

Detection of Angiographic Lesions in the Left Anterior Descending Coronary Artery by Transthoracic Doppler Echocardiography: Usefulness of Non-Invasive Assessment of Coronary Flow Reserve

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Introduction. We evaluated the feasibility of detecting blood flow in the left anterior descending coronary artery and the usefulness of measuring coronary flow reserve to diagnose significant coronary artery disease, both by means of transthoracic Doppler echocardiography using a high-frequency transducer and echo-contrast agent.

Patients and method. We studied 107 patients who were scheduled for coronary arteriography for known or suspected ischemic heart disease. A Doppler signal was recorded by a pulsed wave in the distal left anterior descending artery at baseline and after dipyridamole infusion. An echo-contrast agent was administered to all patients. A coronary flow reserve equal to or higher than 1.7 was considered normal.

Results. We recorded Doppler signals in the left anterior descending coronary artery of 83 patients (78%). Significant stenosis of the left anterior descending coronary artery was observed in 24 out of 83 patients (29%). The prevalence of significant stenosis was higher (62 vs 29%; $p = 0.006$) in patients in which no Doppler signal was detected. The sensitivity, specificity, and accuracy of abnormal coronary flow reserve in detecting significant stenosis of the left anterior descending coronary artery were 87, 74 and 78%, respectively.

Conclusions. The measurement of coronary flow reserve by transthoracic Doppler echocardiography using a high-frequency transducer and echo-contrast agent is a feasible, widely available, and accurate method for detecting significant stenosis of the left anterior descending coronary artery.

Key words: *Echocardiography. Coronary disease. Regional blood flow. Contrast media.*

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DetECCIÓN DE ESTENOSIS ANGIOGRÁFICA DE LA ARTERIA CORONARIA DESCENDENTE ANTERIOR MEDIANTE ECOCARDIOGRAFÍA DOPPLER TRANSTORÁCICA: UTILIDAD DE LA MEDIDA NO INVASIVA DE LA RESERVA DEL FLUJO CORONARIO

Introducción y objetivos. El propósito de este estudio fue evaluar la capacidad de detección de flujo en la arteria descendente anterior y la utilidad de la medición de la reserva de flujo coronario para diagnosticar enfermedad coronaria significativa, empleando ecocardiografía Doppler transtorácica con transductor de alta frecuencia y eco-contraste.

Pacientes y método. Estudiamos a 107 pacientes ingresados por cardiopatía isquémica conocida o sospechada, en los que se indicó una coronariografía. Se obtuvo un registro de Doppler pulsado de la descendente anterior distal en condiciones basales y tras infusión de dipiridamol. En todos los pacientes se administró un agente de eco-contraste. Consideramos que la reserva del flujo coronario era normal si su valor era $\geq 1,7$.

Resultados. Se obtuvieron registros Doppler adecuados de la descendente anterior en 83 pacientes (78%). Encontramos estenosis significativas de la descendente anterior en 24 de 83 pacientes (29%). En los pacientes en los que no se obtuvo el registro Doppler, la prevalencia de estenosis en la descendente anterior fue significativamente mayor (62 frente a 29%; $p = 0,006$). La sensibilidad, especificidad y eficacia diagnóstica de una reserva de flujo coronario menor de 1,7 para detectar estenosis significativa de la descendente anterior fueron, respectivamente, del 87, 74 y 78%.

Conclusiones. La medición de la reserva de flujo coronario por medio de ecocardiografía Doppler transtorácica empleando transductor de alta frecuencia y eco-contraste es un método factible, accesible y con una buena capacidad para detectar estenosis significativas en la descendente anterior.

Palabras clave: *Ecocardiografía. Enfermedad coronaria. Flujo sanguíneo regional. Medios de contraste.*

ABBREVIATIONS

LAD: left anterior descending coronary artery.
 TTDE: transthoracic Doppler echocardiography.
 CFR: coronary flow reserve.

