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ABSTRACT

Aims: To assess the prognostic correlates of Doppler echocardiographically derived coronary flow reserve (CFR) on two coronaries in patients with negative stress echo. Vasodilator stress echocardiography allows dual imaging of regional wall motion and CFR both on left anterior descending (LAD) and right coronary artery (RCA).

Methods: The study group comprised 460 patients with known or suspected coronary artery disease and negative stress echo by wall motion criteria. All underwent dipyridamole (up to 0.84 mg/kg over 6 minutes) stress echo with CFR evaluation of either LAD or RCA by Doppler, and were followed up for a median of 32 months. A CFR value of $\leqslant 2.0$ was taken as abnormal.

Results: CFR was abnormal in 174 patients (38%) (57 in LAD only, 48 in RCA only, and 69 in both LAD and RCA) and normal in 286 patients (62%). During follow-up, there were 77 cardiac events: 5 deaths, 44 acute coronary syndromes (6 STEMI, and 38 NSTEMI) and 28 late (>6 months from stress echo) revascularisations. CFR of $\leqslant 2.0$ on LAD was the strongest multivariable predictor of either definite (death, acute coronary syndrome) and major (death, acute coronary syndrome, late revascularisation) events, followed by diabetes mellitus. Anti-ischaemic therapy at the time of testing and resting wall motion abnormality were also independently associated with major events. Preserved CFR in both LAD and RCA was associated with better ($p<0.0001$) definite and major event-free survival compared to abnormal CFR in one or both coronary vessels.

Conclusion: CFR evaluation of either LAD or RCA allows the identification of distinct prognostic patterns. In particular, preserved CFR in both coronary vessels is highly predictive of a very favourable outcome, while reduced CFR in either coronary vessel, and especially on LAD, is a strong predictor of future cardiac events.

Dual imaging of wall motion and coronary flow reserve (CFR) during dipyridamole stress echocardiography has entered the echo laboratory as an effective modality for both diagnostic and prognostic purposes. In fact, CFR on left anterior descending (LAD) or right coronary artery (RCA) increases the accuracy of conventional wall motion analysis to assess myocardial ischaemia.[1–8] Moreover, CFR on LAD provides additional prognostic value over stress echo result in patients with known or suspected coronary artery disease (CAD),[9 10] and allows effective risk stratification in different clinical settings, including diabetic patients with unchanged wall motion contractility during stress,[11] patients with intermediate coronary stenosis,[12] patients with non-ischaemic dilated[13 14] and hypertrophic cardiomyopathy.[15] Nevertheless, the prognostic information derived by combined assessment of CFR on LAD and RCA remains unknown.

This prospective, observational study was aimed at investigating the prognostic correlates of CFR assessed by transthoracic Doppler of both LAD and RCA in patients with known or suspected CAD and negative stress echo by wall motion criteria.

METHODS

Patients

From August 2003 to December 2006, 1104 patients underwent dipyridamole stress echocardiography at two Italian cardiology institutions (Mestre and Cesena). In all, 497 patients had inadequate imaging of flow Doppler on LAD (n = 58, 5%) or RCA (n = 439, 40%) and were excluded. Of 607 patients with dual imaging of regional wall motion and CFR both on LAD and RCA, 147 were excluded because of positive stress echo for inducible ischaemia. The remaining 460 patients (260 men, 200 women; mean age 62 (SD 12) years) with negative stress echo by wall motion criteria formed the study population. No patient had significant valvular disease, congenital heart disease or significant co-morbidity reducing life expectancy to <1 year. Follow-up data were available for all subjects. The indication for stress echocardiography was suspected CAD in 323 (70%) and risk stratification of known CAD (that is, history of myocardial infarction, coronary revascularisation and/or angiographic evidence of $\geqslant$50% diameter coronary stenosis) in 137 (30%) subjects. Diabetes mellitus,[16] arterial hypertension[17] and hypercholesterolaemia[18] were defined according to standard definitions. According to individual needs and physicians' choices, 266 (58%) patients were evaluated after antianginal drugs had been discontinued, and 194 (42%) patients were evaluated during antianginal treatment (table 1). 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 authorised physicians to use their clinical data. Stress echo data were collected and analysed by stress echocardiographers not involved in patient care.

