Evaluations of left anterior descendant coronary artery stenosis by transthoracic Doppler echocardiography as compared with physiological parameters measured by pressure wire.

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SUMMARY

Background: In coronary angiography (CAG), fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) are widely measured for evaluating physiological ischemia and indication for percutaneous coronary intervention (PCI). On the other hand, the progress of ultrasonic devise and technique has enabled the evaluation of coronary blood flow by non-invasive transthoracic echocardiography although its application is limited to left anterior descending coronary artery (LAD).

Objective: To investigate the correlation between the evaluation of physiological ischemia by catheterization and the evaluation of flow velocities by transthoracic echocardiography.

Methods: In patients undergone CAG for diagnosing angina, physiological evaluation of coronary blood flow was performed using pressure wire in LAD lesions. Transthoracic coronary echocardiography was also performed to evaluate the coronary blood flow velocity in the same lesions.

Results: The peak diastolic flow velocity of the stenotic portion (V-stn) and the ratio of peak diastolic flow velocities of the stenotic and the reference portions (V-stn/V-ref) showed higher correlation efficient (r) values with FFR ($r=0.561$, $p<0.001$ and $r=0.612$, $p<0.001$, respectively) than with % diameter stenosis by quantitative CAG ($r=0.481$, $p<0.001$). On the other hand, iFR was also correlated with V-stn ($r=0.411$, $p<0.001$) but the correlation with V-stn/V-ref was not significant. According to the Receiver operating characteristic curve analysis, the V-stn and the V-stn/V-ref values corresponding to FFR=0.80 were 0.56 m/s (sensitivity 0.90, specificity 0.69) and 2.05 (sensitivity 0.85, specificity 0.69), respectively. Especially, almost all the patients with V-stn>1m/s or V-stn/V-ref >3 had FFR<0.80 and were sent for revascularization therapy.

Conclusion: In LAD region of coronary artery, transthoracic coronary echocardiography is considered to be a practically useful method for evaluating physiological ischemia and

indication for PCI.

Key words: Doppler echocardiography, coronary artery disease, coronary blood flow, coronary stenosis, coronary intervention

INTRODUCTION

Coronary artery disease (CAD) has become a major cardiovascular disease as well as cerebrovascular disease not only in western countries but also in Asian countries including Japan. To improve the prognosis of CAD patients, it is important to detect the existence of coronary blood flow disturbances and resume the coronary blood flow capacity by adequate interventional treatment. As to the indices of coronary blood flow capacity, the fractional flow reserve (FFR) measured by the pressure wire after the administration of a coronary vasodilator is used as a gold standard (1,2). More recently, instantaneous wave-free ratio (iFR) is suggested as a substitute index which can be more conveniently measured without using a coronary vasodilator (3). As to the diagnostic criteria based on these parameters, it has been proposed that FFR less than 0.80 and iFR less than 0.89 are considered to indicate the existence of significant stenosis causing myocardial ischemia (4-6). However, invasive maneuvers such as coronary angiography are generally required in order to obtain these indices of coronary blood flow capacity.

Advancement of the ultrasound imaging equipment with high sensitivity and resolution power has enabled noninvasive evaluation of coronary artery flow by transthoracic approach, although the evaluable coronary artery is limited to the left anterior descending artery (LAD). The blood flow of distal portion of this branch is detectable by transthoracic echocardiography in more than 80% of subjects and the diastolic-to-systolic blood flow velocity ratio has been suggested to reflect the degree of stenosis of in this portion (7), however, it has not yet routinely examined in the clinical practice. On the other hand, the evaluation of blood flow of proximal LAD by transthoracic echocardiography is technically difficult, although the clinical significance of stenotic lesions in this portion is more important.

In the present study, we tried to evaluate the indices of coronary blood flow using

transthoracic echocardiography both in the distal and the proximal portions of LAD and aimed to delineate their validity by compared with FFR and iFR in patients undergone coronary angiography.

