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Clinical Investigations

Comparison of Transesophageal Doppler Coronary Flow Reserve Measurements with Thallium-201 Single-Photon Emission Computed Tomography Imaging in Assessment of Left Anterior Descending Artery Stenoses

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Summary

Background and hypothesis: Recent studies demonstrate the feasibility of coronary flow reserve measurements by transesophageal echocardiographic (TEE) Doppler recordings of coronary sinus or left anterior descending (LAD) coronary artery flow velocity for detecting stenoses of the LAD artery. This study compares coronary flow reserve measurements by Doppler TEE with thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT) in patients with proximal single-vessel LAD stenosis.

Methods: Nineteen patients with various degrees of LAD stenosis (mean area stenosis 71 ± 24%; range 24–96%) were studied. Area stenosis by quantitative coronary angiography was < 75% in 7 patients and > 75% in 12 patients. Transesophageal LAD and coronary sinus Doppler measurements were performed at baseline and after intravenous dipyridamole. Coronary flow reserve was calculated as the ratio of hyperemic to baseline average peak velocities. Predefined coronary flow reserve cut-off values of 1.8 for the coronary sinus method and of 2.0 for the LAD method were used for diagnosis of significant LAD stenosis. Results were compared with qualitative ^{201}Tl dipyridamole SPECT.

Results: Overall predictive accuracy for diagnosis of > 75% LAD stenosis was 79% for ^{201}Tl SPECT, 77% for the transesophageal LAD and 79% for the transesophageal coronary sinus technique. Concordant results between ^{201}Tl SPECT and the LAD and coronary sinus Doppler methods were observed in 79% and 71% of patients, respectively.

Conclusions: Thallium-201 SPECT and transesophageal Doppler assessment of coronary flow reserve have similar accuracy for diagnosing significant proximal LAD stenosis. Therefore, both transesophageal Doppler techniques might constitute another widely available, noninvasive method for assessment of left coronary artery disease, if disease location is proximal.

Key words: coronary flow reserve, transesophageal echocardiography, thallium-201, coronary artery disease

Introduction

Coronary angiography does not always supply sufficient information about the hemodynamic significance of coronary stenosis.[1] In addition to other lumen-assessment techniques, such as intravascular ultrasound, thallium-201 (^{201}Tl) perfusion scintigraphy is commonly used to assess the physiologic significance of coronary luminal stenoses by registering the functional sequelae of a coronary obstruction on the cellular perfusion level.[2–5] Recently, the concept of coronary flow reserve has gained increasing importance as a functional measure of stenosis severity;[6–8] however, quantitative assessment of coronary flow reserve usually requires invasive techniques or positron emission tomography, which are both limited in their widespread application.[9, 10] Recent studies demonstrated the feasibility of noninvasive evaluation of coronary flow reserve by transesophageal echocardiographic (TEE) Doppler recordings of coronary sinus or left anterior descending (LAD) coronary artery flow velocity before and after vasodilator application.[11–14]

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Until now, these new techniques have not been compared with other methods of noninvasive, functional evaluation of coronary artery disease. Thus, the present study was performed to compare transesophageal coronary flow reserve measurements with ^{201}Tl scintigraphy in patients with various degrees of LAD stenosis.

Methods

Study Population

Nineteen consecutive patients (15 men, 4 women; mean age 57 ± 3 years), with typical angina and single-vessel disease of the LAD with various degree of stenosis, were selected to participate in this study. After angiography, all patients underwent stress/redistribution ^{201}Tl scintigraphy and transesophageal Doppler studies for evaluation of coronary flow reserve. Only patients without previous Q-wave myocardial infarction were selected to participate in this study. No patient had angina or ischemic electrocardiographic (ECG) changes at rest. Three patients had a history of previous non-Q-wave infarction, four patients had a history of hypertension, three patients had mild left ventricular hypertrophy as assessed by echocardiography.

The study protocol was in accordance with the guidelines of the human subjects committee. Written informed consent was obtained from all patients. All vasoactive medication with the exception of short-acting nitrates was withheld 24 h before the study. Transesophageal and thallium studies were performed within 24 h. All measurements were performed blinded to angiographic stenosis severity, and readings were done independently of the results of the respective other noninvasive test. Transesophageal studies were performed by two investigators (M.Z. and P.S.).