Table 1 Clinical and echocardiographic findings of the study population

Age (years)	62 (12)
Males	260 (57%)
Clinical history	
Prior myocardial infarction	105 (23%)
Prior CABG	20 (4%)
Prior PCI	75 (16%)
Left bundle branch block	35 (8%)
Family history of CAD	63 (14%)
Diabetes mellitus	84 (18%)
Arterial hypertension	276 (60%)
Hypercholesterolaemia	279 (61%)
Smoking habit	175 (38%)
Anti-ischaemic therapy at the time of test	
β-Blockers	190 (41%)
Calcium antagonists	142 (31%)
Nitrates	83 (18%)
At least one medication	266 (58%)
Echocardiogram	
EF	55 (7%)
Resting WMSI	1.13 (0.24)
Resting left ventricular ejection fraction	55 (7)
Resting WMA	142 (31%)
Mean CFR on LAD	2.41 (0.58)
Mean CFR on RCA	2.35 (0.49)

Data presented are mean value (SD) or number (%) of patients. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; EF, ejection fraction; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; WMA, wall motion abnormality; WMSI, wall motion score index.

Stress echocardiography

Transthoracic stress echocardiographic studies were performed with a commercially available ultrasound machine (Sonos 5500–7500 or IE 33, Philips Ultrasound, Andover, MA, USA) equipped with a multifrequency phased-array sector scan probe (S3-S8 or V3-V7) and with second harmonic technology. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 minutes).[19] Echocardiographic images were semiquantitatively assessed using a 17 segments, four-point scale model of the left ventricle.[20] A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischaemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality. Resting wall motion abnormality was akinetic or dyskinetic myocardium with no thickening during stress.

CFR was assessed during the standard stress echo examination by an intermittent imaging of wall motion and both LAD[20] and RCA[8] flow. Coronary flow in the mid-distal portion of LAD and RCA was imaged, respectively, from the low parasternal long-axis and a modified apical two-chamber view under the guidance of colour Doppler flow mapping.[1] In 162 (35%) patients with no visualisation of colour-coded blood flow from the LAD or RCA at baseline conditions, the procedure was attempted a second time during contrast enhancement with Sonovue (Bracco-Byk-Gulden, Konstanz, Germany) in bolus (0.5 ml intravenously).

All studies were digitally stored to simplify offline reviewing and measurements. Coronary flow parameters were analysed offline 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. CFR was defined as the ratio between hyperaemic peak and basal peak diastolic coronary flow velocities. A CFR value of $\leqslant 2$ was considered abnormal. All observers were trained by the same senior investigator (FR), who granted consistency in data acquisition, storage and interpretation, through intensive joint reading sessions. All investigators at the contributing centres passed quality control criteria for regional wall motion and Doppler interpretation before entering the study as previously described.[21 22] The previously assessed intra- observer and inter-observer variability for measurements of Doppler recordings and regional wall motion analysis assessment were <10%.[2]

Follow-up data

Outcome was determined from patient interview at the out-patient 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 acute coronary syndromes (ST-elevation myocardial infarction (STEMI), or non-ST-elevation myocardial infarction (NSTEMI)), early (<6 months) and late (>6 months) coronary revascularisation (surgery or angioplasty). In order to avoid misclassification of the cause of death,[23] overall mortality was considered. STEMI was defined by typical symptoms, ST-elevation on electrocardiogram and cardiac enzyme changes. NSTEMI was an acute coronary syndrome causing typical chest pain, cardiac enzyme elevation and/or electrocardiographic modifications consistent with acute ischaemia[24] requiring hospitalisation. Late revascularisation was considered as a clinical endpoint, reflecting new or progressive symptoms. Follow-up data were analysed for the prediction of definite events (death, non-fatal acute coronary syndromes) and major events (death, non-fatal acute coronary syndromes, late revascularisation).

