The additive prognostic value of wall motion abnormalities and coronary flow reserve during dipyridamole stress echo

Fausto Rigo, Rosa Sicari, Sonia Gherardi, Ana Djordjevic-Dikic, Lauro Cortigiani, and Eugenio Picano

Aims
The aim of the study was to evaluate the prognostic value of Doppler echocardiographic-derived coronary flow reserve (CFR) over regional wall motion in patients with known or suspected coronary artery disease (CAD) undergoing dipyridamole echocardiography test (DET).

Methods and results
In a prospective, multicentre, observational study, we evaluated 1145 patients (702 males; 64 ± 11 years) who underwent high-dose dipyridamole (0.84 mg/kg over 6 min) stress echo with CFR evaluation of LAD by Doppler. DET was positive for regional wall motion abnormalities in 291 (25%) and negative in 854 (74%) patients. Mean CFR was 2.2 ± 0.5. At individual patient analysis 702 patients had normal (CFR > 2.0) and 443 had abnormal CFR on LAD. During a median follow-up of 27 months, 109 events occurred: 16 deaths, 17 non-fatal myocardial infarctions, 76 re-hospitalizations for unstable angina. The 30 months infarction-free survival showed the best outcome for those patients with negative DET by wall motion criteria and normal CFR and the worst outcome for patients with positive DET by wall motion and abnormal CFR (99 vs. 68%, P < 0.001). At multivariable analysis, CFR on LAD [hazard ratio (HR) 2.4, 95% CI 1.1–5.4, P = 0.030], medical therapy at time of testing (HR 2.8, 95% CI 1.2–6.6, P = 0.022), DET positivity for regional wall motion abnormalities (HR 3.6, 95% CI 1.5–8.7, P = 0.000), and angina on effort (HR 6.3, 95% CI 2.7–14.8, P = 0.000) were independent prognostic predictors of hard cardiac events.

Conclusion
In patients with known or suspected CAD, DET result by wall motion criteria and CFR are additive and complementary for the identification of patients at risk of experiencing hard events.

Keywords
Coronary flow reserve, Dipyridamole stress echocardiography, Prognosis

Pharmacological stress echocardiography is an established cost-effective technique for the detection and prognostication of coronary artery disease (CAD).1 In fact, in patients with known or suspected CAD pharmacological stress echocardiography with either dipyridamole or dobutamine is an independent predictor of cardiac death, incremental to other clinical, rest echocardiographic, and angiographic parameters.2 Coronary flow reserve (CFR) evaluated by pulsed Doppler echocardiography associated with vasodilatory stress has recently entered the stress echo lab.3–6 The combination of conventional, wall motion analysis with 2D-echo and CFR with pulsed Doppler flowmetry of mid-distal left anterior descending (LAD) artery has been proved to increase test sensitivity with only a modest loss in specificity.7–10 The potential prognostic role of CFR through this non-invasive approach has recently been tested in predicting different clinical situations. The presence of an abnormal CFR during dipyridamole infusion in patients with dilated non-ischaemic cardiomyopathy identifies a subgroup of patients with LV dysfunction at high risk of developing progressive ventricular deterioration and heart failure.11,12 The added prognostic role of impairment of CFR in

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* Corresponding author. Tel: +39 050 3152397, Fax: +39 050 3152216, Email: rosas@ifc.cnr.it

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patients with normal dipyridamole stress echo has previously been demonstrated: these patients showed a worse outcome during a mean follow-up of 24 months.13 The aim of the present study was to assess the additional prognostic value of CFR over regional wall motion analysis in patients with known or suspected CAD.

Methods

Patients

We prospectively initially considered 1177 in-hospital patients with chest pain syndrome. They were enrolled in the study starting August 2002 to June 2005 from the Cardiology Division of Mestre, Venezia, Cesena, Lucca, Pisa, in Italy and Belgrade (Serbia). All patients met the following inclusion criteria: (i) stable chest pain syndrome; (ii) eligibility to dipyridamole stress echo by standard wall motion criteria; (iii) enrolment in a follow-up program.