METHODS

The study subjects are arbitrarily recruited from 113 patients who underwent coronary angiography (CAG) and the measurements of FFR (fractional flow reserve) and iFR (instantaneous wave-free ratio) using pressure guidewire for the purpose of diagnosing or evaluating coronary artery disease during the period from April 2015 to June 2020 in our hospital. The transthoracic echocardiography was performed at the same time within 3 days before or after CAG and the patients whose LAD blood flow velocity could be measured were incorporated into the analyses. The exclusion criteria were: 1) left ventricular hypertrophy, 2) undergoing renal replacement therapy, 3) old anteroseptal myocardial infarction with asynergy, 4) diffuse or tandem stenotic lesions of LAD. Thus, 14 patients were excluded from the study analyses and basic characteristics of the 99 study subjects were shown in Table 1. Seventy-four % patients were aged 65 years or more and 75% were men. Most patients had risk factors for CAD such as hypertension, dyslipidemia and diabetes mellitus. Forty-five patients (45%) showed reduced renal function with estimated glomerular filtration rate (eGFR) less than 60mL/min/1.73m^2 when calculated from their age, gender and serum creatinine (8).

Transthoracic echocardiography was performed using Vivid 7 or 9 echocardiography system (GE Yokogawa Medical System, Japan) with 2.5-MHz transducer. The LAD blood flow was evaluated with flow velocity ranging 10-90 cm/s, 1.8-2.8 MHz frequency, 5-10 mm sample volume and incident angle less than 40°. In addition to the parasternal and apical approaches, epigastric approach was adopted to detect LAD blood flow

with low incident angle according to the individual patient. V-stn was measured as the peak diastolic flow velocity of the stenotic portion and V-stn/V-ref was calculated as the ratio of peak diastolic flow velocities of the stenotic and the reference portions. The time velocity integral (TVI) is the area outlined by flow velocity changes in each cardiac cycle and the Doppler-%DS was calculated from the TVI at the stenotic (TVIstn) and the reference (TVIref) portions as 1 – TVIref/TVIstn. Left ventricular ejection fraction (EF) as the index of left ventricular systolic function was calculated by the standard formula of Teichholz. The peak early velocity (E) and peak late velocity (A) of left ventricular filling at the tips of mitral valves were measured, and their ratio (E/A) was used as an index of left ventricular diastolic function.

CAG was performed by the standard Judkins technique. The stenosis of coronary artery was analyzed on the basis of multiple projection. The % diameter stenosis (QCA-%DS) was quantitatively determined using the CMS software (Medical Imaging Systems, Netherlands). The coronary blood flow capacity was also evaluated by cardiac catheterization using Verrata Plus pressure guide wire (Philips Volcano, Netherlands) or PressureWire X guidewire (Abbot Cardiovascular, USA). The iFR was calculated as the ratio of pressures at the distal and the proximal portions of stenotic lesion in the wave-free period of late diastolic phase (3). After the intracoronary injection of 12mg papaverine, the FFR was determined as the ratio of mean pressures at the distal and the proximal portions of stenotic lesion (2).

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects and was approved by the institutional review board (R3-12). Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means ± standard deviations (SD). Statistical analyses were carried out using the JMP statistical software Ver 10.0.2 (SAS Institute Inc.,

USA). Correlations between the parameters are assessed by linear regression analysis. Receiver operating characteristic curve (ROC) analysis was used to evaluate cutoff values based on FFR<0.80 and iFR<0.89 with corresponding sensitivity and specificity. The cutoff value with the highest Youden's index (sensitivity + specificity-1) was assumed as the optimally discriminant level. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Average QCA-%DS in the 99 study subjects was 49.7% (22.5-75.0%). Patients with QCA-%DS more than 75% have the indication for intervention without examinations using pressure wire and who were excluded in this study. In the measurements of functional capacity of coronary blood flow, the average FFR was 0.73 (range 0.48-0.88) in 82 patients, and the average iFR was 0.86 (range 0.38-0.96) in 81 patients. In this study, 58 patients (70.7%) showed FFR less than 0.80 and 44 patients (54.6%) showed iFR less than 0.89 suggesting the existence of significant stenosis causing myocardial ischemia (4-6).

