

Transthoracic measurement of left coronary artery flow reserve improves the diagnostic value of routine dipyridamole-atropine stress echocardiogram

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Abstract

Introduction: We hypothesized that coronary flow reserve (CFR) in the left anterior descending artery (LAD) can be effectively measured during an accelerated dipyridamole-atropine stress echocardiography (DASE) protocol to improve the diagnostic performance of the test.

Material and methods: In 64 patients with suspected or known coronary artery disease scheduled for coronary angiography DASE with concomitant CFR measurement in LAD was performed.

Results: Coronary flow reserve measurement and calculation were feasible in 83% of patients. The positive predictive value of undetectable LAD flow was 81% for severe LAD disease. Measured values of CFR were in the range 1.3–4.1 (mean: 2.2 ± 0.7). Significantly lower CFR was found in patients with LAD disease (1.97 ± 0.62 vs. 2.55 ± 0.57 , $p = 0.0015$). The optimal cutoff for detecting $\geq 50\%$ stenosis was $CFR \leq 2.1$ (ROC AUC 0.776), corresponding with 68% sensitivity and 84% specificity. In patients with negative DASE results 67% of patients with LAD disease had abnormal CFR, whereas in patients with a positive DASE result 92% of patients with normal LAD had normal CFR. The DASE diagnostic accuracy for the detection of coronary artery disease (CAD) increased from 75% to 85% when CFR measurement was added to wall motion abnormality (WMA) analysis. No test with both abnormalities was false positive for the detection of coronary disease.

Conclusions: Incorporation of CFR measurement into WMA-based stress echocardiography is feasible even in an accelerated DASE protocol and can be translated into an approximate gain of 10% in overall test accuracy.

Key words: coronary circulation, cardiac ultrasound, stress echocardiography.

Introduction

Assessing the state of coronary circulation via stress echocardiography is an important tool in evaluating patients with angina and in determining the prognosis and severity of their condition [1, 2]. Echocardiographic assessment of myocardial ischemia is most often indirectly inferred from inducing wall motion abnormalities in stress conditions. Two main avenues exist by which stress echocardiography can be performed: through exercise or pharmacologically. Stress echocardiography by either method, based on evaluation of wall motion abnormalities, has comparable sensitivity and specificity for the detection of coronary artery disease [2, 3]. Anoth-

er option is direct visualization of coronary arteries, which may be challenging from either a transesophageal or a transthoracic window. Nevertheless, a careful study technique allows for direct visualization of stenotic sites [4, 5].

Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demand and can be assessed using transthoracic Doppler echocardiography (TDE) [6]. The method has been studied in various clinical conditions [7–9]. However, the usual pharmacological protocol used for CFR calculation (with adenosine) is less convenient for concomitant assessment of wall motion abnormalities (WMA) – a basic marker of coronary ischemia in stress echocardiography [10]. We hypothesized that CFR in left anterior descending (LAD) can be effectively studied during a high-dose dipyridamole-atropine stress protocol to improve the diagnostic performance of the test.

Material and methods

Patients

The study group comprised 64 consecutive patients with suspected or known coronary artery disease (CAD) scheduled for coronary angiography in our institution. Exclusion criteria included: recent history of acute coronary syndrome (less than 14 days prior to study enrolment), clinical and hemodynamic instability, contraindications for dipyridamole and atropine, previous angiographic diagnosis of non-coronary myocardial disease, and any change in clinical status in the period between enrolment and coronary angiography. Table I presents characteristics of the study group.

Study protocol

Within 7 days preceding coronary angiography dipyridamole-atropine stress echocardiography (DASE) was performed using an accelerated protocol – dipyridamole (0.84 mg/kg) was infused intravenously over 4 min [11]. In patients without new or worsening WMA who did not achieve 85% of age-predicted maximal heart rate (220-age) atropine (up to 1.0 mg) was injected. After the examination, a dose of 250 mg aminophylline was given to all patients.

