itself does not reflect the localization of the stenosis.

The aim of this study was to search for the correlation between the severity of perfusion abnormality detected by scintigraphy and FFR value, as well as the localization of a particular coronary lesion. Based on our hypothesis, a combined index using FFR values and the corresponding left ventricular segments gives a better correlation with myocardial ischemia than the FFR parameter alone.

## Methods

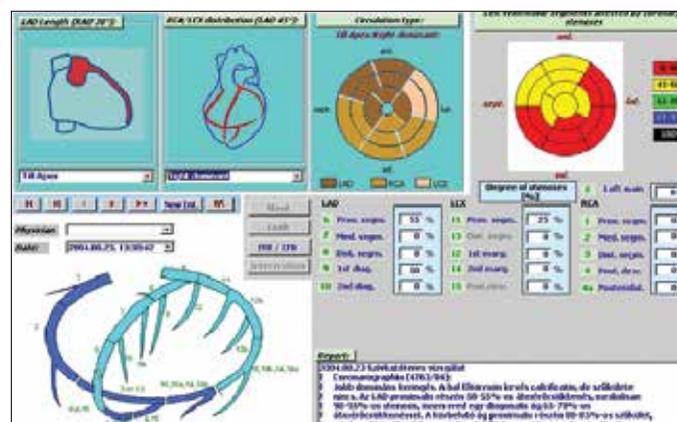
The coronary angiograms of 28 patients (male: 22, female: 6, age 62±7.6) were analyzed using Holistic Coronary Care (HCC-Coronart Ltd., Debrecen, Hungary) (14). The software registered 23 epicardial coronary segments using the modified SYNTAX (15) segmentation system. The supplied left ventricular segments on the standard 17-segment polar map were rendered to each coronary branch by an appropriate algorithm (Fig. 1).

All 28 patients had stress/rest SPECT acquisition followed by FFR measurements within 6 (100.6±31 days). The patients' anamnestic data are shown in Table 1. Regarding pressure wire measurements, commonly, one vessel was examined in one patient; however, 2 vessels/patient and 3 vessels/patient were measured in 6 cases and in one case, respectively. In every case, one stenosis was studied in one vessel. Measurements were performed in all intermediate stenoses (40%-60%) except on the culprit vessels of prior myocardial infarctions. Thus, 36 vessels with 36 intermediate stenoses were compared with the myocardial perfusion SPECT studies. We introduced a new ischemic index by combining the FFR value with the number of corresponding myocardial segments (N) determined by HCC software: the left ventricular ischemic index [LVli=N x (1-FFR)]. This index was correlated with the regional myocardial perfusion defects identified on the scintigrams. A regional perfusion reversibility score, which was calculated automatically from the regional summed stress and regional summed rest scores, of 2 or above was considered indicative of active ischemia (regional

**Table 1. Patients' anamnestic data**

Variable	Patients (n=28)
Mean age	62±7.6 years
Male	22 (78%)
Female	6 (22%)
Severity of disease based on coronary angiography	
1-vessel disease	5 (18%)
2-vessel disease	13 (46%)
3-vessel disease	10 (36%)
Prior myocardial infarction based on anamnestic data	
Diabetes mellitus	7 (25%)
Smoking habit	4 (14%)
Hypertension	17 (60%)
Dyslipidemia	5 (17%)
Prior coronary artery bypass graft surgery	1 (3%)

Cx - circumflex artery; FFR - fractional flow reserve; LAD - left anterior descending artery; LVli - left ventricular ischemic index; RCA - right coronary artery



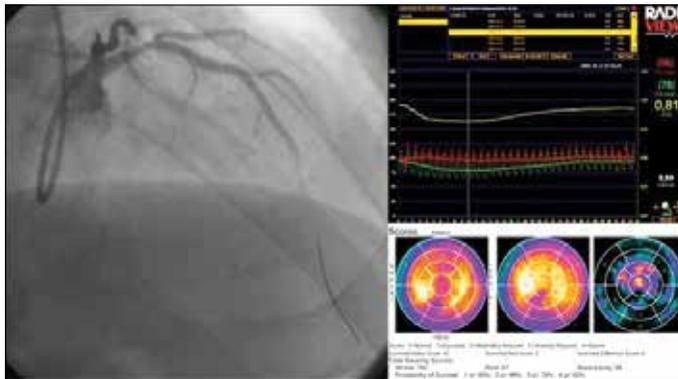
**Figure 1. The lesion-associated segments on the polar map of the HCC (Holistic Coronary Care)**

Difference Score: rDSc). Regional segments on the scintigram were the same as those determined by HCC.