Transthoracic echocardiographic data of LAD blood flow velocity could be obtained in all the 99 patients. Figure 1 presents the typical recordings of Doppler blood flow signals at the stenotic and the reference portions of LAD. The average V-stn was 0.99 (0.22-2.90) m/s and the average V-S/R was 3.58 (1.17-11.43). TVI could be traced in 63 patients and the average Doppler-%DS calculated from TVIstn and TVIref was 69.2 (31.8-100.0) %. The average EF was 63.5% and 10 patients (10.1%) had reduced left ventricular systolic function showing EF less than 50%. As to the index of left ventricular diastolic function, the average E/A was 0.82 and 50 patients (50.5%) had values less than 0.80 indicating the reduced diastolic function.

Table 2 indicates the correlations between the parameters of coronary artery stenosis

measured in this study. As the echocardiographic indices of coronary artery stenosis, V-stn and V-stn/V-ref showed significant correlations with the morphological index, QCA-%DS, and the functional index, FFR. The correlation coefficient (r) with FFR was higher in V-stn or V-S/R than in QCA-%DS (Figure 2). On the other hand, QCA-%DS and V-stn showed significant correlations with iFR, however, the r values were lower than those with FFR and the correlation of V-stn/V-ref or Doppler-%DS with iFR was not significant. There are naturally significant correlations between the 3 echocardiographic parameters, V-stn, V-S/R and %DS, with high r values. However, the calculation of %DS did not provide higher r value with FFR as compared with V-stn or V-stn/V-ref.

Figure 3A shows the plotted line graph of ROC analysis of diagnostic sensitivity and specificity of V-stn corresponding to the threshold FFR value of <0.80 as positive for coronary artery stenosis. The area under the curve (AUC) is 0.768 and the cutoff value of V-stn at 0.56 m/s provides the maximum Youden's index of 0.583 with sensitivity of 0.896 and specificity of 0.688. The ROC graph analyzing the cutoff value of V-stn/V-ref corresponding to FFR<0.80 is presented in Figure 3B and the AUC is 0.814. When the cutoff V-stn/V-ref value is adopted at 2.05, the Youden's index gets highest as 0.538 with 0.851 for sensitivity and 0.688 for specificity.

DISCUSSION

In the era of global aging and low birth rate, it becomes greatly desired to promote health of elderly population and enhance their activity to maintain productivity of the society. As to the diseases which impair the health and the prognosis of elderly subjects, disorders of cardiovascular system including the brain and the kidneys take major places as well as malignancies and infectious diseases. Especially, chronic failures of cardiovascular organs such as heart failure and renal failure not only impair the health state of elderly subjects but

also impose a social burden on medical resources. As CAD is a prevalent cause of heart failure, its adequate management including primary and secondary prevention is important. To attain favorable outcomes and good prognosis of CAD patients, it is required to detect the existence of significant coronary artery stenosis and apply interventional revascularization.

CAG is generally performed for the purpose of morphological evaluation of the extent of coronary artery stenosis for patients with CAD such as angina pectoris and myocardial infarction, however, the cardiac catheterization technique is invasive technique with the risks of bleeding and adverse effects derived from the use of contrast media such as allergic reactions and acute kidney injury. Although exercise electrocardiogram, exercise myocardial scintigram and coronary computed tomography angiography may be less invasive, specialized equipment and/or laborious procedures are often needed and the burden of stress or the use of contrast media can still cause some adverse effects. As compared to these, evaluation of coronary blood flow by transthoracic echocardiography can be easily performed readily and repeatedly without imposing unfavorable effects on patients.

It has been reported that the blood flow velocity of LAD could be detectable by transthoracic echocardiography in 83.7-86.3% of studied subjects and the diastolic to systolic ratio was predictable of the existence of significant stenosis or the perfusion defect in myocardial scintigram (7,9,10). However, the evaluated area of LAD was mostly limited to the distal portion and the blood flow of proximal portion is often hard to detect because of high incident angle although the existence of significant stenosis in this portion is clinically important for the indication of the coronary intervention. In addition, the measurement of blood flow velocity is inevitably inaccurate for the evaluations of bifurcated, tandem or diffusely stenotic lesions. In the present study, we evaluated the blood flow velocity of the proximal LAD by adding the epigastric approach in addition to the parasternal and apical approaches. Improvement of the skill of this technique is expected to increase the clinical

implication of coronary blood flow evaluation by transthoracic echocardiography in the management of CAD.