INTRODUCTION

Coronary flow reserve (CFR) measurement is useful in determining the physiological significance of coronary artery stenosis¹ and microvascular function.² To date, CFR assessment procedures have been invasive (intracoronary Doppler guide wire³) or semi-invasive (transesophageal Doppler echocardiography⁴), which limits their use in the clinical setting. Recently, technical advances in ultrasound equipment have permitted noninvasive assessment of Doppler signals in arteries such as the left internal thoracic artery⁵ or left anterior descending coronary artery (LAD).^{6,7} High frequency transducers have increased the success of noninvasive assessment of CFR in the distal LAD.^{6,8} Second harmonic techniques and echo-contrast agents have proved useful in increasing both the number of patients for whom Doppler signals are detected and the quality of the signals.^{9,10} These technical advances have raised the success rate in detecting flow in the LAD to between 78% and 100%.^{11,12}

Research into the use of transthoracic Doppler echocardiography (TTDE) to measure CFR in the LAD has focused on a variety of populations. Some groups included patients with valve conditions or cardiomyopathy^{10,11} whereas others excluded patients with myocardial infarction,¹³ diabetes⁶ or unstable angina.¹¹ Such diverse populations and the range of techniques used explains the wide variety of published data on sensitivity and specificity.^{6,10,12} This led us to study CFR noninvasively in a population more representative of patients attended in daily clinical practice in our setting, using state-of-the-art technology.

Our objective was to determine the usefulness of CFR assessment to diagnose significant coronary artery disease of the LAD in an unselected patient population using TTDE with a high frequency transducer and echo-contrast agent.

PATIENTS AND METHOD

Population

We studied 107 patients hospitalized with confirmed or suspected ischemia. All were in a stable condition

as a consequence of treatment, in sinus rhythm, and had been referred for coronary angiography by their specialists. Patients were assessed in consecutive order and were not selected. Patients were excluded if dipyridamole administration was unadvisable due to second or third degree atrioventricular block, disease affecting the sinuses, bronchial asthma, or mild or severe chronic obstructive lung disease. Caffeine and long-acting theophylline intake were avoided during 24 h prior to testing. Cardiologists decided on a patient by patient basis whether or not to continue with anti-ischemic and anti-platelet medication on the day of TTDE examination. All patients provided written informed consent.

Transthoracic Doppler echocardiography

Echocardiographic examinations were performed using a Sonos 5500 (Philips, Andover, Massachusetts), and a high frequency transducer S12 (5-12 MHz).

Ultrasound images were obtained from a view near the mid-clavicular line in intercostal space 4 or 5 with the patient in left lateral position. When the interventricular sulcus had been located along the short axis, the examination plane was rotated sideways to image the distal LAD for high frequency color Doppler flow mapping⁶ (5 MHz). Velocity range was ± 15 to ± 19 cm/s and depth adjusted to 7 cm (Figure 1). Pulsed wave Doppler signals of blood flow velocity were recorded while keeping the examination plane aligned, as far as possible, parallel to the distal LAD flow (Figure 1). Pulsed Doppler frequency was 5 MHz with sample size set at 1.9 mm. We attempted to hold the transducer stable throughout. All studies were recorded on super-VHS videotape and some cycles were digitalized for follow-up analysis.

We used an echo-contrast agent (Levovist, Schering AG, Berlin, Germany) to improve visualization of color pulsed wave Doppler signals. The agent was administered in a 300 mg/mL concentration by means of an intravenous infusion of a volume of 7 mL at a rate of 1 mL/min using an infusion pump. Infusion rate was adjusted within the range from 2.0 to 0.5 mL/min according to the quality of the Doppler signals.¹²

Coronary flow reserve study protocol

Patients had to have been symptom-free for at least 48 h prior to CFR measurement. Pulsed Doppler signals were recorded in the distal LAD in baseline conditions and 10 min after dipyridamole infusion started (0.84 mg/kg/min over 6 min). The Echo-contrast agent was administered at baseline and on terminating dipyridamole infusion. All patients underwent continuous ECG and heart rate monitoring. Blood pressure was recorded at baseline and every minute throughout dipyridamole infusion. Once the Doppler signal had

Fig. 1. The image on the left is a modified short axis view showing an elongated canal with «red coded» diastolic color Doppler corresponding to the distal LAD. The image on the right corresponds to the pulsed Doppler signal obtained on locating the sample in this canal. A systolic and a prevalent diastolic component are depicted. LAD indicates left anterior descending coronary artery.