### Coronary angiography and FFR measurement

Cardiac catheterization was performed under local anesthesia from the femoral or radial approach. The image acquisition was executed by an Axiom Artis (Siemens Medical Solutions of Siemens AG, Erlangen, Germany) X-ray machine at a speed of 15 frames/second.

During cardiac catheterization, a 6 F guiding catheter without side holes was positioned at the orifice of the left or right coronary artery to detect the proximal (aortic) pressure without damping. The distal pressure was recorded by a pressure-sensor guide-wire (PressureWire Certus, Radi Medical, Uppsala, Sweden), advanced at about 3 cm distally from the stenosis. Maximal hyperemia was induced by an intracoronary injection



**Figure 2.** Example of an LAD proximal lesion with a negative FFR value and apical reversible perfusion defect on the bull's eye polar map. The coronary angiogram shows the pressure wire in the LAD with 55% proximal stenosis (left). During maximal vasodilatation induced by intracoronary injection of adenosine, an FFR value of 0.81 was measured (right on the top). Despite the non-significant FFR value, reversible perfusion defects were found in the LAD territory on SPECT just before performing invasive coronary angiography (right bottom)

FFR - fractional flow reserve; LAD - left anterior descending artery; SPECT - single-photon emission tomography

of 100 micrograms of adenosine. The aortic pressure at the guide tip (Pa) and distal coronary pressure (Pd) were measured simultaneously (Fig. 2). The FFR value was calculated as the ratio of these pressures: Pa/Pd.

### Exercise perfusion scintigraphy

A separate-day non-gated stress/rest perfusion scan protocol was performed before FFR-guided PCI in all cases. The patients had fasted overnight. Coffee and medication containing caffeine or aminophylline were withdrawn for at least 12 hours. Approximately 400-450 MBq technetium-99m SestaMIBI was injected intravenously for stress (3 minutes after the dipyridamole injection) and on another day at the same doses for rest acquisition, respectively. Acquisition was initiated 60-90 minutes after the injections. Data acquisition was performed with a double-headed Cardio-C camera (Mediso Ltd., Budapest, Hungary). The energy discrimination was centered on 140 keV with a 20% window; 64 projections were acquired on 180° using a high-resolution collimator, with 64x64 matrices. Short-axis slices were reconstructed using InterviewXP (Mediso Ltd., Budapest, Hungary), and then, the Emory Cardiac ToolBox 3.0 was applied for quantitative analysis using 17 segments. A severity score was assigned to each segment by the software automatically, ranging from 0 (normal perfusion) to 4 (for a total perfusion defect). Significant defect reversibility was defined if the summed difference score was at least 2 in the affected region.

### Data management- HCC and statistical considerations

A complex cardiac database management program, called Holistic Coronary Care (HCC - Coronart Ltd., Debrecen, Hungary), was developed using Microsoft Office 2003. The desktop version is running on Java Runtime Environment at <http://hcc.nycis.hu/> (14).