Statistical analysis

Continuous variables are expressed as mean (SD). Continuous variables were compared using the Student unpaired t test, while differences of categorical variables were assessed by the χ^2 test. The Kaplan-Meier curves were used for estimation of definite event-free survival and major event-free survival. Patients undergoing coronary revascularisation within 6 months from testing were censored at the time of the procedure. Annual event rates were obtained from Kaplan-Meier estimates to take censoring of the data into account. Only the first event was taken into account. The association of selected variables with outcome was assessed with the Cox's proportional hazard model using univariate and stepwise multivariate procedures. A significance of 0.05 was required for a variable to be included in the multivariate model, while 0.1 was the cut-off value for exclusion. Hazard ratios (HR) with the corresponding 95% confidence intervals (CI) were estimated. Moreover, clinical findings, stress echo parameters and CFR were sequentially included in the model. The global χ^2 value of the model was calculated from the log likelihood ratio; a significant increase after the addition of further variables indicated incremental prognostic value. Statistical significance was set at $p<0.05$. The Statistical Package for the Social Sciences (SPSS) was used for analysis.

RESULTS

Stress echocardiography

The main clinical and echocardiographic characteristics of the study population are shown in table 1.

Table 2 Univariate and multivariate indicators of definite events (death, myocardial infarction) and major events (death, myocardial infarction, late revascularisation)

	Definite events				Major events			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (years)	1.02 (1.00 to 1.05)	0.06			1.03 (1.01 to 1.05)	0.006		
Gender (female)	1.52 (0.87 to 2.67)	0.15			1.08 (0.69 to 1.70)	0.73		
Prior myocardial infarction	1.63 (0.88 to 3.04)	0.12			2.07 (1.29 to 3.33)	0.003		
Prior CABG	2.09 (0.75 to 5.82)	0.16			1.99 (0.86 to 4.57)	0.11		
Prior PCI	0.43 (0.16 to 1.21)	0.11			0.57 (0.27 to 1.18)	0.13		
Left bundle branch block	0.94 (0.29 to 3.01)	0.91			0.97 (0.39 to 2.41)	0.96		
Family history of CAD	1.28 (0.55 to 3.03)	0.58			1.18 (0.59 to 2.37)	0.64		
Diabetes mellitus	2.01 (1.09 to 4.05)	0.03	1.97 (1.01 to 3.86)	0.05	2.63 (1.61 to 2.30)	<0.0001	2.22 (1.30 to 3.79)	0.003
Arterial hypertension	2.65 (1.38 to 5.10)	0.004			2.13 (1.29 to 3.51)	0.003		
Hypercholesterolaemia	1.32 (0.74 to 2.36)	0.35			1.64 (1.01 to 2.67)	0.04		
Smoking habit	0.73 (0.39 to 1.35)	0.31			1.06 (0.66 to 1.68)	0.82		
Anti-ischaemic therapy at the time of test	3.23 (1.61 to 6.47)	0.001			3.31 (1.80 to 5.44)	<0.0001	2.14 (1.13 to 4.03)	0.02
Resting WMSI	1.46 (0.51 to 4.21)	0.48			2.29 (1.10 to 4.76)	0.03		
Resting EF	*0.98 (0.95 to 1.02)*	*0.37*			*0.97 (0.94 to 0.99)*	*0.02*		
Resting WMA	1.62 (0.90 to 2.89)	0.11			2.31 (1.47 to 3.63)	<0.0001	3.43 (1.60 to 7.34)	0.001
CFR ⩽2.0 on LAD	13.76 (7.15 to 26.48)	<0.0001	11.97 (5.49 to 26.11)	<0.0001	7.17 (4.48 to 11.46)	<0.0001	5.30 (2.91 to 9.63)	<0.0001
CFR ⩽2.0 on RCA	4.68 (2.67 to 8.23)	<0.0001			4.68 (2. 98 to 7.37)	<0.0001		

CI, confidence interval; HR, hazard ratio.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; EF, ejection fraction; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; WMA, wall motion abnormality; WMSI, wall motion score index.

No major complications occurred during the test. CFR was abnormal in 174 patients (38%) (57 in LAD only, 48 in RCA only and 69 in both LAD and RCA) and normal in 286 patients (62%). Patients with abnormal CFR in one or both coronary vessels were older (65 (11) vs 61 (13) years; p<0.0001), had higher frequency of prior myocardial infarction (35% vs 15%; p<0.0001), diabetes mellitus (25% vs 14%; p = 0.002), arterial hypertension (71% vs 53%; p = 0.0001), hypercholesterolaemia (71% vs 55%; p = 0.0006), higher resting WMSI (1.17 (0.28) vs 1.10 (0.21); p = 0.001) and underwent stress echo more frequently while taking anti-ischaemic drugs (73% vs 49%; p<0.0001) than those with preserved CFR in both LAD and RCA. Hypercholesterolaemic patients had a significantly lower CFR both in the LAD (2.30 (0.53) vs 2.56 (0.63); p<0.0001) and RCA (2.26 (0.45) vs 2.49 (0.52); p<0.0001) compared to non-hypercholesterolaemic patients.

