DOI: 10.1111/j.1540-8175.2007.00478.x

Noninvasive Assessment of Coronary Flow Reserve in the Left Anterior Descending Artery by Transthoracic Echocardiography before and after Stenting

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Background: Noninvasive assessment of coronary flow reserve in the left anterior descending artery (LAD) by transthoracic Doppler echocardiography (TTDE) has been already validated as a new method for determining the degree of stenosis over the proximal flow. Objectives: The aim of the study is to determine, by TTDE, the feasibility and the value of the coronary flow reserve (CFR) (defined as the maximal increase in coronary blood flow above its basal pressure for a given perfusion pressure when coronary circulation is maximally dilated) in the mid-to-distal LAD before and after percutaneous angioplasty and to demonstrate the early recovery of microvascular tone immediately after stenting. Methods: The study population consisted of 36 patients with significant isolated LAD stenosis (70–90%) identified by coronary angiography. CFR was recorded in the mid-to-distal LAD at rest and during hyperemia obtained after adenosine intravenous infusion before and after stenting. Results: Adequate visualization of the LAD was obtained in 25 out of 36 patients (70%). At rest the mean CFR was 1.5132 ± 0.33 (1.1–2.58). However, after stenting the mean CFR was significantly higher: 2.18 ± 0.55 (1.3–3.8), with P <0.01. Conclusions: CFR can be easily determined by TTE in approximately 70% of patients. Noninvasive Doppler echocardiography shows impaired CFR in patients with LAD disease. After stenting CFR is restored, demonstrating early recovery of microvascular tone. These results are comparable to those published in the same conditions. Larger series with a long-term follow-up may allow identifying patients at high risk for restenosis after stenting. (ECHOCARDIOGRAPHY, Volume 24, September 2007)

Introduction

Coronary flow reserve (CFR) estimated by drug-induced coronary vasodilation is an important functional parameter for evaluating the degree of coronary artery stenosis.[1,7] It used to be assessed by invasive procedures such as intracoronary Doppler flow wire,[2] or more recently by expensive methods such as PET scan.[3] Recently, several reports have shown that CFR measured by transthoracic Doppler echocardiography (TTDE) can be very useful in the assessment of significant LAD stenosis.[4–8]

The aim of our study is to determine, by TTE, the feasibility and the results of the coronary flow reserve (CFR) (defined as an increase in coronary blood flow after maximal microvascular dilation using adenosine) calculated over the mid-to-distal LAD before and after percutaneous intervention, and to demonstrate the early recovery of microvascular reactivity immediately after stenting.

Patients and Methods

We prospectively studied 36 patients (27 males, 9 females; ages 50 to 77 years; mean age: 62 years) who had a significant isolated LAD stenosis (70–90%).

Patients with anterior infarction, unstable angina, left bundle branch block, atrial

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fibrillation, severe chronic obstructive pulmonary disease or bronchospasm were excluded. There were no patients with echocardiographic signs of left ventricular hypertrophy (Septal or posterior wall at diastole >12 mm). All patients underwent TTDE before and after stenting. All vasoactive medications were stopped 24 hours before the study. All participants gave informed consent to the protocol approved by the Committee of ethics in our hospital.

Transthoracic echocardiography (TTE) was performed on Acuson Sequoia C256 machine (Mountain View, CA, USA) with a 7 MHz probe by a single operator.

To image the mid-to-distal LAD the transducer was put either at the cardiac apex or one intercostal space above, along the inteventricular groove, and focused on the proximal field. Then the transducer was rotated until the LAD could be visualized with color Doppler flow ("intramural" machine settings). Aligning ultrasound beam direction parallel to the mid-to-distal LAD flow was not important given that the CFR is the ratio between flow at rest and flow velocity during maximal hyperemia. Coronary flow velocity was sampled by pulsed Doppler echocardiography to obtain the best signal[8] during diastole.

CFR Measurement by TTDE

We first recorded baseline spectral Doppler signals in the distal portions of the LAD. Each patient underwent three Doppler recordings of the LAD at baseline and after infusion of 140 μg/kg/4 mn of adenosine. This protocol was done 1 hour before the stenting and 24 hours thereafter. All patients had continuous blood pressure and heart rate monitoring. CFR was calculated as the ratio between the velocity time integral (VTI) at maximal hyperemia state and the baseline measurements.