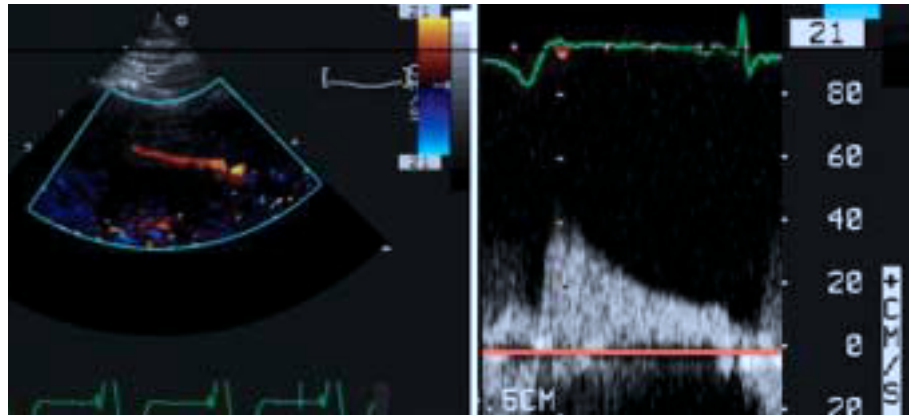
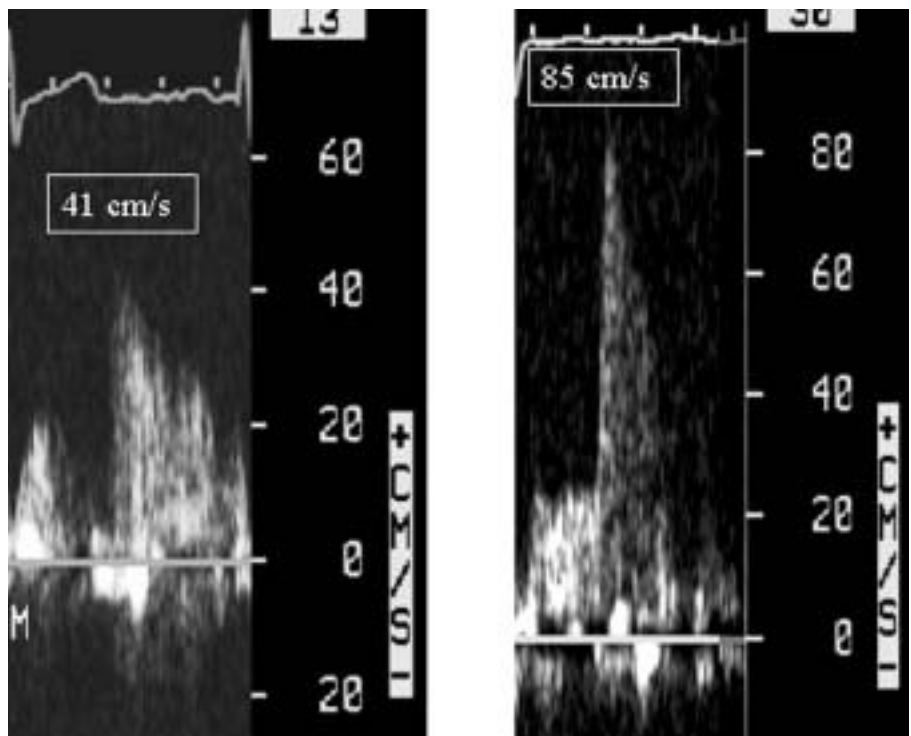


Fig. 2. Peak diastolic velocities before and after dipyridamole infusion in a patient with 2.07 CFR (normal). CFR indicates coronary flow reserve.



been recorded on terminating dipyridamole infusion, the effect was neutralized by administering aminophylline. CFR was assessed by an experienced echocardiographer blinded to the angiographic data. The Doppler signal parameters analyzed before and after dipyridamole infusion were peak systolic and diastolic velocities. For each parameter the results of five readings were averaged. CFR was calculated as the ratio of peak diastolic velocities during hyperemia to baseline and at rest. We defined normal CFR as $\geq 1.7^{14}$ (Figures 2 and 3).