Echocardiographic images for WMA analysis were acquired at baseline and peak stress in 3 standard apical views using grayscale harmonic imaging (Acuson Sequoia C256, Siemens Medical Solutions USA, Inc.). Coronary flow reserve was calculated based on 2 measurements of distal LAD flow – the first measurements were taken at baseline and the next ones during the peak phase of DASE after completion of routine WMA-directed imaging (Figure 1). Two investigators blinded to clinical and angiographic data together reviewed all the studies. Differences

in opinion were resolved by consensus. Wall motion was assessed qualitatively at baseline and during stress using the 18-segment model (each wall in each apical view was divided into basal, middle, and apical segments). Wall motion was scored in each of the 18 segments as normal, hypokinetic, akinetic, or dyskinetic. Inducible WMA was defined as worsening of wall motion during stress in 2 or more adjacent segments that were initially normal or hypokinetic. Wall motion abnormalities was considered fixed if its relative magnitude remained unchanged between rest and stress.

Selective coronary angiography was performed using the Judkins or Sones technique. The angiograms were analyzed quantitatively (Centricity AI 1000 GEMnet GE QCA 2.0, Camtronics Medical Systems Inc., Hartland, WI, USA) by a single investigator blinded to all other data. Left anterior descending disease was defined as $\geq 50\%$ of arterial diameter stenosis as measured by quantitative coronary angiography.

The study protocol was approved by the Ethics Committee of our institution and written consent was obtained from all participants.

Statistical analysis

Continuous and categorical variables are expressed as mean \pm SD and as percentages (%), respectively. The sensitivity, specificity and predictive values were calculated according to standard formulas. The relationships were evaluated using linear univariate regression analysis between the variables. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value for CFR, diagnostic for LAD disease. A *p*-value < 0.05 was considered statistically significant.

Table I. Study population characteristics

Parameter	Results
Patients	64
Male	44
Female	20
Age [years]	58 \pm 9 (36–77)
Height [cm]	168 \pm 9
Weight [kg]	76 \pm 15
BMI [kg/m ²]	27 \pm 4
History of MI, <i>n</i> (%)	20 (31)
Mean CCS class, <i>n</i> (%)	2.4
History of hypertension, <i>n</i> (%)	32 (50)
Diabetic, <i>n</i> (%)	10 (16)
Hypercholesterolemia, <i>n</i> (%)	34 (53)
Smoker, <i>n</i> (%)	16 (25)
Previous smoker, <i>n</i> (%)	27 (42)