QCA-%DS is a morphological quantitative analysis of the coronary angiography using the computer software. On the other hand, FFR and iFR calculated by the measurements using pressure wire during CAG indicate functional capacity of coronary blood flow and are supposedly related more directly to the indication for revascularization therapy than QCA-%DS. Especially, considerable amount of evidence has been accumulated regarding the implications of FFR as the index of coronary artery blood flow capacity as compared with iFR (4,5). In the present study V-stn and V-stn/V-ref are more closely correlated with FFR than QCA-%DS

V-stn was the peak diastolic flow velocity of the stenotic portion and V-stn/V-ref was the ratio of peak diastolic flow velocities of the stenotic and the reference lesions. In fluid dynamics, Bernoulli's principle states that an increase in the speed of a fluid occurs simultaneously with a decrease in pressure or the fluid's potential energy. In the field of echography, the simplified Bernoulli's equation has been clinically used in the vascular and valvular stenosis, the peak flow velocity means the decrease in the pressure of stenotic portion. However, V-stn and V-stn/V-ref were weakly correlated QCA-%DS. QCA could only measure percentage of the maximal stenosis of the coronary artery. However, the real stenotic lesion was nonuniform such as variation of the stenotic length, morphology (i.e. diffuse, slit and tandem plaque) and/or condition of inner vessel (i.e. smooth, irregular, hard and soft). Consequently, V-stn and V-stn/V-ref may be able to reflect physiological condition of whole coronary stenotic lesion compared with QCA-%DS only in the resting condition. V-stn and V-stn/V-ref were moderately correlated with FFR. This difference may be induced by the different physiological condition, since V-stn and V-stn/V-ref were measured at resting coronary flow condition and FFR was measured at maximal coronary flow condition.

Although left ventricular hypertrophy, undergoing renal replacement therapy, old anteroseptal myocardial infarction and diffuse or tandem stenotic lesions of LAD were excluded in this study, the coronary flow reserve depends on the coronary perfusion pressure which is influenced by the factors such as increasing coronary flow at rest and peripheral vascular resistance of the coronary artery. However, FFR is the pressure ratios between the proximal and distal portions of stenosis at the maximal coronary artery dilation, and the value is theoretically constant when the perfusion pressure decreased or when the resting coronary flow varied. Thus, to date, FFR is a reliable and useful index for decision making of the coronary intervention (1,2,4,5). On the other hand, it is suggested that iFR may be affected by autoregulatory function of the peripheral vascular resistance of the coronary artery. The V-stn correlated with iFR less closely than FFR and the correlation between V-stn/V-ref and iFR was not significant. Such variations may have also blunted the correlations of iFR with other parameters (11).

The Doppler-%DS determined from TVI at stenotic and non-stenotic lesions of LAD did not yield higher r value of correlation with FFR than V-stn or V-stn/V-ref. Furthermore, the correlation of Doppler-%DS with QCA-%DS was not significant, while V-stn and V-stn/V-ref showed significant correlations of with QCA-%DS. It seems that the time-course profile of blood flow velocity cannot be always traced accurately and the calculation of Doppler-%DS does not provide additional diagnostic value on V-stn and V-stn/V-ref.

As to the threshold values of V-stn and V-stn/V-ref corresponding to FFR<0.80, The ROC analyses indicated that V-stn>0.56 and V-stn/V-ref >2.05 provide optimal distinction in terms of the balance between sensitivity and specificity. Yoshida et al have invasively measured coronary blood flow velocity before and after the intravenous administration of dipyridamole using Doppler guidewire and suggested the ratio less than 2.0 is indicative of diameter stenosis greater than 70% (12). Regarding the LAD blood flow evaluation by