Coronary angiography

We obtained standard coronary angiograms of all patients during hospitalization. Experienced hemody-

namics specialists, blinded to TTDE results, assessed data. We determined stenosis severity by means of quantitative angiography using the software package Inturis Cardioview 1.2 (Philips, Holland). Results were expressed in terms of percentage narrowing of luminal diameter. Significant stenosis was defined as $\geq 70\%$ narrowing. Patients were then classified in two groups: A (stenosis $\leq 70\%$) and B (stenosis $> 70\%$).

Statistical analysis

Numerical variables are expressed as mean \pm SD. Qualitative variables are given as percentages and univariate comparison was carried out by χ^2 using Fisher's correction as necessary. Differences between

TABLE 1. Population characteristics

	Doppler signals obtained in the LAD		
	Yes (n=83)	No (n=24)	P
Age, years	66.0 ± 1.2	66.3 ± 11.0	NS
Men	54 (65%)	17 (71%)	NS
Tobacco	13 (16%)	9 (37%)	.04
Hypercholesterolemia	36 (43%)	12 (50%)	NS
Hypertension	57 (69%)	18 (75%)	NS
Diabetes	27 (32%)	9 (37%)	NS
History of myocardial infarction	28 (34%)	6 (25%)	NS
Beta-blockers	53 (64%)	12 (50%)	NS
Nitrates	29 (34%)	11 (46%)	NS
Calcium channel blocking agents	8 (10%)	2 (8%)	NS
Diagnosis			
Chest pain	21 (25%)	5 (21)	NS
Angina	38 (46%)	9 (37%)	NS
AMI	24 (29%)	9 (37%)	NS
Significant heart disease	54 (65%)	18 (75%)	NS
Significant stenosis in the LAD	24 (29%)	15 (62%)	.006
Significant stenosis in the circumflex coronary artery	28 (34%)	9 (37%)	NS
Significant stenosis in the right coronary artery	32 (39%)	8 (33%)	NS

LAD indicates left anterior descending coronary artery; AMI, acute myocardial infarct; NS, nonsignificant.

numerical variables were compared using Student’s unpaired *t* test. Within each group, differences between baseline velocities and after hyperemia were compared with Student’s paired *t* test. We used Spearman’s correlation coefficient to measure the relationship between CFR and percentage of stenosis in the LAD. Statistical significance was defined as *P* ≤ .05. Data were analyzed with the statistical software package SPSS.

We used standard procedures to calculate sensitivity, specificity, positive and negative predictive values and diagnostic efficiency in detecting significant stenosis in the LAD. Sensitivity and specificity are given with the corresponding confidence intervals.

We assessed inter- and within-observer variability by measuring velocities in 10 randomly selected patients. Interobserver variability was calculated as SD of the differences between measures recorded by 2 independent observers expressed as a percentage of the average. Within-observer variability was expressed as a percentage of the average. Variability was calculated as SD of the differences between the first and second recordings made by the same observer, at an interval of 2 weeks, and expressed as a percentage of the average.

TABLE 2. Doppler recordings in patients with and without significant stenosis in the LAD

	Group A	Group B	P
	(stenosis ≤70%) (n=59)	(stenosis ≥70%) (n=24)	
Baseline systolic velocity, cm/s	16.8 ± 13.3	14.3 ± 9.1	NS
Systolic velocity after dipyridamole, cm/s	29.8 ± 17.9	22.6 ± 19.3	NS
Baseline diastolic velocity, cm/s	31.1 ± 1.8	27.9 ± 14.0	NS
Diastolic velocity after dipyridamole, cm/s	58.4 ± 21.4	38.6 ± 18.1	.001
CFR	1.92 ± .44	1.49 ± .59	.001

LAD indicates left anterior descending coronary artery; CFR, coronary flow reserve.