Coronary Angiography

Coronary angiography was done on a Philips Integris 5000 machine (Philips, Andover, MA, USA). Lumen Diameter measurements were obtained by electronic calipers calibrated to catheter tip. Prior to stenting, all patients received clopidogrel and 7500 IU heparin bolus. Stenting was performed in all 36 patients. Balloon predilatation was deemed necessary in 9 patients (25%).

Data Analysis

Data are expressed as the mean value ± standard deviation. We used two-tailed paired *t*-test to compare CFR measurements pre- and post-PCI within the same group. The same test was used to compare VTI pre- and post-adenosine at baseline level and after PCI.

Intraobserver variability was calculated as the SD of the differences between the highest and the lowest determined CFR and expressed as a percentage of the average value. (Each patient underwent three CFR recordings by the same operator before and after stenting).

Results

Under the guidance of color Doppler flow mapping, adequate spectral Doppler recordings of coronary flow in the distal portion of the LAD for the assessment of the CFR were obtained in 25 of 36 patients (70%) (Table I). At baseline the mean CFR was 1.51 ± 0.33 (1.1–2.58), however CFR increased to 2.18 ± 0.55 (1.3–3.8) (P <0.01) following percutaneous angioplasty (Fig. 1).

The mean of the differences ± SD between CFR post-PCI and CFR pre-PCI was 0.64 ± 0.44.

The same paired *t*-test was used to compare VTI base (before adenosine infusion) with VTI post-PCI base. The observed value of *t* was 0.58 whereas the critical value of *t* was 2.06. The null hypothesis was accepted and therefore there was no statistically significant difference between VTI base and VTI post-PCI base.

The comparison between VTI post-PCI adenosine and VTI pre-PCI adenosine was statistically significant (0.208 ± 0.102 vs. 0.152 ± 0.068, respectively), P <0.01.

Percutaneous coronary intervention did not improve baseline VTI but improved VTI after adenosine infusion and thus there was a statistically significant difference between CFR pre-PCI and CFR post-PCI (1.513 ± 0.337 vs. 2.154 ± 0.554, respectively), P <0.01.

Paired *t* test comparisons between VTI base and VTI post-adenosine infusion pre-PCI (0.105 ± 0.0516 vs. 0.152 ± 0.068) and VTI base with VTI after adenosine infusion post-PCI (0.097 ± 0.05 versus 0.208 ± 0.102) also showed statistically significant differences, P <0.01.

A one-sample *t* test was used to compare between CFR post-PCI and CFR = 2.0 given that a

TABLE I.

CFR and VTI Base and after Adenosine Infusion in All 25 Patients

At Baseline				Post-PCI			
Patient	VTI base	VTI post-adenosine	CFR	Patient	VTI base	VTI post-adenosine	CFR
1	0.064	0.079	1.23	1	0.059	0.11	1.86
2	0.055	0.071	1.29	2	0.047	0.091	1.94
3	0.049	0.08	1.63	3	0.045	0.09	2
4	0.163	0.212	1.7	4	0.21	0.39	1.86
5	0.066	0.117	1.77	5	0.059	0.166	2.81
6	0.04	0.058	1.45	6	0.129	0.38	2.94
7	0.086	0.161	1.87	7	0.044	0.169	3.8
8	0.086	0.133	1.63	8	0.089	0.153	1.72
9	0.041	0.067	1.27	9	0.044	0.099	2.25
10	0.115	0.146	1.34	10	0.2	0.39	1.95
11	0.109	0.147	1.41	11	0.075	0.134	1.78
12	0.110	0.157	1.42	12	0.1	0.21	2.1
13	0.112	0.29	2.58	13	0.11	0.35	3.18
14	0.169	0.192	1.13	14	0.171	0.39	2.28
15	0.11	0.199	1.8	15	0.1	0.21	2.1
16	0.06	0.1	1.66	16	0.055	0.11	2
17	0.045	0.061	1.36	17	0.04	0.071	1.77
18	0.114	0.22	2	18	0.1	0.23	2.3
19	0.07	0.11	1.57	19	0.06	0.13	2.16
20	0.12	0.21	1.75	20	0.09	0.2	2.22
21	0.088	0.106	1.2	21	0.111	0.198	1.78
22	0.145	0.165	1.14	22	0.162	0.22	1.35
23	0.2	0.25	1.25	23	0.117	0.22	1.88
24	0.22	0.281	1.28	24	0.119	0.3	2.52
25	0.19	0.21	1.1	25	0.172	0.223	1.3
Mean	0.10508	0.15288	1.5132	Mean	0.09733	0.20879	2.154
Max	0.22	0.29	2.58	Max	0.21	0.39	3.8
Min	0.04	0.058	1.1	Min	0.04	0.071	1.3
SD	0.05167	0.06890	0.33777	S D	0.05058	0.10288	0.5543