Follow-up events

During a median follow-up of 32 months (first quartile 12, third quartile 42), there were 77 cardiac events: 5 deaths, 44 non-fatal acute coronary syndromes (6 STEMI, and 38 NSTEMI) and 28 late revascularisations (4 surgery, and 24 angioplasty). There were 63 cardiac events in patients with reduced CFR in one or both coronary vessels and 14 cardiac events in those with normal CFR in both LAD and RCA (36% vs 5%; p<0.0001). In addition, 42 patients underwent early revascularisation (9 surgery, and 33 angioplasty). Of these, 39 had reduced CFR in

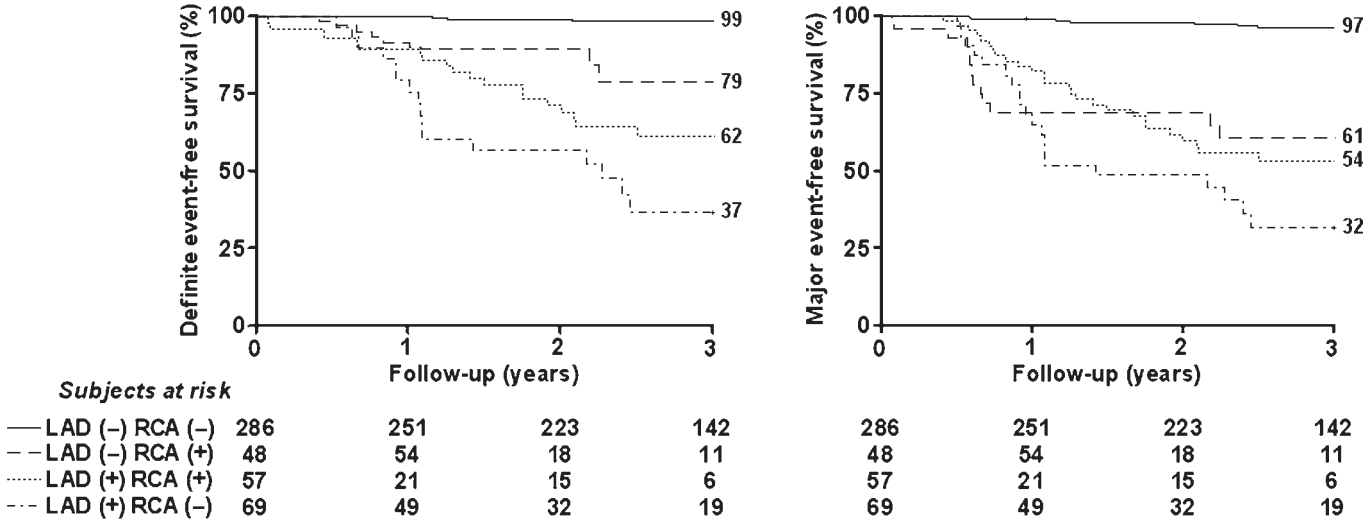

Figure 1 Definite event-free survival and major event-free survival according to the presence of preserved (−) or reduced (+) coronary flow reserve in the left anterior descending (LAD) and the right coronary artery (RCA). Number of patients per year is shown.