TABLE 3. Relationship between CFR and percentage of stenosis in the LAD

	Group A (stenosis ≤70%) (n=59)	Group B (stenosis ≥70%) (n=24)
CFR ≤ 1.7	15	21
CFR ≥ 1.7	44	3

LAD indicates left anterior descending coronary artery; CFR, coronary flow reserve.

RESULTS

Transthoracic Doppler echocardiography recordings

We recorded satisfactory Doppler signals in the LAD both before and after administering dipyridamole for 83 out of 107 patients (78%). Our success rates was 68% for the first 50 patients and 86% for the following 57 (*P* = .04). None of the patients developed complications as a consequence of the dipyridamole infusion. Clinical characteristics of the population appear in Table 1.

Average baseline systolic velocity was 16.3 ± 12.2 cm/s. This increased significantly to 27.7 ± 18.5 cm/s (*P* = .0001) after administering dipyridamole. Diastolic velocity behaved in the same way (30.2 ± 11.8 vs 52.7 ± 22.3 cm/s; *P* = .0001).

Coronary angiogram results

We found significant stenosis in the LAD in 24 out of 83 patients (29%). Only one patient presented significant stenosis in two locations (proximal and medial LAD, 85% and 100% respectively). Proximal, medial and distal LAD stenosis was located in pa-

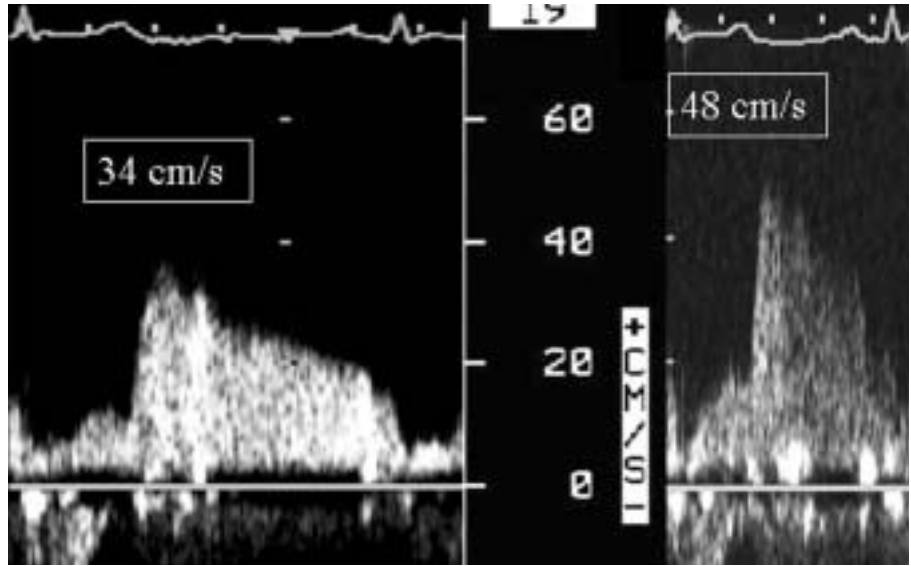


Fig. 3. Peak diastolic velocities before and after dipyridamole infusion in a patient with 1.41 CFR (pathological). CFR indicates coronary flow reserve.