Exclusion criteria were (i) technically poor acoustic window precluding satisfactory imaging of left ventricle (for 2D echo) or of LAD coronary artery flow Doppler (for CFR assessment); (ii) severe valvular heart disease; (iii) unwillingness to give informed consent.

Of the 1177 patients initially selected for the study, 11 (1%) were excluded for inadequate echocardiographic image quality during stress precluding satisfactory imaging of LAD flow, 17 (1.4%) were excluded for inadequate wall motion analysis, and four additional patients (0.3%) were lost to follow-up. Thus, 1145 patients (702 males; 64 ± 11 years) represent the final study group. Of them, 541 had angiographically significant CAD (stenosis >70%), Hypercholesterolaemia14 was defined according to standard definition. According to individual needs and physician’s choices, 562 patients were evaluated after antianginal drugs had been discontinued, and 583 patients were evaluated during antianginal treatment (nitrates and/or calcium antagonists and/or beta-blockers). The study was approved by the Institutional review board. All patients gave their written informed consent when they underwent stress echocardiography. When patients signed the written informed consent they also authorized physicians to use their clinical data. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care. All patients were followed-up for a median of 27 months (first quartile 23.9, third quartile 30) with a minimum pre-defined follow-up time of 3 months.

Resting and stress echocardiography

Transthoracic stress echocardiographic studies were performed with commercially available ultrasound machine (Sonos 5500–7500 Philips Ultrasound, Andover, MA, Sequoia C256 Acuson Siemens Mountain View, CA, and Vivid System 7, GE/Vingmed, Milwaukee, WI) equipped with multifrequency phased-array sector scan probe (S3–S8 or V3–V7) and with second harmonic technology. All standard echocardiographic views were obtained when possible: parasternal long- and short-axis, apical 2, 3, and 4 chamber, and sub-sternal views. Besides the classic projections for stress echocardiography testing, specific projection for LAD coronary artery imaging is integrated into the cardiac imaging sequence. Two-dimensional echocardiography and 12-lead electrocardiographic (ECG) monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 min) in accordance to well-established protocol15,16 (Figure 1). During the procedure, blood pressure and ECG were recorded each minute. The left ventricle was divided into 17 segments as suggested by the American Heart Association and American Society of Echocardiography.17,18 Segmental wall motion was graded as follows: normal = 1; hypokinetic = 2; akinetic = 3; and dyskinetic = 4. Wall Motion Score Index (WMSI) was derived by dividing the sum of individual visualized segments scores by the number of visualized segments.15

CFR was performed during the standard stress echo examination by a semi-simultaneous imaging of both wall motion and LAD flow.7 Coronary flow in the mid-distal portion of LAD was searched in the low parasternal long-axis cross-section under the guidance of colour Doppler flow mapping.15 If no colour-coded blood flow from the LAD was visualized at the baseline condition, the procedure was attempted a second time during contrast enhancement with Sonovue (Bracco-Byk-Gulden, Konstanz, Germany) in bolus (0.5 mL intravenously) in 279 patients (24% of the total population).

All studies were digitally stored to simplify off-line reviewing and measurements. Coronary flow parameters were analysed off-line by use of the built-in calculation package of the ultrasound unit. Flow velocities were measured at least twice for each study: at baseline and at peak stress (before aminophylline injection). At each time point, three optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. Coronary blood flow velocity reserve was defined as the ratio between hyperaemic and basal peak diastolic coronary flow. CFR was considered normal when it was >2.19