**Table 2. Parameters of lesions (n=36)**

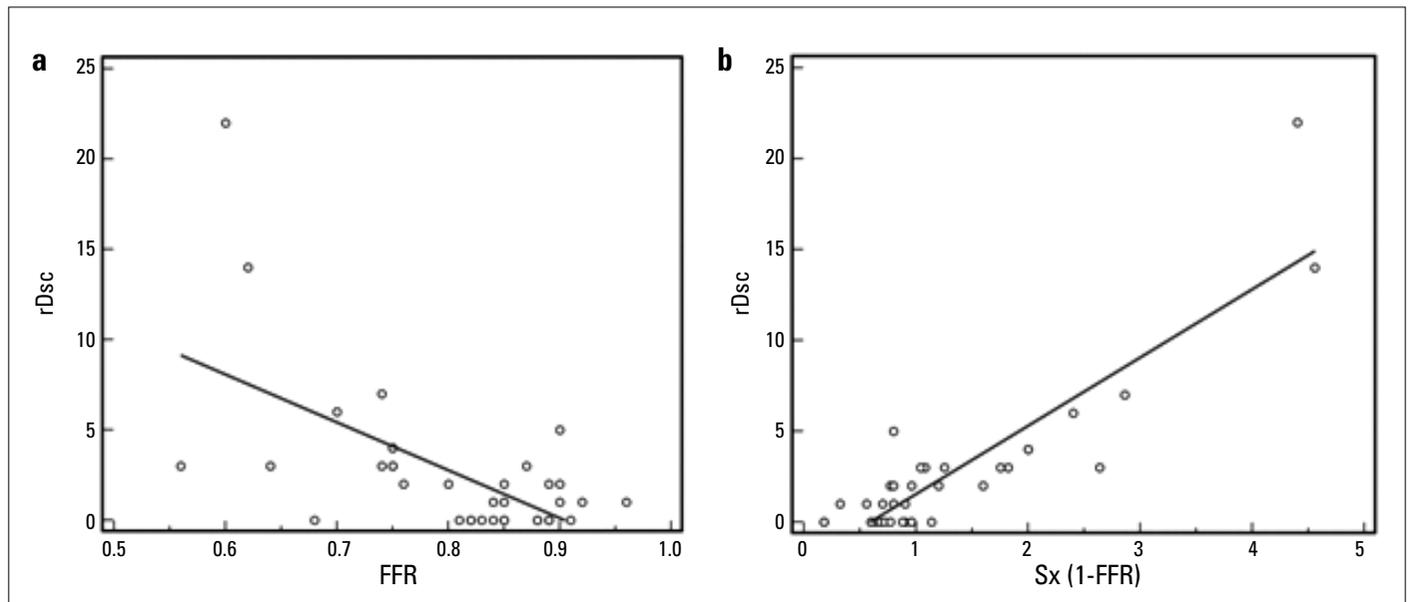
Variable	Study Group		
	FFR ≤0.75 (n=13)	FFR >0.75 (n=23)	Σ (n=36)
LAD	6	14	20
Cx	4	2	6
RCA	3	7	10
No. of reversible segments/ supplied left ventricular segments	50/92	18/141	68/233
Mean supplied left ventricular segments (1 measured lesion)	7.07±3.09	6.13±2.02	6.47±2.47
	Min: 2	Min: 1	
	Max: 12	Max: 8	
Σ regional difference score (all lesion)	74	21	95
Mean regional difference score (1 lesion)	5.69±5.94	0.91±1.27	2.63±4.31
	Min: 0	Min: 0	
	Max: 22	Max: 5	
Mean FFR	0.69±0.06	0.86±0.03	0.80±0.09
	Min: 0.56	Min: 0.8	
	Max: 0.75	Max: 0.96	
Mean LVli	2.18±1.21	0.78±.31	1.28±1.01
	Min: 0.64	Min: 0.18	
	Max: 4.56	Max: 1.60	
≥2 regional difference score/ No. of all lesions	12/13	6/23	18
Mean diameter stenosis (%)	54.23±4.93	48.04±6.52	51.97±8.34
	Min:45	Min:35	
	Max:60	Max:55	

Cx - circumflex artery; FFR - fractional flow reserve; LAD - left anterior descending artery; LVli - left ventricular ischemic index; RCA - right coronary artery

Linear regression analysis (created by MedCalc software, Ostend, Belgium) was used for the statistical analysis to compare the parameters of FFR, LVli, and rDSc and to find the correlations among these parameters. Receiver operating characteristic (ROC) curve analysis was used to test the relationship between sensitivity and specificity at different cut-off values.