transthoracic echocardiography, Hozumi et al have calculated the prestenotic to the stenotic diastolic flow velocity ratio in patients undergone percutaneous coronary angioplasty and reported that the optimal cutoff value was 0.45 for indicating the ≥50% restenosis (13). Okayama et al have also used transthoracic echocardiography for the evaluation of LAD blood flow and found that distal to proximal diastolic peak velocity ratio equal to or less than 0.5 predicted significant stenosis equal to or more than 50% (14). The present study, for the first time, compared the parameters of coronary blood flow measured by transthoracic echocardiography with physiological parameters of coronary blood flow such as FFR and iFR measured by pressure guidewire. It is indicated that the suggested cutoff value of V-stn/V-ref in this study mostly corresponds to the threshold values indicated in previous studies based on coronary angiographic images or blood flow measurements using Doppler guidewire.

In the present study, the study subjects were not necessarily selected in a strictly random manner depending on the patients' will and availability of laboratory facilities. Therefore, it seems possible that this may have caused some influence as selection bias on the background characteristics of study subjects enrolled in this study and such possibility should be considered as the limitation of this study.

In conclusion, the results of this study showed that parameters of LAD blood flow such as V-stn and V-stn/V-ref measured by transthoracic echocardiography have strong correlations with FFR which indicates functional capacity of coronary blood flow. As transthoracic echocardiography can be performed easily and noninvasively without imposing risks of adverse effects, the measurements of V-stn and V-stn/V-ref are thought to be useful especially in the practical management of acute coronary syndrome for evaluating the emergent indication of revascularization therapy. Considering that almost all the patients with V-stn>1m/s or V-stn/V-ref >3 had FFR<0.80, it seems plausible to conduct CAG immediately for such patients and determine if revascularization is to be performed. Especially, V-stn is

easier to measure than V-stn/V-ref and may be more suitable for the evaluation of LAD blood flow in emergency medical practice.

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FIGURE LEGENDS

Figure 1. Representative recording images of Doppler flow signals from the stenotic and the reference portions of left anterior descending artery obtained by the apical approach view. The transmission wave frequency and flow velocity range were set at 2.0MHz and 0.42m/s, respectively. The peak diastolic flow velocities of stenotic, proximal (reference) and distal portions were determined as 1.09, 0.44 and 0.43 m/s.

Figure 2. Correlations of the coronary angiographic parameter (A: QCA-%DS) and the echocardiographic parameters (B: V-stn, C: V-stn/V-ref) of coronary artery stenosis with the index of functional flow reserve (FFR). QCA-%DS: % diameter stenosis by quantitative coronary angiography, V-stn: peak diastolic flow velocity of the stenotic lesion, V-stn/V-ref: ratio of peak diastolic flow velocities of the stenotic and reference portions, FFR: fractional flow reserve, r: correlation coefficient.

Figure 3. Line graphs of receiver operating characteristic curve (ROC) evaluating the cutoff values of V-stn (A) and V-stn/V-ref (B) corresponding to functional flow reserve (FFR) less than 0.80 as the diagnostic criteria of significant coronary artery stenosis. V-stn: maximum diastolic flow velocity of the stenotic lesion, V-stn/V-ref: ratio of maximum diastolic flow velocities of the stenotic and non-stenotic lesions, FFR: fractional flow reserve.

Figure 1.