Quality control of the diagnostic performance in the different centres was of critical importance to acquire meaningful information into the data bank. In the enrolled centres, the quality control was performed based upon two criteria, each one having to be met to fulfill the quality control requirements. The first criterion was tested on digitally acquired 20 stress echo studies prepared in the coordinating centre (Institute of Clinical Physiology in Pisa). In all these 20 studies, the reading of two experienced independent observers was concordant as to presence and site of dysynergy, and the stress results were in full agreement with presence and site of coronary stenoses during coronary angiography. The unanimous reading of the two observers was arbitrarily assumed to be the ‘gold standard’ against which to evaluate the reading of each participating centre. The reader from each centre interpreted the images of the 20 cases in a blinded fashion, with no access either to clinical and angiographic data or to the interpretation given by other observers. It was assumed a priori that the minimum threshold of concordance to pass this part of the quality control had to be ≥90%. The second criterion consisted in random sampling 20 consecutive studies from each contributing centre. These 20 studies were examined in a blinded fashion by an experienced cardiologist—echocardiographist of the coordinating centre—whose reading was arbitrarily assumed to be the ‘gold standard’. It was assumed a priori that the minimum threshold of concordance to pass the quality control had to be ≥80%. The lower concordance cutoff in comparison with the first type of reading is due to the fact that this second set of digital images was not selected on the basis of the superior quality but randomly sampled from each centre in a consecutive fashion.10–12

Doppler technique is more technically demanding than 2D wall motion study: the meaningful signal is more difficult to acquire, but much easier to measure. All our readers were accredited to enter the study after three conditions were met: long-standing experience with the technique; previous accreditation with 2D echo quality control criteria (discussed earlier); intense hands-on training period with interpretation of > 100 studies with the same senior investigator (F.R.) with ad hoc stress echo schools.7,19

Follow-up data

Outcome was determined from patients interview at the outpatient clinic, hospital chart reviews, and telephone interviews with the
patient, his/her close relative, or referring physician. The clinical events recorded during the follow-up were death, non-fatal myocardial infarction, and re-hospitalization for unstable angina. In order to avoid misclassification of the cause of death, overall mortality was considered. Myocardial infarction was defined by typical symptoms, ST changes on electrocardiogram, and cardiac enzyme changes. Unstable angina was an acute coronary syndrome causing typical chest pain, cardiac enzyme elevation and/or, ECG modifications consistent with acute ischaemia requiring hospitalization. Follow-up data were analysed for the prediction of death, non-fatal myocardial infarction, or re-hospitalization for unstable angina. The primary end-point is hard events and the secondary end-point is spontaneous events. When more than one of these events occurred, the patient was censored at the time of the most severe event. When revascularization was performed, follow-up was censored at the time of revascularization procedure.

Statistical analysis
The statistical analyses included descriptive statistics (frequency and percentage of categorical variables and mean and standard deviation of continuous variables), Kaplan–Meier survival curves. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model. The individual effect of certain variable on event-free survival was evaluated with the use of the Cox regression model (SPSS statistical software, SPSS Inc., Chicago, IL and S-plus 6.1). To adjust for several risk factors, multivariable Cox analysis was performed with all the variables found to be significant at the univariable analysis entering in a single step. The proportional hazards assumptions of Cox’s model was verified with the linear correlation test. A significance of 0.05 was required for a variable to be included into the multivariable model, while 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence interval (CI) were estimated.

Results
The main clinical and echocardiographic data are reported in Table 1.

Stress echocardiographic findings
Test was positive for wall motion criteria in 291 patients (25%). Mean CFR value was 2.23 ± 0.6. At individual patient analysis, 702 patients had normal (CFR >2.0) and 443 had abnormal CFR on LAD. Patients with an abnormal CFR had a higher WMSI at rest and at peak stress compared with those with a normal CFR (1.2 ± 0.3 vs. 1.1 ± 0.2, p = 0.001, and 1.3 ± 0.4 vs. 1.16 ± 0.25, p = 0.001, respectively). In the patients with angiographically assessed CAD (Table 1), LAD with a significant stenosis >70% was involved in 163 of those with single-vessel disease and in 215 of those with multivessel disease. Of the 541 patients with significant CAD at angiography, 121 were in the DET ➔ CFR <2 class, 74 of these were under anti-ischaemic medical therapy (61%).
Follow-up data: hard and spontaneous cardiac events

During a median follow-up of 27 months (first quartile 23.9, third quartile 30), a total of 109 (9.4%) events (16 deaths and 17 non-fatal myocardial infarction and 76 re-hospitalization for unstable angina) occurred. Myocardial revascularization was performed in 261 (23%) patients who were censored from follow-up at this time. The 30 months infarction-free survival showed a significant better outcome for those patients with negative dipyridamole echocardiography test (DET) by wall motion criteria and normal CFR ([Figures 2 and 3]), whereas the worst outcome was observed in patients with positive DET and impaired CFR.