Coronary Angiography

Coronary angiography was performed via the femoral artery using an 8F guiding catheter. After positioning the guiding catheter in the coronary ostium, 0.1–0.3 mg nitroglycerin was injected through the guiding catheter to achieve maximal vasodilation. Two to three orthogonal projections of the target lesion were obtained using a biplane angiography system (HICOR, Siemens Inc., Forchheim, Germany). Severity of stenosis was assessed by quantitative coronary angiography (QCA), using a second-generation QCA system (CMS, Version 2.3D, Cardiovascular Measurement System; Medis Medical Imaging Systems BV, Nuenen, The Netherlands). Two to three end-diastolic images were analyzed to obtain percent luminal area reduction of the stenosis and the highest stenosis grade was included for further analysis.

Thallium-201 SPECT

After overnight fasting, patients were placed in supine position and an intravenous line was inserted in a large cubital vein. Adenosine was infused at a constant rate of 140 μg/kg/min. Symptoms, heart rate, and ECG were monitored throughout the study. Three min after the start of the adenosine infusion, a dose of 2–3 mCi thallium was injected as a bolus and the adenosine infusion was continued for an additional 3 min.

Thallium images were obtained with a single-head large field-of-view SPECT gamma camera equipped with a low-energy, medium-resolution, parallel-hole collimator (Apex 415, APC, Elscint, Haifa), using a 20% energy window centered at the 68 keV photopeak. The camera head was continuously rotated on a circular 180° arc starting from a 55° right anterior oblique projection to obtain 30 projection images. Filtered backpropagation (5th order Butterworth) was used to reconstruct transaxial tomographic images, which were then reoriented under operator control to generate standardized orthogonal views of the myocardial tracer distribution on vertical and horizontal long-axis and short-axis images. Redistribution images were obtained 2–4 h later. All images were interpreted in a blinded manner by two experienced observers. Visual grading was defined as normal (no perfusion defect) and abnormal (stress perfusion defect with or without redistribution). Disparate visual interpretations were resolved by consensus between the two observers.

Transesophageal Flow Measurements

The echocardiographic study was performed with a VINGMED 800 system (SONOTRON European Headquarters, Zug, Switzerland) using a multiplane 5 MHz transesophageal probe. Transesophageal echocardiography was performed without sedation using topical anesthesia to the oropharynx. Continuous ECG recording was obtained and arterial blood pressure was measured noninvasively at baseline and after dipyridamole administration.

Recording of coronary sinus flow velocity (TEE-CS): A modified four-chamber view with dorsal angulation of the transducer was used to visualize the ostium of the coronary sinus. The position of the probe was optimized until the coronary sinus with its ostium into the right atrium could be visualized throughout the cardiac cycle. Coronary sinus flow velocity recordings were performed with the Doppler sample volume placed in the coronary sinus within a distance of no more than 10 mm from its ostium. In all patients, the angle between the Doppler beam and the long axis of the coronary sinus was < 30°. Flow signals were recorded during expiration and were repeated until constant flow signals of acceptable quality were obtained.

Recording of LAD flow velocity (TEE-LAD): The proximal LAD was visualized by positioning the transducer in a cross-sectional plane slightly superior to the aortic valve. In most patients, anterior and lateral angulation of the transducer was necessary for optimal imaging. Flow was recorded by placement of the Doppler sample volume in the proximal LAD. As with coronary sinus flow recordings, attempts were made to achieve the smallest possible angle between the long axis of the vessel and the Doppler beam.