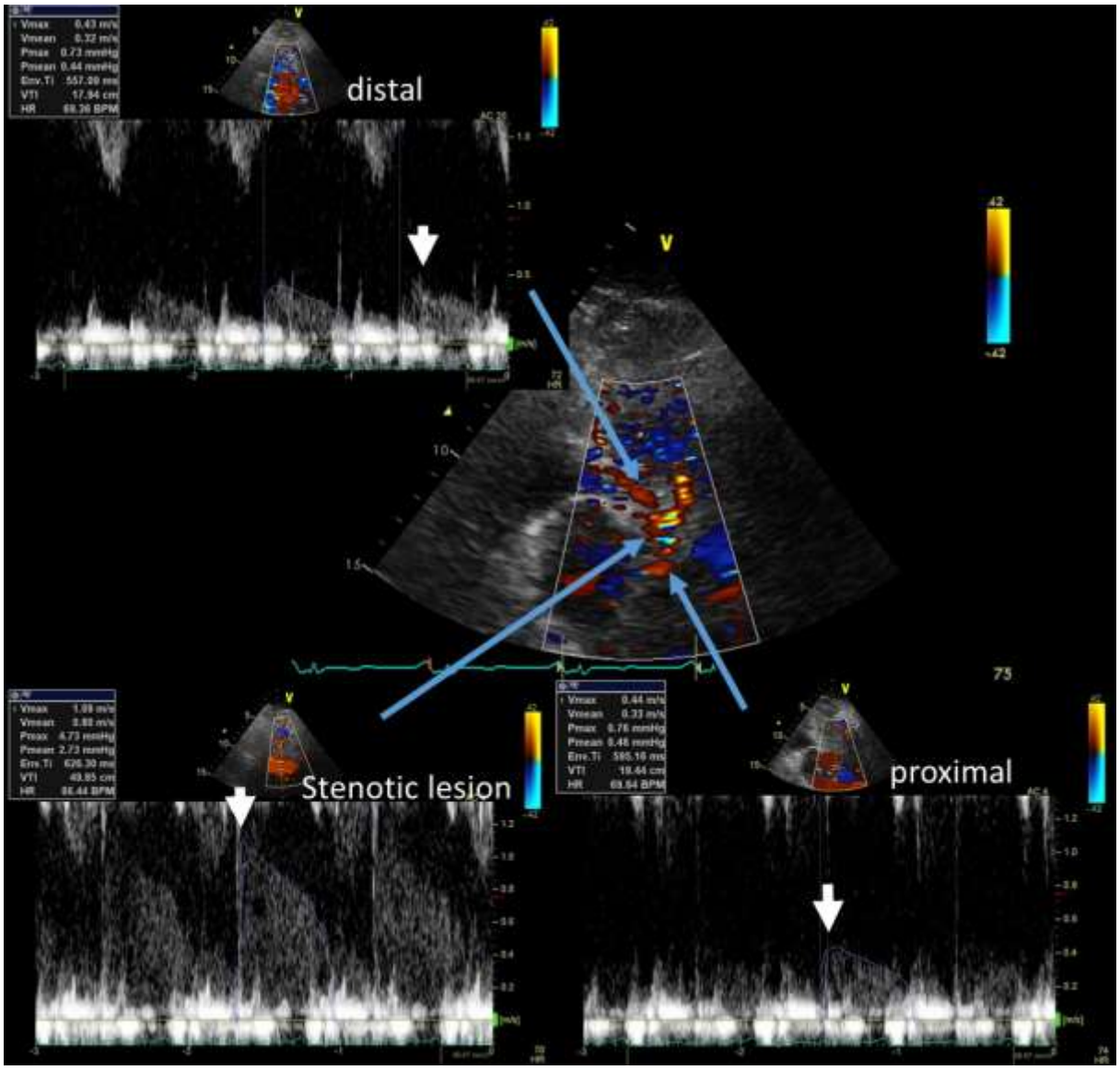

Figure 2.

Figure 3.