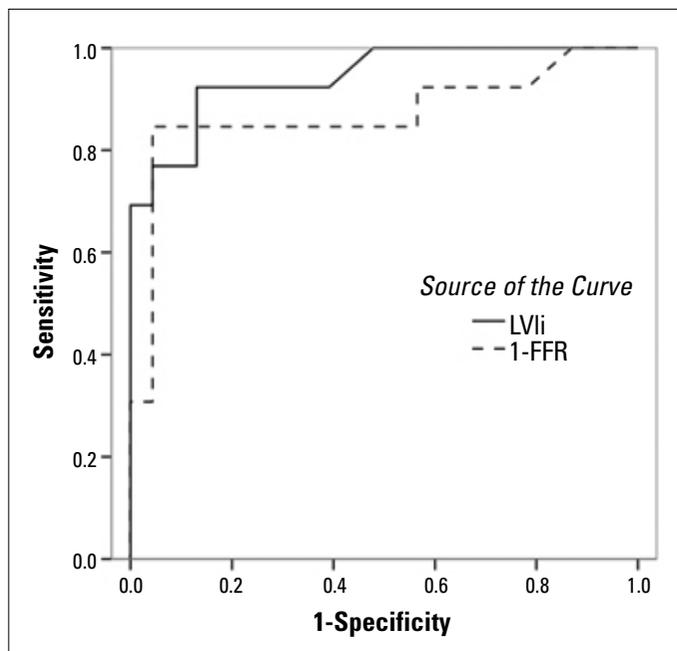
## Results

The parameters of the lesions are given in Table 2. Thirteen lesions (6 lesions on the LAD, 3 lesions on the RCA, 4 lesions on the CX) supplied by 92 left ventricular segments proved to be significant based on intracoronary pressure measurements (FFR ≤0.75). Fifty segments showed reversibility out of the 92 segments. The sum of reversible difference scores was 74. The remaining non-significant 23 FFR values (>0.75) (14 on the LAD, 7 on the RCA, 2 on the Cx) corresponded to 141 LV segments (sum of reversible difference scores was 21 in 18 segments). Out of



**Figure 3. a, b. Linear regression analysis between two parameters [rDSc and FFR on (a); rDSc and LVli on (b)].**

LVli - left ventricular ischemic index; rDSc - regional difference score



**Figure 4. ROC analysis of predicting scintigraphic ischemia by LVli >0.96 and by FFR ≤0.75. Areas under the curves are 0.943 and 0.870, respectively**

FFR - fractional flow reserve; LVli - left ventricular ischemic index

these 23 lesions, 6 (26%) lesions showed a reversibility score of 2 or above regionally after processing of the SPECT images.

Stepwise linear regression analysis revealed that LVli is a significant predictor of rDSc ( $p < 0.0001$ ), while adding FFR does not significantly improve the model ( $p > 0.1$ ) (Fig. 3). LVli predicted active ischemia ( $>2$  rDSc) on myocardial scintigraphy with 78% sensitivity and 94% specificity when the cut-off value was set to 0.96. The FFR value alone predicted ischemia on the scintigraphy with 72% sensitivity and 94% specificity at the best 0.8 cut-off value. The odds ratios for active ischemia of FFR and LVli were

121 and 80, with 95% confidence intervals of 9.9-1485 and 7.5-859, respectively. The area under the ROC curve was significantly higher for LVli than FFR (0.94 vs. 0.87;  $p < 0.05$ ) (Fig. 4).

### Discussion

We have developed an algorithm combining the FFR value and the number of supplied segments, characterizing the clinical significance of ischemia resulting from a stenosis. HCC software provided the possibility for direct comparison between the predicted ischemia on the generated coronary polar map and the ischemia detected on the SPECT images. We introduced a new ischemic index (LVli) that correlates with the severity of regional myocardial perfusion defects identified on scintigrams.

During FFR measurements, a value  $< 0.75$  implies significance; lesions with an FFR value below 0.75 prove myocardial ischemia with the accuracy of 100%. Above 0.8, the FFR value indicates a lack of ischemia with an accuracy of 90% (4). According to the current ESC guidelines, the deferral of PCI or CABG surgery in patients with an FFR value of 0.80 is safe, and the clinical outcome is excellent (12, 16). Values between 0.75 and 0.80 are considered a "gray zone" (none among our patients). In earlier studies, some cases in the "gray zone" showed abnormalities on noninvasive tests, especially on myocardial perfusion scintigraphy (4, 17). Therefore, it raises the point that reversible ischemia can occur at FFR values above 0.75, mainly in the case of proximal stenosis. In the FAME study, the cut-off point of intervention was raised to 0.80 (10). Recently, in clinical practice, the interventional cardiologist decides about the intervention at close to 0.80 stenosis. In clinical practice, interventional cardiologists have recently agreed about the intervention at close to 0.8 stenosis.

In spite of the fact that MPI has a lower accuracy in detecting clinically significant stenosis compared to pressure measurements (17, 18), SPECT was chosen to determine the efficiency of FFR values, including the supplied territory, in our study. There is proof in the literature in relation to the angiographic dominance of vascular territories (19, 20).

However, these summaries differentiate territories with undetermined vessel supplies on the polar map, which are called "watershed regions." In 2001, Chamuleau et al. (21) used a different segmentation system for FFR validation, which is generally known in the literature as attaching the watershed region to a vascular bed as an extension of a defect.