Univariate predictors of hard and spontaneous events are reported in Table 2. At multivariable analysis, CFR on LAD (HR 2.4, 95% CI 1.1–5.4, \(P = 0.030\)), medical therapy at time of testing (HR 2.8, 95% CI 1.2–6.6, \(P = 0.022\)), DET positivity for regional wall motion abnormalities (HR 3.6, 95% CI 1.5–8.7, \(P = 0.000\)), angina on effort (HR 6.3, 95% CI 2.7–14.8, \(P = 0.000\)) were independent prognostic predictors of hard cardiac events. CFR on LAD maintains its additive and independent prognostic value over WMSI at peak stress when the two variables are analysed in the same model: WMSI at peak stress (HR 2.3, 95% CI 1.5–3.5, \(P = 0.000\)), CFR on LAD (HR 4.9, 95% CI 3.2–7.6, \(P = 0.000\)).

### Table 1 Rest and stress findings in the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1145</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>702/443</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>333 (29%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>711 (62%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>226 (20%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>706 (62%)</td>
</tr>
<tr>
<td>Angina on effort</td>
<td>266 (23%)</td>
</tr>
<tr>
<td>Angina at rest</td>
<td>89 (8%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>390 (34%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>291 (25%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>86 (8%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>54 ± 7</td>
</tr>
<tr>
<td>Wall motion score index at rest</td>
<td>1.18 ± 0.3</td>
</tr>
<tr>
<td>Wall motion score index at peak stress</td>
<td>1.22 ± 0.3</td>
</tr>
<tr>
<td>Test positivity for wall motion criteria</td>
<td>291 (25%)</td>
</tr>
<tr>
<td>Delta wall motion score index</td>
<td>0.36 ± 0.13</td>
</tr>
<tr>
<td>Coronary flow reserve on LAD</td>
<td>2.23 ± 0.6</td>
</tr>
<tr>
<td>Patients with CFR &gt;2</td>
<td>702 (61%)</td>
</tr>
<tr>
<td>Test performed on antianginal therapy</td>
<td>583 (51%)</td>
</tr>
<tr>
<td>Beta-blocking agents</td>
<td>406 (35%)</td>
</tr>
<tr>
<td>Calcium-antagonists</td>
<td>307 (27%)</td>
</tr>
<tr>
<td>Long-acting nitrates</td>
<td>220 (19%)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>960 (84%)</td>
</tr>
<tr>
<td>Non-significant CAD</td>
<td>419 (44%)</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>286 (30%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>255 (27%)</td>
</tr>
</tbody>
</table>

LAD, anterior descending artery; CFR, coronary flow reserve; PCI, coronary angioplasty; CABG, coronary artery bypass grafting; CAD, coronary artery disease.

### Figures

**Figure 2** Kaplan–Meier survival curves (considering hard cardiac events as an endpoint) in patients stratified according to presence (DET+) or absence (DET−) of myocardial ischaemia at high-dose dipyridamole stress echocardiography and normal (CFR >2) or abnormal (CFR <2) coronary flow reserve at Doppler echocardiography. Survival rate in CFR >2/DET− class is significantly different from CFR <2/DET− (\(P < 0.001\)), from CFR >2/DET+ (\(P < 0.000\)), from CFR <2/DET+ (\(P < 0.000\)). The best survival is observed in patients with no inducible ischaemia and normal coronary flow reserve; the worst survival is observed in patients with inducible ischaemia and impaired coronary flow reserve.