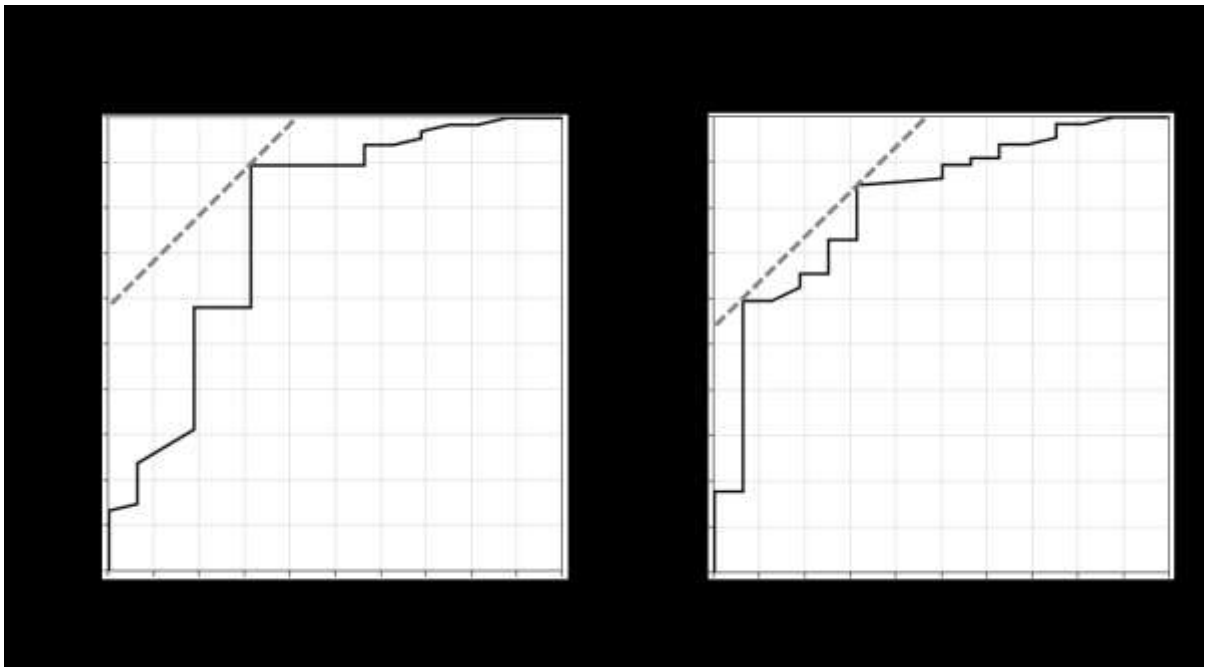

Table 1. Basic characteristics of the study subjects

Age, years	69 ± 10
Gender, male/female	74 (74.7%) / 25 (25.2%)
Revascularization therapy	
Performed	70 (70.7%)
Deferred	29 (29.3%)
Risk factor	
Smoking, yes/no	60 (60.6%) / 39 (39.4%)
Hypertension, yes/no	64 (64.6%) / 35 (35.4%)
Dyslipidemia, yes/no	85 (85.9%) / 14 (14.1%)
Diabetes mellitus, yes/no	36 (36.4%) / 63 (63.6%)
Serum creatinine, mg/dL	1.01 ± 0.82
eGFR, mL/min/1.73m^2	61.4 ± 17.6
Serum LDL cholesterol, mg/dL	97 ± 33
Serum triglycerides, mg/dL	142 ± 80
Echocardiographic parameters	
LVDd, mm	45.4 ± 5.8
LVDs, mm	29.9 ± 6.8
EF, %	63.5 ± 10.9
E/A	0.82 ± 0.29

Continuous and categorical values are presented as mean ± standard deviation and number (percentage), respectively. eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, LVDd: left ventricular diastolic diameter, LVDs: left ventricular systolic diameter, EF: ejection fraction, E/A: early to late peak diastolic transmitral flow velocity ratio.

Table 2. Correlations between the measured parameters of stenosis in the left anterior descending branch of left coronary artery.

	V-stn	V-stn/V-ref	Doppler-%DS	iFR	FFR
QCA-%DS	r=0.293 p=0.003	r=0.348 p<0.001	r=0.185 p=0.147	r=-0.344 p=0.001	r=-0.485 p<0.001
V-stn		r=0.698 p<0.001	r=0.623 p<0.001	r=-0.411 p<0.001	r=-0.561 <0.0001
V-stn/V-ref			r=0.771 p<0.001	r=-0.207 p=0.063	r=-0.612 p<0.001
Doppler-%DS				r=-0.229 p=0.105	r=-0.494 p<0.001
iFR					r=0.476 p<0.001

QCA-%DS: % diameter stenosis by quantitative coronary angiography, V-stn: peak diastolic flow velocity of the stenotic portion, V-stn/V-ref: ratio of peak diastolic flow velocities of the stenotic and reference portions, Doppler-%DS: degree of stenosis calculated from the time velocity integrals at the stenotic and the reference portions, iFR: instantaneous wave-free ratio, FFR: fractional flow reserve, r: correlation coefficient.