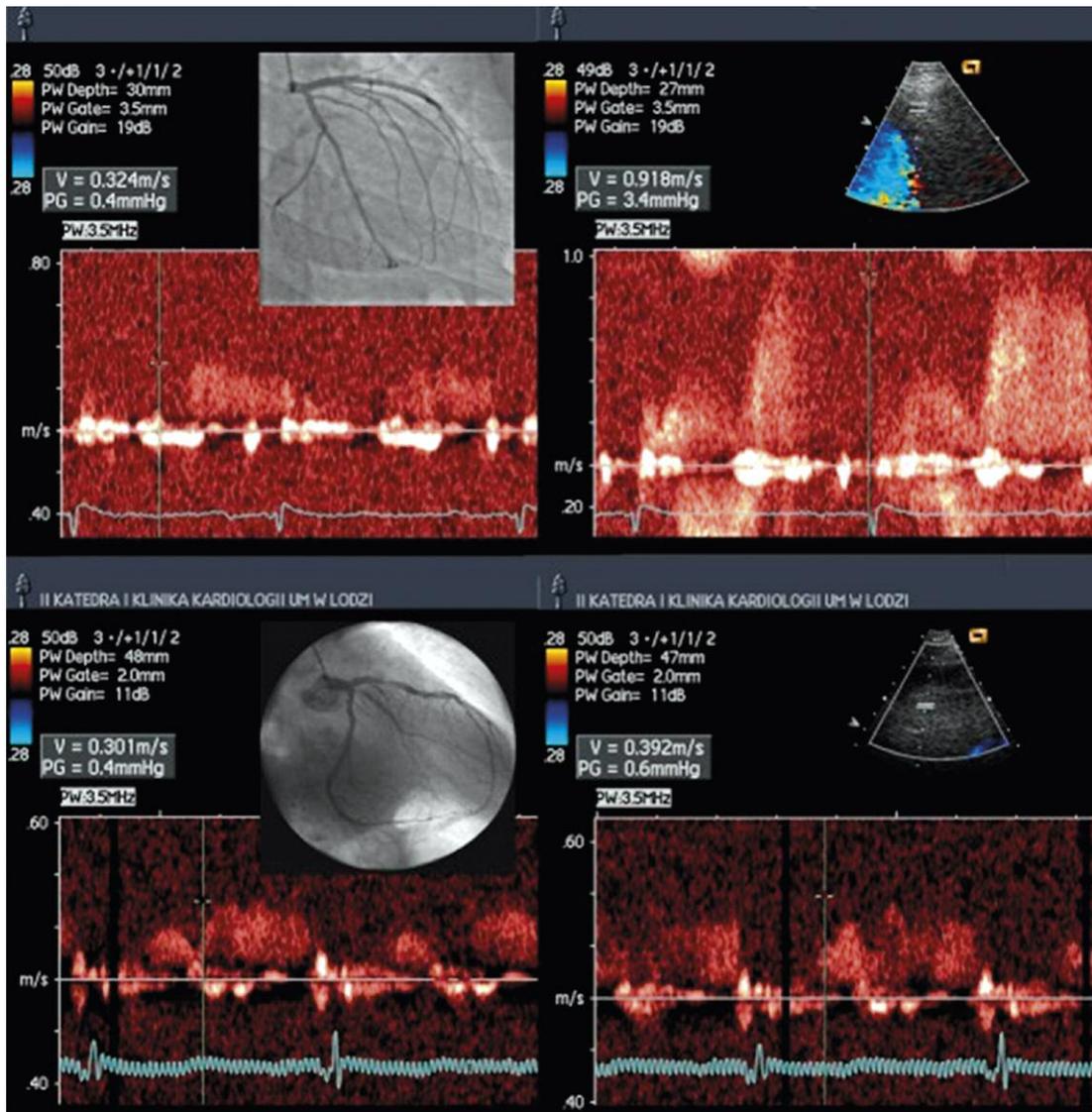


Figure 1 Examples of CFR measurements. Left panels represent baseline flow in distal portion of LAD, right panels represent flow at peak stress. Upper panels – CFR in a patient with normal LAD (inset). Lower panels – Reduced CFR in a patient with significant LAD stenosis (inset)

Results

Significant ($\geq 50\%$) LAD disease was present in 42 patients, including 7 with total arterial occlusion. The rapid DASE protocol was well tolerated and all studies were completed. Atropine was administered in 49 out of 53 patients (92%). Relevant measurements obtained during clinical and echocardiographic examination are reported in Table II. During DASE there was an average increase in heart rate of 36 bpm and an insignificant change in blood pressure.

Coronary flow reserve and left anterior descending disease

Coronary flow reserve measurement and calculation were feasible in 53 patients (83%). Eleven

patients had undetectable distal LAD flow. In 9 cases it was due to severe LAD disease: either total occlusion (6 cases) or critical (95%) stenosis (3 cases). With the protocol applied, the positive predictive value of undetectable LAD flow was thus 81% for severe LAD disease.

Measured values of CFR were in the range 1.3–4.1 (2.2 ± 0.7) corresponding with resting LAD flow of 14–60 cm/s (mean 28 ± 9) and peak LAD flow of 29–119 cm/s (mean: 58 ± 21). A significantly lower CFR was characteristic in patients with LAD disease (1.97 ± 0.62 vs. 2.55 ± 0.57 , $p = 0.0015$). There was also a significant ($p = 0.008$) negative linear relationship between CFR and maximal diameter stenosis of LAD (Figure 2).

The optimal cutoff for detecting $\geq 50\%$ stenosis was $\text{CFR} \leq 2.1$ (ROC AUC 0.776), corresponding

Table II. Results of CFR measurements during DASE

Parameter	Results
Patients, <i>n</i> (%)	64
CFR measurements performed	53 (83)
CFR unattainable	11 (17)
HR [bpm]	
Before	66 ±10
Peak phase	102 ±15
BP [mm Hg]	
Baseline	123 ±22/68 ±13
Peak phase	123 ±24/70 ±15
CFR	2.2 ±0.7 (1.3–4.1)
LAD disease	1.97 ±0.62
Without LAD disease	2.55 ±0.57
LAD flow [cm/s]	
Resting	28 ±9 (14–60)
Peak flow	58 ±21 (29–119)

with a sensitivity of 68% and specificity of 84% (Figure 3). There were no false positive cases with $CFR \leq 1.8$.