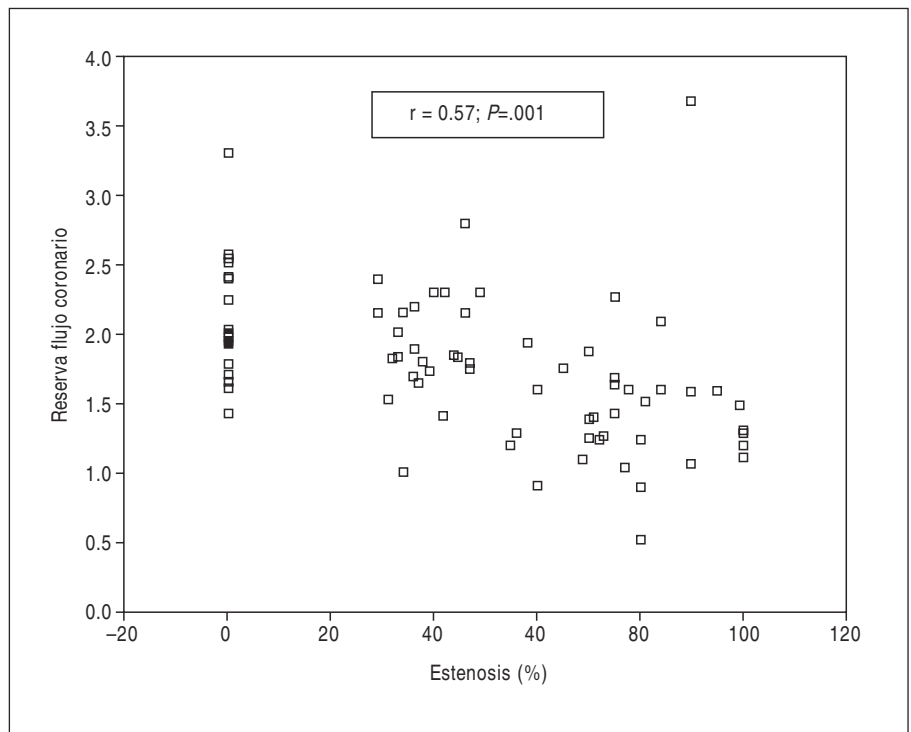


Fig. 4. Correlation coefficient describing the relationship between CFR and percentage of stenosis in the LAD. LAD indicates left anterior descending coronary artery; CFR, coronary flow reserve.

tients 14, 9 and 2, respectively. In 4 patients we detected significant stenosis in the main left artery and in another segment of the LAD.

We studied the differences found in coronary angiograms according to whether or not Doppler signals had been detected in the LAD (Table 1). Prevalence of stenosis was significantly greater among patients for whom we could not obtain Doppler signals (62% vs 29%; $P = .006$).

Doppler recordings and significant stenosis in the left anterior descending coronary artery

Table 2 shows Doppler velocity recordings for each of the two groups. CFR values were significantly higher in Group B than in Group A, although diastolic velocity with dipyridamole was lower. No significant differences in CFR appeared when comparing patients who were treated with or without nitrates either in the population

as a whole (1.86 ± 0.64 vs 1.76 ± 0.45 ; $P=.4$), or in the groups: group A (2.05 ± 0.52 vs 1.86 ± 0.40 ; $P=.1$) and Group B (1.62 ± 0.70 vs 1.32 ± 0.36 ; $P=.2$).

Table 3 presents CFR distribution according to the percentage of stenosis in the LAD. $CFR < 1.7$ had 87% (74%-100%) sensitivity, 74% (63%-85%) specificity, and 78% diagnostic efficiency in detecting significant stenosis in the LAD. Positive and negative predictive values were 58% and 94%, respectively. Figure 4 presents a comparison of CFR with the percentage of stenosis in the LAD and Spearman's correlation coefficient.

Within- and interobserver variability

Intraobserver variability in estimating the velocity to be used in calculating CFR (peak diastolic velocities) was 4.5% at baseline and 2.4% after dipyridamole infusion. Interobserver variability for peak diastolic velocities was 4.9% at baseline and 2.9% after dipyridamole infusion.

DISCUSSION

We have shown that by using state-of-the-art ultrasound technology, lower CFR values identify patients presenting significant stenosis in the LAD with high indexes of sensitivity and specificity.

Coronary flow reserve measurement by transthoracic Doppler echocardiography

Correlations between coronary angiogram results and coronary function are weak in patients with intermediate coronary stenosis.¹⁵ However, the value of CFR to determine functional deterioration in more serious stenosis,^{1,16} is in no doubt. Initial attempts to determine CFR in clinical practice were based on invasive Doppler technology.^{3,17} Doppler techniques were also used semiinvasively in transesophageal echocardiography.⁴ High frequency transducers incorporated into state-of-the-art ultrasound equipment enable us to assess CFR noninvasively by means of TTDE. Correlations between CFR measured by TTDE and CFR measured using intracoronary Doppler technology are strong.^{11,12} Similarly, it has been proven that CFR measured by TTDE in order to determine the importance of stenosis in the LAD¹³ provides data equivalent to that obtained by scintigraphy.