**Figure 3** Kaplan–Meier survival curves (considering spontaneous cardiac events as an endpoint) in patients stratified according to presence (DET+) or absence (DET−) of myocardial ischaemia at high-dose dipyridamole stress echocardiography and normal (CFR >2) or abnormal (CFR <2) coronary flow reserve at Doppler echocardiography. Survival rate in CFR >2/DET− class is significantly different from CFR <2/DET− (\(P < 0.001\)), from CFR >2/DET+ (\(P < 0.000\)), from CFR <2/DET+ (\(P < 0.000\)). The best survival is observed in patients with no inducible ischaemia and normal coronary flow reserve; the worst survival is observed in patients with inducible ischaemia and impaired coronary flow reserve.
Of the 960 patients who underwent coronary angiography, 541 had significant CAD. When we analysed the survival rate in those with LAD involvement vs. those with other CAD disease no difference was observed both for hard and spontaneous events \((\log-\text{rank} \ 0.023, \ P = 0.879, \text{and } 1.88, \ P = 0.170, \text{respectively})\). In the Cox model, CFR did not predict hard events both in patients with LAD involvement and in those with other CAD disease: \((\text{HR } 3.3, \ 95\% \ CI \ 0.86–12.9, \ P = 0.079)\) and \((\text{HR } 2.0, \ 95\% \ CI \ 0.76–5.5, \ P = 0.152)\), respectively. When the prediction of spontaneous events was analysed in the Cox model, an abnormal CFR had an HR of 2.6. 95\% CI 1.5–4.7, \(P = 0.001\) in patient with no LAD involvement and an HR of 3.2, 95\% CI 1.3–7.8, \(P = 0.007\) in patients with LAD involvement.

## Discussion

In patients with known or suspected CAD wall motion changes and Doppler-derived CFR during dipyridamole stress echocardiography are additive and complementary for the identification of patients at higher risk of experiencing hard events. A reduced CFR is an additional parameter to be considered in the risk stratification of the stress echocardiographic response, whereas patients with a negative test and normal CFR have a favourable outcome.

## Comparison with previous studies

The assessment of CFR adds sensitivity for LAD disease—with a modest loss in specificity. In reality, the inherently quantitative information of LAD flow reserve allows a stratification of the response, integrating many different tests into one: greatly reduced CFR \((<1.5)\) yields extraordinary specificity while mildly reduced CFR \((<2.0)\) offers outstanding sensitivity. The independent prognostic value of pulsed Doppler-derived CFR during dipyridamole stress echocardiography was already demonstrated in patients with known or suspected CAD.\(^{13}\) In a series of 327 patients with a negative high-dose dipyridamole stress echo, Rigo et al.\(^{13}\) showed that the presence of an abnormal CFR was related to a worse outcome. It was also demonstrated that CFR is a good predictor of adverse events relative to the relationship with left ventricular remodelling after anterior myocardial infarction treated with coronary angioplasty.\(^{24}\) The prognostic impact of CFR has been recently proved also in patients with non-ischaemic dilated cardiomyopathy:\(^{12}\) an abnormal CFR detectable by Doppler echocardiography identifies a subset of patients at higher risk of spontaneous events (death and worsening of clinical status). In patients with idiopathic dilated cardiomyopathy, a reduced CFR and the absence of an inotropic response during vasodilator stress are additive in predicting a worse prognosis.\(^{12}\) CFR provides independent prognostic information also in diabetic and non-diabetic patients with known or suspected CAD and negative dipyridamole stress echocardiography for wall motion criteria.\(^{25}\) The present data confirm and expand the additive information obtained during dual imaging stress echocardiography in which the wall motion analysis is evaluated in the same setting with CFR. A positive stress echo by wall motion criteria identifies patients at higher risk of experiencing hard cardiac events as demonstrated in large patient populations and in several clinical