Combining assessment of wall motion abnormalities and coronary flow reserve

In patients with negative DASE results (no induced WMA), 6/9 patients (67%) with LAD disease had abnormal CFR, whereas in patients with a WMA-positive DASE result 12/13 patients (92%) with normal LAD had normal CFR.

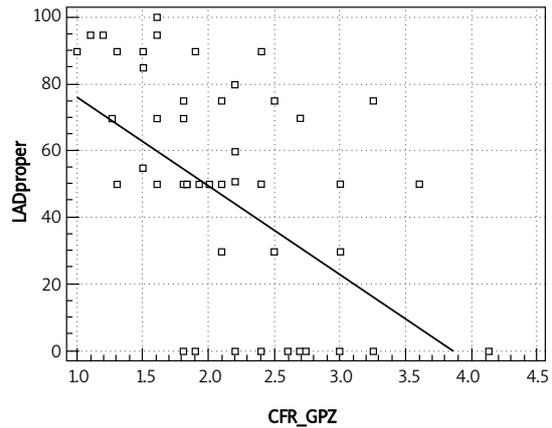


Figure 2. Relationship between CFR of LAD (horizontal axis) and vessel stenosis severity (vertical axis). Regression equation: $\%stenosis = 102 - 26.5 \times CFR$; $r = 0.44$, $p = 0.008$

The diagnostic accuracy for coronary disease using either abnormal WMA or CFR as a criterion for positivity increased from 75% to 85%. No test with both abnormalities was false positive for the detection of coronary disease.

Discussion

In our study, WMA and CFR measurements of LAD assessed in concert provided better diagnostic accuracy for detecting underlying coronary disease involving LAD than WMA alone. Coronary flow reserve of LAD can be measured as an extension of accelerated DASE with a success rate of 83% (most cases of recording failure correspond with critical

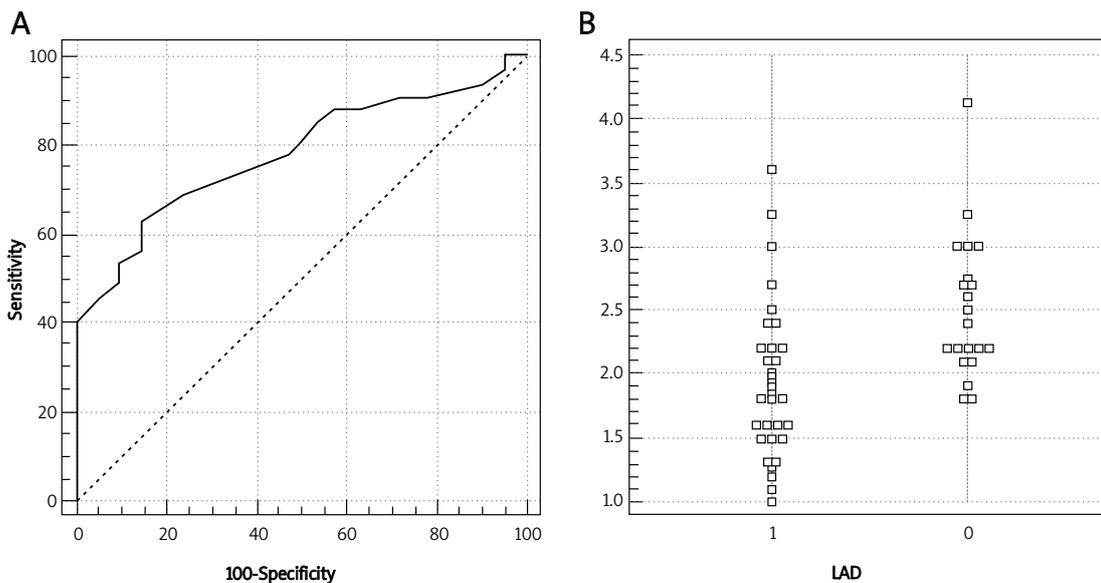


Figure 3. **A** – ROC curve of CFR measurement for the detection of significant LAD disease. **B** – Distribution of CFR values in patients with (group 1) and without significant LAD disease (group 2)

LAD disease and resting WMA). The efficacy of CFR as an adjunct to WMA analysis was demonstrated by its ability to reveal underlying disease of the LAD in 67% of patients who had a false-negative DASE test and concomitantly exclude 92% of false-positive DASE results.