CFR = Coronary flow reserve; VTI = Velocity time integral.

mean CFR <2.0 predicts significant LAD stenosis (>70%) with a specificity and a sensitivity of 92% and 86%, respectively.[7] The test showed a calculated value of $t = 1.3891$, which is included inside the interval [–2.0639; 2.0639]. Hence, there was no difference between the two means. This could explain the early recovery of micro vascular tone in the coronary arteries immediately after percutaneous coronary intervention even though CFR was still impaired.

Intraobserver variability for the measurements of Doppler velocity recordings during diastole before and after PCI was 3.0%.

Side Effects

After adenosine infusion, 7 patients experienced hyperpnea and 3 patients experienced flushing. Hence there was no evidence of bradycardia, dizziness, dysrhythmia, hypotension, bronchospasm, or atrioventricular bloc.

Discussion

Noninvasive assessment of CFR is gaining acceptance as a valuable tool for the assessment of the hemodynamic significance of moderate coronary stenosis. A number of noninvasive strategies such as transthoracic echocardiography,[4–8] dichromatic synchrotron radiation,[9] electron beam tomography,[10,11] multislice spiral computed tomography,[12,13] and magnetic resonance imaging[14] have been tried for coronary imaging and assessment of stenosis. Invasive CFR assessment using Doppler flow wire or pressure wire is limited by the need for instrumentation, proper central wire position, and may be affected by distal embolization

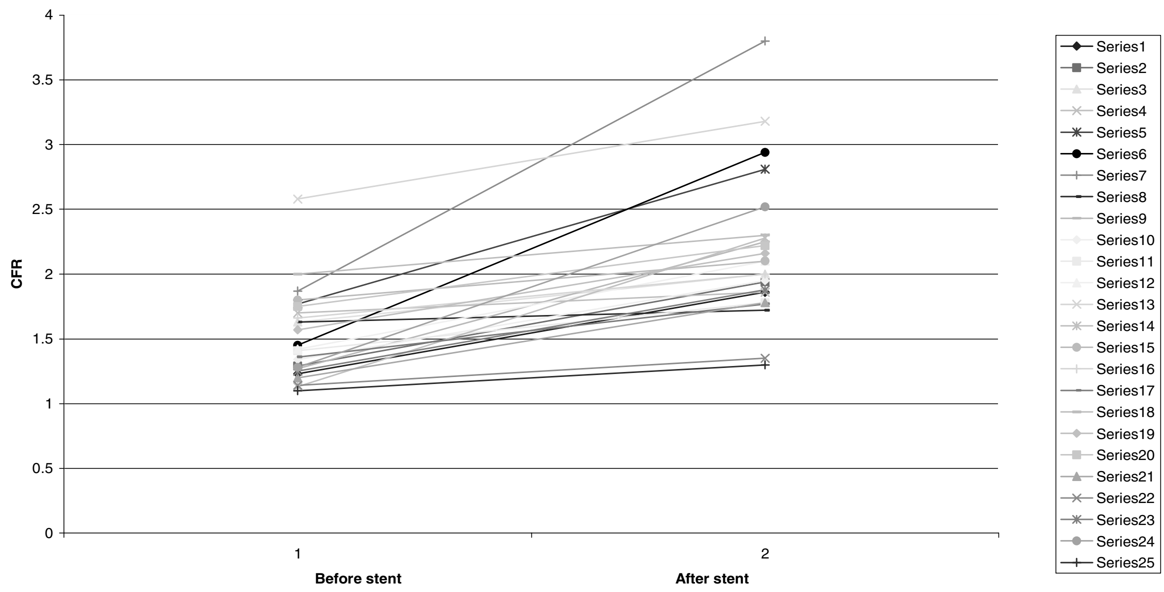

Figure 1. Comparison of CFR before and after percutaneuous intervention.

during PCI. In addition, the influence of the guide wire or guiding catheter on the vascular endothelium and coronary flow dynamics is unpredictable. For these reasons, we have elected to measure CFR by a noninvasive procedure, which is TTE, before and one day after stenting, although we know that measuring CFR by TTDE 3.7 ± 2 days after successful stenting would result in a lower rate of postprocedural impaired CFR.[15] Echocardiography has widespread availability and therefore, can be easily applied to a large patient population.