### Table 2: Univariate predictors of hard (death and non-fatal myocardial infarction) and spontaneous events (death, non-fatal myocardial infarction, and re-hospitalizations for unstable angina)

<table>
<thead>
<tr>
<th></th>
<th>Hard events</th>
<th></th>
<th>Spontaneous events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (0.9–1.06)</td>
<td>0.055</td>
<td>1.0 (1.0–1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>3.3 (1.4–8.0)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.9 (0.4–1.8)</td>
<td>0.88</td>
<td>1.4 (0.9–2.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>1.6 (0.7–3.2)</td>
<td>0.19</td>
<td>0.9 (0.6–1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0 (0.9–4.2)</td>
<td>0.06</td>
<td>1.8 (1.2–2.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>LBBB</td>
<td>1.2 (0.2–5.0)</td>
<td>0.8</td>
<td>1.1 (0.4–2.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>1.3 (0.2–4.0)</td>
<td>0.7</td>
<td>1.0 (0.5–1.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous MI</td>
<td>5.4 (2.5–11.7)</td>
<td>0.000</td>
<td>1.9 (1.3–2.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2.7 (1.4–5.5)</td>
<td>0.004</td>
<td>1.5 (1.0–2.2)</td>
<td>0.035</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2.6 (1.0–6.9)</td>
<td>0.043</td>
<td></td>
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<tr>
<td>Angina on effort</td>
<td>11.8 (5.6–24.8)</td>
<td>0.000</td>
<td>3.3 (2.2–4.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Angina at rest</td>
<td>6.7 (3.0–15.1)</td>
<td>0.000</td>
<td>2.7 (1.5–4.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rest WMSI</td>
<td>5.2 (2.5–11.0)</td>
<td>0.000</td>
<td>2.38 (1.4–4.0)</td>
<td>0.001</td>
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<tr>
<td>Peak WMSI</td>
<td>6.5 (3.5–11.8)</td>
<td>0.000</td>
<td>3.6 (2.3–5.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Test positivity for wall motion criteria</td>
<td>11.6 (5.6–23.8)</td>
<td>0.000</td>
<td>5.9 (4.0–8.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Medical therapy at time of testing</td>
<td>3.2 (1.5–7.2)</td>
<td>0.003</td>
<td>1.8 (1.2–2.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>CFR on LAD</td>
<td>4.3 (2.1–8.8)</td>
<td>0.000</td>
<td>5.6 (3.7–8.5)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; WMSI, wall motion score index; CFR, coronary flow reserve; LAD, anterior descending artery.
Figure 4 (A) Pathophysiological and prognostic heterogeneity behind normal wall motion response during stress. In the upper panel, we show epicardial coronary arteries: normal in the first two columns, with moderate disease in the third column, and moderate-to-severe disease but concomitant, effective anti-ischaemic therapy in the last column. The myocardium is shown as a square box, with small vessels as circles. Coronary small vessel disease is shown (second columns) as bold circles (structural or functional impairment). All the four very different pathophysiological conditions show the negativity of wall motion response. The abnormal coronary flow reserve response is present in the last three columns, with abnormality of micro- or macro-circulation. (B) Pathophysiological and prognostic heterogeneity behind abnormal wall motion response during stress. Symbols as in (A). The coronary flow reserve can be normal in spite of wall motion abnormality when anterior descending artery is not significantly involved and microcirculatory level is not impaired (left panel).
conditions. In this patient population, the subset with a positive test and an abnormal CFR are further risk stratified, identifying patients with more prognostically malignant test response. At intermediate risk are those patients with test positivity and preserved CFR and those with a negative test and reduced CFR. In keeping with previous findings, concomitant anti-ischaemic therapy was also a strong predictor of unfavourable outcome. In the context of a relatively low risk clinical setting, as that of patients with negative stress echo result off therapy, a preserved CFR identified patients with better survival. On the basis of present results, a negative test off therapy with normal CFR confers a benign prognosis. A watchful surveillance is strongly recommended in those with a test negativity under medical therapy and abnormal CFR.