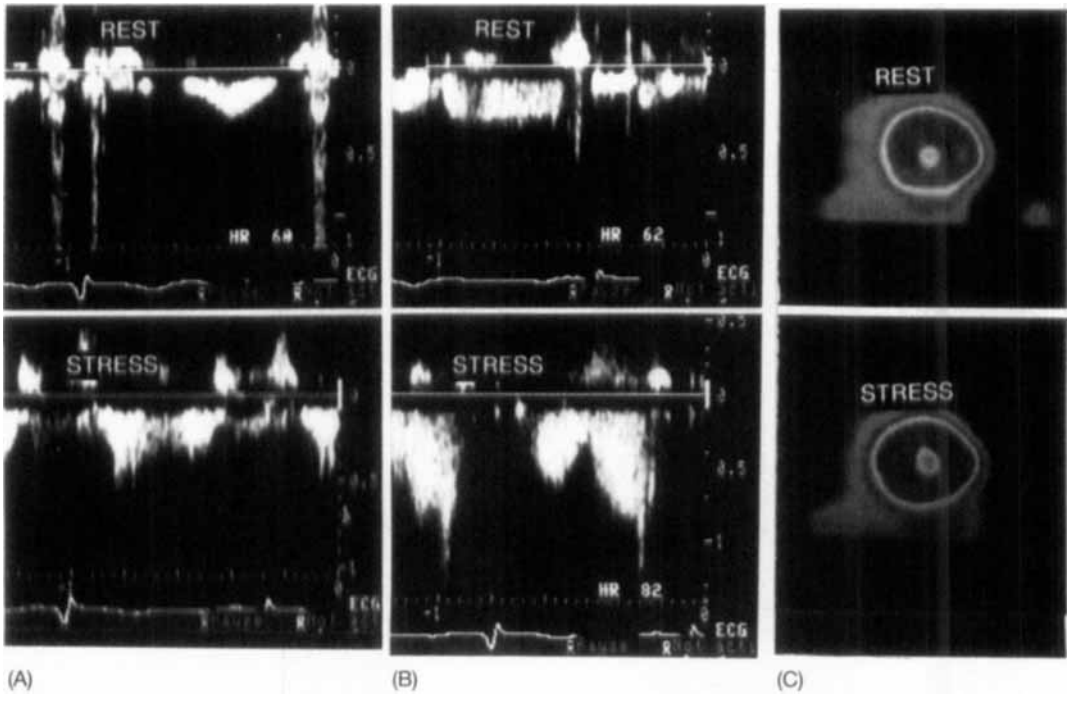

FIG. 1 Patient with 44% area stenosis of the proximal left anterior descending (LAD) artery. (A) Transesophageal Doppler flow velocity recording in the coronary sinus at baseline and after dipyridamole resulting in a coronary flow reserve of 2.3. (B) Transesophageal Doppler flow velocity recording in the proximal LAD at baseline and after dipyridamole resulting in a coronary flow reserve of 2.4. (C) Short-axis adenosine stress/redistribution tomograms at the midventricular level demonstrating normal perfusion.

After recording coronary sinus and LAD flow velocity at baseline, dipyridamole was administered intravenously at a constant infusion rate of 0.6 mg/kg over 5 min.[15] In patients with inadequate increase of heart rate of < 10%, an additional dipyridamole infusion of 0.28 mg/kg over 2 min was given. Two min after cessation of dipyridamole infusion, coronary sinus and LAD velocity recordings were repeated. In case of anginal pain during dipyridamole infusion, a bolus of aminophylline (0.12–0.24 g) was administered intravenously. Recordings of LAD and coronary sinus flow velocity were performed in random order to avoid any method-related error due to different time intervals between dipyridamole administration and the respective flow velocity recordings.

Videotape recordings of three cardiac cycles with optimum quality before and after dipyridamole were analyzed. Using commercially available integrated software (VINGMED 800, Sonotron), peak average flow velocity was calculated from manual tracings of the contour of the Doppler velocity curve. Coronary flow reserve was calculated as the ratio of hyperemic to basal average peak velocity by the respective methods.

Statistical Analysis

Data are expressed as mean ± standard deviation. Statistical significance was considered at a p value of <0.05. According to the results of quantitative coronary angiography, patients were stratified into two groups with area stenosis of $<75\%$ and $\geq 75\%$. Sensitivity, specificity, and overall predictive accuracy for diagnosing significant coronary lesions (area stenosis $>75\%$) were evaluated for reversible thallium defects and both transesophageal methods. On the basis of previous studies, a cut-off value of coronary flow reserve of 2.0 for measurements in the LAD[16] and of 1.8 for measurements in the coronary sinus were applied.[13, 14]

Results

Mean area stenosis as assessed by QCA was 71.7 ± 24.1% (range 24–96%) Area stenosis was $<75\%$ in 7 patients and $\geq 75\%$ in 12 patients. Two typical examples of transesophageal Doppler flow velocity recordings and ^{201}Tl scintigrams are presented in Figures 1 and 2.