Therefore, many studies have been performed using ultrasound in order to assess the severity of coronary artery stenosis and to define a cutoff line CFR of 2.0 below which critical stenosis is suspected.[4–8] One study[16] showed a mean CFR of 2.88 in 24 patients with <40% stenosis, 2.09 in 17 patients with >40% to <75% stenosis, and 1.51 in 34 patients with >75% stenosis.

Coronary flow reserve is defined as the maximal increase in coronary blood flow above its baseline level for a given perfusion pressure when coronary circulation is maximally dilated. Adenosine was used in order to dilate the LAD microcirculation and calculate the CFR by dividing velocity time integral (VTI) after adenosine infusion with VTI at baseline. CFR is reduced by many parameters other than coronary artery stenosis such as congestive heart failure, dilated or hypertrophic cardiomyopathy, and microcirculatory disorders (diabetes mellitus, hypercholesterolemia, hypertensive heart disease, syndrome X). Therefore, an accurate assessment of CFR is subject to changes due to many factors and comparison of differences in CFR among patients is very challenging. We have tried to limit these factors in our study by using the above-mentioned exclusion criteria although we could not eliminate all variables that affect the accurate calculation of CFR.

Ultrasound (US) has been widely used to assess CFR.[4–8] We should therefore note that US assessment of CFR is a time-consuming technique (mean 30 minutes per exam), requires a high experience, and is restricted to mid-to-distal LAD.

In our experience CFR was adequately measured in 70% of the cases before and after stenting, whereas the feasibility of the test may be up to 98% with the use of contrast agent.[16]

This study describes the ability of TTDE to measure CFR changes in the mid-to-distal LAD before and after successful stent implantation. CFR of <2.0 has been used as the cutoff line for severe LAD stenosis in many studies.[17,18] Our study showed a mean CFR of 1.54 correlating with severe LAD stenosis as assessed by angiography. Only patient number 13 (refer to table) had a CFR of 2.58 before stenting although he had 75% stenosis of his LAD artery on angiography. This finding had no obvious explanation. Twenty-four hours after stenting, CFR was calculated again. Eleven of 25 patients had a CFR of <2.0 (patients number 1, 2, 4, 8, 10, 11, 17, 21, 22, 23, and 25—refer to table) even though the mean CFR post-PCI was 2.154. This phenomenon has been explained by two conflicting theories: microvascular stunning, where the microcirculation is not able to increase flow; or reactive hyperemia, where high postischemic baseline flow velocities mask a normal reserve. After stenting we found a significant increase in CFR compared to that before stenting in all patients. This finding along with a mean CFR above 2.0 demonstrates that the coronary flow recovers toward normal after angioplasty, proof of early recovery of the microvascular tone.

Clinical Implications

TTE can be used as a reliable method for determining the degree of stenosis on the proximal-to-mid LAD and the complete revascularization of the coronary artery by the stenting procedure. It would be an excellent method for the assessment of restenosis following percutaneous coronary intervention.[19] It would also decrease the number of angiographies, minimizing at once the inappropriate indications of invasive procedures and the rate of complications that would result.

Study Limitations

All CFR measurements were done by one operator and the study was not double blinded; therefore, interobserver variability was not assessed.

The number of patients was small, no comparison was made with intracoronary Doppler and there was no subgroup analysis (no patients with diabetes, hyperchesterolemia, two or more stenoses on the LAD).

Only LAD was studied; hence, posterior descending artery stenosis studies are promising, with an overall feasibility of 80%.[20]

The follow-up of the patients was not done to prove whether TTE could be useful in assessing restenosis or not.

Conclusion

CFR of the LAD can be determined easily by TTE (70% of patients), and noninvasive Doppler echocardiography shows significantly impaired CFR in patients with LAD disease. After stenting CFR is restored, demonstrating early recovery of microvascular tone. These results do concur with those published by invasive techniques in the same conditions.

Larger series with a long-term–follow-up may allow identifying patients at high risk for restenosis after stenting according to the amelioration of the CFR after the PCI.

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