**Pathophysiological mechanisms**

Haemodynamically significant coronary artery stenosis limiting CFR is the recognized pathophysiological substrate of regional wall motion abnormalities during stress echocardiography. However, regional wall motion and CFR provided additive, not redundant, prognostic information. Indeed, coronary endothelial dysfunction, left ventricular hypertrophy, and coronary microcirculatory dysfunction do not normally induce wall motion abnormalities but have been linked to adverse outcome. Explanations for reduced CFR in the absence of stress-induced wall motion abnormalities include mild-to-moderate epicardial coronary artery stenosis, moderate-to-severe epicardial coronary artery stenosis in the presence of anti-ischaemic therapy, and severe microvascular disease in the presence of patent epicardial coronary arteries. All these three conditions are schematically represented in Figure 4A and may adversely affect prognosis. In the presence of inducible ischaemia wall motion abnormalities, CFR can be preserved, most typically when the regional dysfunction occurs in the non-LAD district and there is no significant stenosis in the LAD territory, in the absence of microcirculatory impairment (Figure 4B). More frequently, CFR is also reduced in the presence of wall motion abnormalities, due to severe LAD disease (with concomitant wall motion abnormality in the same district) and with wall motion abnormality in the non-LAD district but concomitant significant LAD stenosis and/or severe microcirculatory disease (Figure 4B).

**Study limitations**

In this study, there was no central reading. Stress echocardiography and CFR measurement were interpreted in the peripheral centres and entered directly in the data bank. This system allowed substantial sparing of human and technological resources but it was also the logical pre-requisite for a large-scale study, designed to represent the realistic performance of the test rather than the results of a single lab—or even a single person—working in a highly dedicated echo laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centres. However, all our readers in individual centres had a long lasting experience in echocardiography, passed the quality control in stress echo reading as previously described, had extensive experience on execution and interpretation of CFR also through joint reading sessions.

The CFR was sampled only on LAD: there is no doubt that the three coronaries approach would be more fruitful, but at present it remains too technically challenging for a large-scale assessment. Fifty-one % of the patient population underwent dipyridamole stress echocardiography on anti-anginal medical therapy; this is a major limitation since the concomitant anti-anginal therapy may have offset myocardial ischaemia but the effect on CFR should be addressed in appropriate studies. In the present study, the follow-up was censored at the time of revascularization and no data are available on the effect of treatments (PCI or CABG). The treatment effect was not assessed since the study protocol did not envisage a second stress echo exam to assess the efficacy of the revascularization procedure.

**Clinical implications**

CFR and 2D echocardiography offer complementary information during vasodilator stress testing under many aspects. From the pathophysiological viewpoint, wall motion positivity requires ischaemia as a necessary pre-requisite, whereas CFR can be impaired in the absence of inducible ischaemia. Wall motion is easy to acquire, but can be difficult to analyse. CFR can be more difficult to acquire, but is usually straightforward in its quantitative interpretation of a Doppler signal. From the prognostic viewpoint, the reduced CFR can be considered a parameter of ischaemia severity to be added to the more conventional ones obtained during pharmacological stress echocardiography. Stress echo positivity represents per se a negative prognostic marker. Nonetheless, inside this group with an unfavourable prognosis, a subset with worse outcome can be identified on the basis of CFR. At the opposite side of the spectrum of possible stress echo responses, negativity for wall motion criteria identifies a low risk subset, but within this heterogeneous group of patients, negativity under medical therapy and abnormal CFR values is related to a less benign prognosis.

**Conclusions**

In patients with known or suspected CAD vasodilator stress echocardiography by semi-simultaneous dual imaging provides critical prognostic information. Stress echocardiography in this set of patients can be employed to identify the different strata of risk in relation to the type of response obtained. The stress echocardiographic parameters allow the non-invasive identification of a subgroup of patients with inducible ischaemia and abnormal CFR at high risk of developing hard cardiac events.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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References


18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–1463.