Thallium-201 Scintigraphy

Myocardial ^{201}Tl adenosine scintigraphy was feasible in all patients. Two patients developed chest pain during adenosine infusion, but premature termination of adenosine infusion was not required in any patient. After adenosine, reversible perfusion defects were observed in 8 of 19 patients. Redistribution scintigrams were normal in all patients. All perfusion abnormalities were confined to the territory of the LAD. Mean area stenosis was 91 ± 4% in patients with positive and 57 ± 22% in patients with negative stress scintigrams, respectively ($p = 0.001$).

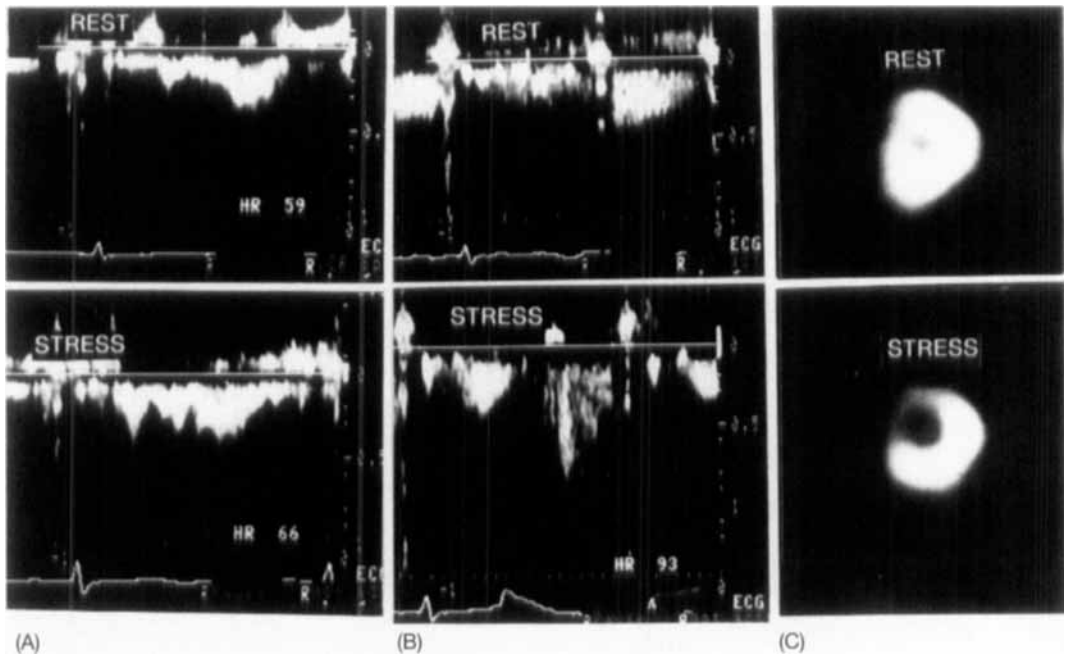

FIG. 2 Patient with 86% area stenosis of the proximal left anterior descending (LAD) artery. (A) Transesophageal Doppler flow velocity recording in the coronary sinus at baseline and after dipyridamole resulting in a coronary flow reserve of 1.3. (B) Transesophageal Doppler flow velocity recording in the proximal LAD at baseline and after dipyridamole resulting in a coronary flow reserve of 1.8. (C) Short-axis adenosine stress/redistribution tomograms at the midventricular level demonstrating a reversible perfusion defect.

Transesophageal Flow Reserve Measurements

Flow reserve measurements were feasible in all patients by the transesophageal coronary sinus method and in all but two patients using the LAD technique. In these two patients, LAD flow velocity recordings of adequate quality could not be achieved. After dipyridamole, chest pain developed in three patients, but no patient required administration of aminophylline. In the total group of patients, mean coronary flow reserve was significantly lower by the transesophageal coronary sinus method compared with LAD measurements (1.74 ± 0.58 vs. 2.28 ± 0.62; $p = 0.0001$).