Despite the differences found in the populations studied in order to measure CFR by means of TTDE,^{6,10,11,13} the diagnostic accuracy of pathologic CFR in detecting significant stenosis in the LAD has been good, with 86%-92% sensitivity and 76%-90% specificity.^{6,10,12} In our population, 87% sensitivity and 74% specificity were found, which are both good re-

sults.

We used 1.7 as our criterion for abnormal CFR. However, an optimal cut-off value has not been clearly established and most researchers use 2.^{6,8,10} It has been proved that in patients with moderate stenosis only a weak correlation exists between the angiographic severity of stenosis and invasively assessed CFR.¹⁴ Receiver-operator characteristic curve analysis of CFR¹⁴ and functional repercussions of thallium-201 infusion scintigraphy gave an optimum value of 1.7. Consequently, we believe that 1.7 was an adequate choice as it was based on the functional repercussion of a stenosis and not just its angiographic severity.

In 2 of the 3 patients with normal CFR and significant stenosis in the LAD, stenosis was situated in the distal segment. Prestenotic recording of Doppler signals could have caused the normal CFR due to the vasodilatory response to the blood flow to territory via branches without lesions that originate in the areas situated between that of the Doppler signal and the distal stenosis.

Coronary flow reserve can be affected by factors other than the presence of coronary artery stenosis such as diabetes,¹⁸ left ventricular hypertrophy¹⁹ or previous heart attack.²⁰ In this study, we did not exclude patients with conditions that might affect CFR in order to reflect routine clinical practice as far as possible.

Significant stenosis and inability to detect flow in the left anterior descending coronary artery

The introduction of echo-contrast agents has improved the rate of detection of Doppler signals in the LAD. In studies using echo-contrast, the success rate ranges from 89% to 97%.^{9,21} In the present study, we obtained Doppler signals in 78% of patients, which is clearly below the general range and may constitute a limitation on the clinical value of the test. However, we would stress that those patients for whom we could not obtain Doppler signals in the LAD had a significantly higher prevalence of severe stenosis than those for whom we did obtain Doppler signals (62% vs 29%; $P=.006$). Furthermore, this 62% prevalence is greater than the 30% reported in the only study on this topic.⁹ We believe that the greater prevalence of significant stenosis in the LAD in our study prevented us from obtaining adequate Doppler signals despite the use of the echo-contrast agent.

In our analysis of sensitivity, specificity and diagnostic efficiency, the patients for whom Doppler signals could not be detected were excluded. However, the prevalence of significant stenosis among them was greater and this may affect the usefulness of the test. If we accept that our inability to obtain Doppler signals may indicate stenosis, we can recalculate sensitivity, specificity and diagnostic efficiency and include the

24 patients for whom we did not obtain a signal on the grounds that these are patients with an abnormal CFR. This would increase sensitivity, but decrease specificity.

We should also consider the learning curve. The difference in success rates between the first 50 patients and the remainder (68% vs 86%; $P=.04$) was significant. Perhaps the most recent echo-contrast agents would reduce these differences and improve our success rate in obtaining Doppler signals in the LAD.

Limitatons of the study

The diameter of the coronary artery cannot be measured by TTDE; consequently, the ratio of velocities is only a reflection of CFR if coronary artery diameter remains constant. Some authors suggest maximizing dilation of the epicardial arteries with nitrates to avoid changed of diameter⁹ due to vasodilation secondary to supranormal flow.² Baseline velocities of Doppler signals in patients who have not previously been treated with nitrates are greater than those of patients who have. This means that CFR could be underestimated, especially in patients without lesions in the LAD. In our population, two thirds of patients were not receiving nitrates prior to assessment. However, we did not observe significant difference in CFR between patients treated with or without nitrates.

CONCLUSION

Coronary flow reserve assessment by TTDE using a high frequency transducer and echo-contrast is a feasible and accessible method capable of detecting significant stenosis in the LAD in a population representative of that found in routine clinical practice.

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