In our study, a complex cardiac database management program (HCC) was used to establish the adequacy of the supplied left ventricular segments of the individual coronary anatomy. It is a Java application in which, after correct typing of coronary morphology (type of dominance, length of LAD), the affected region can be found visually on the polar map (22). Pathological validation of the HCC program as a predictor of angiographic area at risk has been recently published (22). In this paper, we found a significant correlation between the HCC method and autopsy findings with regard to the area at risk of the culprit coronary lesions.

The relation of regional summed difference scores and localization-independent FFR parameters can be recognized in Figure 3. While previous papers described a linear relationship between FFR and rDSc (3, 4, 7), we found that LVli is a better linear predictor of rDSc. Furthermore, when we compared the predictive value of FFR alone with our combined parameter of the LVli values, the ROC analysis (Fig. 4) revealed a bigger area under the latter curve, as well as higher sensitivity and specificity.

An LVli >0.96 indicates a clinically significant stenotic lesion. This additive information may be especially helpful in the "gray zone" of pressure measurements. It is important to note that FFR measurements obtained just distal to the lesion can have a higher value than the value detected with a sensor positioned as distally as possible. This common result has been explained in the literature by diffuse invisible disease of the distal epicardial segments, small-vessel disease, and left ventricular hypertrophy (7, 23). However, since the distal segments in the lesion-associated region always exhibit a higher degree of perfusion abnormality than the proximal segments, we hypothesize that the better-collateralized proximal part shows a higher FFR value just distal to the lesion than at a very distal position without real resistance of the distal segments of the epicardial artery. This hypothesis implies that an FFR measurement at a position not reaching the very distal part of the run-off will show a value characterizing the average drop in the perfusion pressure of the distal segments. Considering the inhomogeneous longitudinal perfusion, distal myocardial ischemia can not be ruled out, despite an FFR value above the upper limit of significance (0.80) (Fig.1). An LVli >0.96 can be a helpful indicator revealing ischemia in these scenarios. Another type of pressure measurement using intravenously injected adenosine makes it possible to measure FFR continuously through the coronary artery. This

technique, called pull-back recording, can help confirm the average drop and our hypothesis above.

The other possible clinical relevance of LVli is the functional assessment of the relevance of the lesion placed in the distal part of the coronary artery. An FFR value under 0.75 at a lesion with a small supplied region obviously has little clinical relevance. Unnecessary interventions can lead to increased risk. In that case, an LVli value <0.96 suggests that the intervention be deferred. In our approach, the LVli should be taken into consideration in cases with borderline FFR values. It can help interventional cardiologists make the appropriate decision in uncertain cases.

Our results can be interpreted with some limitations. A small study group was analyzed, especially in the case of FFR-positive lesions. A larger population would be needed for further analysis. Our SPECT results may be less accurate due to the lack of CT attenuation correction or the use of prone acquisition, which is useful in correcting attenuation artifacts, such as mamma and diaphragm, resulting in false-positive areas on SPECT. Unfortunately, in our clinical practice, we did not have the possibility to use CT for correcting attenuation. Prone acquisition is also not part of our routine clinical protocol. However, in clinical settings, the stress/rest protocol without attenuation correction is generally accepted for the detection of myocardial ischemia, because it is assumed that the attenuation features can not change significantly between two examinations; therefore, the reversibility of the perfusion defects can be assessed reliably. Myocardial PET examination is the most accepted method and the "gold standard" for quantitatively measuring the severity of coronary perfusion abnormalities, with better spatial resolution than SPECT (24, 25). Thus, PET examinations may further confirm the real relevance of our results. We evaluated MPI using an automated program (Emory Cardiac Tool Box). It is well known that all automated evaluations have limiting factors. A visual semi-quantitative approach would give additional information. We used intracoronary adenosine administration for the FFR measurements; however, some recent studies suggest that i.v. adenosine injection can produce different values (26). To examine this kind of correlation, further examinations need to be performed.

## Conclusion

Our results show that an LVli >0.96 indicates a clinically relevant stenotic lesion. Based on our hypothesis and our results, the FFR value, together with the number of corresponding left ventricular segments, predicts the severity of myocardial ischemia better than FFR value alone.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - B.K., Z.K.; Design - B.K., Z.K.; Supervision - G.T.S., C.J.; Resource - I.G., S.B.; Material - C.J., R.K.; Data collection and/or processing - I.G., S.B., I.R., B.T.; Analysis and/or Interpretation - J.V., R.K.; Literature search - B.K., G.T.S.; Writing - B.K., R.K.; Critical review - Z.K., J.V.

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