Comparison of Thallium-201 SPECT and Transesophageal Flow Reserve Measurements

Comparable diagnostic accuracy between ^{201}Tl scintigraphy and both transesophageal methods for prediction of area stenosis >75% was obtained (Table I). Thallium-201 SPECT was positive in 8 of 12 patients with area stenosis of ≥75% and negative in all patients with area stenosis <75%. Using predefined coronary flow reserve cut-off values, 8 of 11 and 9 of 12 patients with an area stenosis of ≥75% were correctly identified by the transesophageal LAD and coronary sinus methods, respectively. Results of both transesophageal techniques concordantly indicated stenosis ≥75% in 9 of 11 (82%) and stenosis <75% in 6 of 6 (100%) patients, respectively. Figure 3 demonstrates the relation between results of transesophageal LAD and coronary sinus methods and percent area stenosis. Results of ^{201}Tl scintigraphy and the transesophageal LAD and coronary sinus method were concordant in 12 of 17 (71%) and 15 of 19 (79%) patients, respectively.

Discussion

Coronary flow reserve measurements are used increasingly to assess the physiologic significance of coronary stenoses.[6–8] However, until now, assessment of coronary flow reserve has required invasive catheter procedures or the availability of positron emission tomography (PET) and is therefore limited to specialized centers. Recently, Doppler TEE has emerged as

TABLE I Accuracy of coronary flow reserve and thallium-201 SPECT for diagnosis of >75% left anterior descending (LAD) area stenosis

Parameter	TEE-LAD (%)	TEE-CS (%)	Thallium (%)
Sensitivity	8/11 (73)	9/12 (75)	8/12 (67)
Specificity	5/6 (83)	6/7 (86)	7/7 (100)
OPV	13/17 (77)	15/19 (79)	15/19 (79)

Results are calculated for a cut-off coronary flow reserve of 2.0 for the LAD and of 1.8 for the coronary sinus method.

Abbreviations: OPV = overall predictive value, TEE-CS = transesophageal coronary sinus flow reserve, TEE-LAD = transesophageal LAD flow reserve.

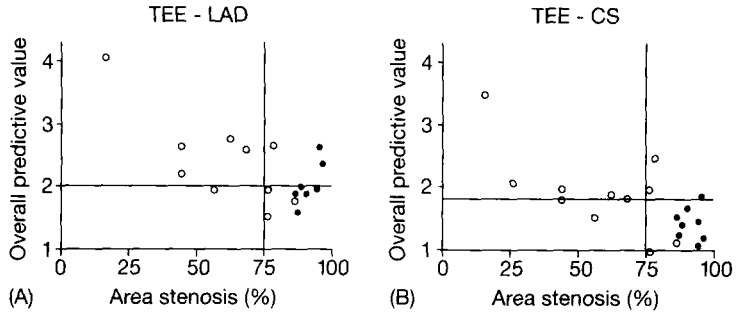

FIG. 3 Relation between results of (A) transesophageal left anterior descending artery (TEE-LAD), (B) coronary sinus (TEE-CS) method and percent area stenosis. A positive result is designated by a coronary flow reserve < 2.0 for TEE-LAD, < 1.8 for TEE-CS, and percent area stenoses > 75%. TL+ = presence of reversible thallium-201 perfusion defect, TL− = absence of reversible thallium perfusion defect. ● = TL+, ○ = TL−.

an alternative noninvasive method for assessment of coronary flow reserve.[11-14]

The present study compared coronary flow reserve measurements by Doppler TEE with ^{201}Tl stress/redistribution SPECT in patients with various degree of proximal LAD stenoses. Concordant results between ^{201}Tl SPECT and transesophageal Doppler measurements were obtained in 71% of patients using the LAD, and in 79% of patients using the coronary sinus technique. Previous studies have compared the results of myocardial scintigraphy with various invasive techniques of coronary flow reserve measurements. Legrand *et al.*, using a digital angiographic technique, reported a coronary flow reserve of < 2.0 to be associated with abnormal myocardial perfusion scintigraphy in 64% of patients.[17] A markedly higher concordance of 94% and 96%, respectively, was obtained when ^{201}Tl SPECT was compared with coronary flow reserve by intracoronary Doppler guidewire measurements.[16, 18] This improved agreement could indicate the superiority of intracoronary Doppler guide wire measurements, but might have also resulted from the nonblinded study design[18] or from different patient selection criteria, as this study included several patients with borderline stenosis.