Improvement of the diagnostic value of stress echocardiography

Current guidelines, from both the American Society of Echocardiography and the European Association of Echocardiography on stress echocardiography, base interpretation of the test solely on WMA [2, 3]. Nevertheless, in an attempt to increase the diagnostic accuracy of standard techniques, various modifications have been proposed – one of them is concomitant assessment of CFR. A meta-analysis on the combined diagnostic value of the assessment of WMA along with CFR during standard dipyridamole stress echocardiography by 5 studies indicated a diagnostic accuracy of $89 \pm 7\%$ compared to $79 \pm 5\%$ with WMA analysis alone. The vast improvement was attributable to a large increase in sensitivity (90 ± 3 vs. 67 ± 9) at the expense of a modest decrease in specificity (86 ± 12 vs. 93 ± 2) [6]. Interestingly, the increase in sensitivity and subsequent improvement of diagnostic accuracy of 10% as reported by Rigo paralleled our result. It was suggested that improved sensitivity may be partially explained by the ability of CFR to unmask coronary disease in those treated with anti-anginal medication. In general, it can be expected that CFR will become abnormal earlier than the absolute flow is decreased to the degree causing detectable wall motion abnormalities. Thus, patients who do not cross the ischemic threshold during the test may present with an abnormal CFR value alone [6].

Other modifications of stress echocardiography aimed at improvement of the technique's diagnostic and prognostic value include contrast echocardiography and quantitative assessment of regional myocardial function (strain and strain rate measurements). The approved indication for use of contrast during stress echocardiography is based on improvement of endocardial border delineation in patients with suboptimal image quality [12]. It translates into an increase in confidence of interpretation and improved reproducibility and accuracy of left-ventricular function assessment [13]. Even more promising is the potential use of contrast for myocardial perfusion imaging during stress echocardiography [14]. The scientific evidence for increase in diagnostic accuracy resulting from incorporation of myocardial contrast echocardiography into stress echocardiography protocols is substantial [11, 15, 16]. However, so far, neither has it been registered as an official indication for contrast use, nor is it

recommended in current guidelines [2, 3]. The quantitative assessment of regional myocardial function (strain and strain rate measurements) as an aid to analysis of stress echocardiography has also been shown to increase the technique's diagnostic value [17, 18]. However, due to often time-consuming off-line analysis the widespread clinical use of this innovation awaits introduction of reliable semi-automatic tools.

Despite its usefulness, CFR assessment has some limitations. Obtaining CFR measurements via transthoracic echocardiography requires specific expertise and may sometimes be time-consuming. While in most cases LAD assessment may be easily performed, other coronary arteries remain challenging to evaluate due to both technical and anatomical constraints. Moreover, CFR alone cannot distinguish between microvascular and macrovascular coronary disease and is relatively nonspecific when other myocardial abnormalities coexist [6].

As mentioned above, to avoid referral bias, in our study we included patients who were already scheduled for coronary angiography. Therefore, the study group comprised a large number of high-risk patients and patients with history of myocardial infarction. Not surprisingly, the percentage of patients with significant CAD was high. This could have influenced the sensitivity, specificity and diagnostic accuracy of the analyzed methods. Similarly, the pharmacological treatment could have influenced the results, but due to the relatively small number of patients such sub-analysis was not feasible.

The presented data are promising, but need confirmation on a larger study group.

In conclusion, our study demonstrates that the incorporation of CFR measurement into WMA-based stress echocardiography is feasible even in an accelerated DASE protocol and can be translated into an approximate gain of 10% in overall test accuracy. Thus, the inclusion of CFR in the DASE protocol for the identification of coronary artery disease should be considered.

Acknowledgments

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