Both transesophageal techniques and thallium scintigraphy demonstrated similar diagnostic accuracy for prediction of angiographic stenosis severity, ranging from 77 to 79%. Thallium scans were negative in three of our patients with borderline stenosis severity of 76, 76, and 78%, respectively. Notably, coronary flow reserve by both transesophageal techniques was normal in two of these patients, reflecting the discrepancy of anatomic severity and functional significance of coronary stenoses. However, false negative scintigraphic results and residual vasodilator reserve may occur also in patients with significant single-vessel disease. As shown by PET, collateral-dependent myocardium maintains a residual vascular tone and vasodilator capacity despite resting hypoperfusion.[19] In contrast, abnormal flow reserve has been found by PET in myocardial regions remote from the territory of the primary angiographic stenosis.[19, 20]

Recent studies demonstrated the feasibility of transesophageal coronary sinus and LAD flow velocity recordings for the assessment of coronary flow reserve. Initial experience has demonstrated the ability to characterize patient groups with reduced coronary flow reserve as well as to separate patients with various degrees of LAD stenosis.[11-14] However, several methodological problems of the transesophageal Doppler techniques have to be considered. The transesophageal LAD method is limited to the assessment of stenoses within the territory of the LAD and will fail to detect stenoses of other major coronary vessels. Due to the physiology of coronary venous drainage, coronary sinus flow measurements may also reflect other vascular territories. Moreover, quantitative flow measurements cannot be obtained, since the diameter of the LAD is too small to be measured precisely and coronary sinus diameter varies considerably throughout the cardiac cycle. Therefore, coronary flow reserve was derived from the comparison of flow velocity recordings before and after dipyridamole. This is based on the presence of a constant diameter of the LAD and the coronary sinus during vasodilator application.[14, 21] In addition, coronary flow reserve measurements may be influenced by factors other than epicardial coronary stenosis, such as the presence of small vessel disease or left ventricular hypertrophy. In contrast, thallium scintigraphy provides regional information within the territories of all three major coronary vessels and may also facilitate quantitative analysis, although it, too, may have inherent problems.[3,4] Scintigraphic defects despite a normal coronary angiogram have been described in patients with syndrome X, left ventricular hypertrophy, or left bundle-branch block.

Study Limitations

Different vasodilators were used for thallium and transesophageal measurements. However, the dosages of adenosine and dipyridamole in the present study were reported to produce comparable coronary hyperemia in the majority of patients.[22] Although considerable variation of individual vasodilator response to these agents may occur, average flow ratios were similar for both agents (4.3 ± 1.6 for adenosine and 4.0 ± 1.3 for dipyridamole).[22] Also, in clinical studies no significant difference between detection rates of significant coronary lesions has been reported when using dipyridamole or adeno-

sine.[5] Thus it seems unlikely that the use of different vasodilative stressors would have altered the results significantly.

The present study only incorporated highly selected patients with typical chest pain and single-vessel disease of the proximal LAD. This appears to be also a potential disadvantage when compared with direct intracoronary Doppler and ^{201}Tl imaging techniques, which both can deliver information of all territories, although tracer techniques as well, which are based on relative differences of perfusion, may have limitations in multivessel disease, with a decreasing sensitivity from the most severe lesion to other coronary stenoses. The present results are therefore not necessarily applicable for patients with low or medium likelihood of coronary artery disease. Further studies will be necessary to evaluate patients with more distal stenoses as well as patients with stenoses of the left circumflex coronary artery.

Conclusion

This study suggests that the accuracy of transesophageal Doppler assessment for diagnosing significant proximal LAD stenosis is similar to ^{201}Tl scintigraphy. Therefore, the transesophageal Doppler techniques might constitute an alternative, noninvasive method for the evaluation of significant LAD coronary artery disease, especially if radionuclide imaging is not available.

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