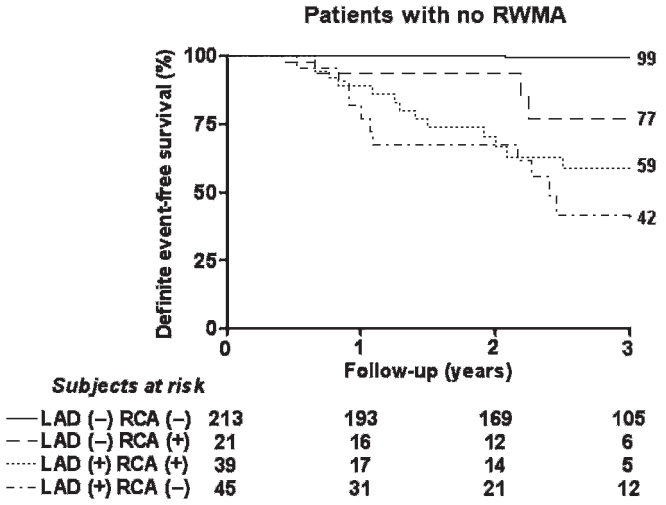

Figure 2 Definite event-free survival and according to the presence of preserved (−) or reduced (+) coronary flow reserve in the left anterior descending (LAD) and the right coronary artery (RCA) in patients with no resting wall motion abnormalities (RWMA). Number of patients per year is shown.

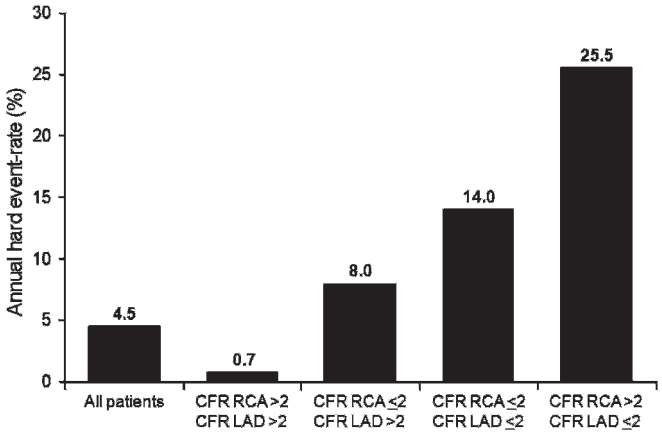

Figure 3 Annual definite event rate in the study population separated in the different subgroups according to coronary flow reserve (CFR) normal/abnormal in the two vascular vessels— left anterior descending (LAD) and posterior right coronary artery (RCA).

one or both coronary vessels and 3 had normal CFR in both LAD and RCA (22% vs 1%; p<0.0001).

Outcome prediction

The univariate and multivariate prognostic indicators of definite and major events are listed in table 2. CFR of ⩽2.0 on LAD was the strongest multivariable predictor of both definite and major events, followed by diabetes mellitus (table 2). Anti-ischaemic therapy at the time of testing and resting wall motion abnormality were also independently associated with major events (table 2). The definite and major event-free survival was markedly (p<0.0001) better for patients with preserved CFR in both LAD and RCA than for those with abnormal CFR in one or both coronary vessels (fig 1). When patients with wall motion abnormalities were excluded from survival analysis, the same dynamic of stratification was observed for definite event-free survival (fig 2). Compared to patients with abnormal CFR in LAD, those with abnormal CFR in both coronary vessels or in RCA had higher definite event-free survival (p = 0.03 and p = 0.008, respectively); the former showed also higher major event-free survival (p = 0.04) (fig 1). Annual definite event-rate according to the CFR result in the two vascular vessels is reported in figure 3. At incremental analysis, CFR on LAD stress echocardiography showed an incremental value versus clinical evaluation and conventional stress echo parameters for the prediction of both definite and major events (fig 4).

DISCUSSION

Dual imaging of wall motion and CFR on LAD is now the state-of-the art technique for vasodilator stress echo, because of the very high feasibility,[2 3 11] and excellent diagnostic[1–7] and prognostic[9–12] value compared to standard wall motion analysis. Although it has suboptimal feasibility,[1] CFR on RCA also provides useful diagnostic information.[1 8] However, the prognostic effect of the combined assessment of CFR on LAD and RCA has not been addressed previously. In the present study on patients at relatively low risk, such as those with negative stress echo by wall motion criteria, abnormal CFR on LAD was the strongest independent predictor of future definite and major events among clinical and echocardiographic parameters. This is consistent with previously reported experiences in an unselected cohort of patients,[10] and in diabetic patients.[11] The novel aspect of the study was that the combination of CFR in both LAD and RCA allowed the identification of distinct prognostic patterns. In particular, a normal CFR in both coronary vessels was highly predictive of a very favourable outcome, indicating absence of either prognostically meaningful epicardial artery stenosis and/or coronary microcirculation impairment. Explanations for reduced CFR in the absence of stress-induced wall motion

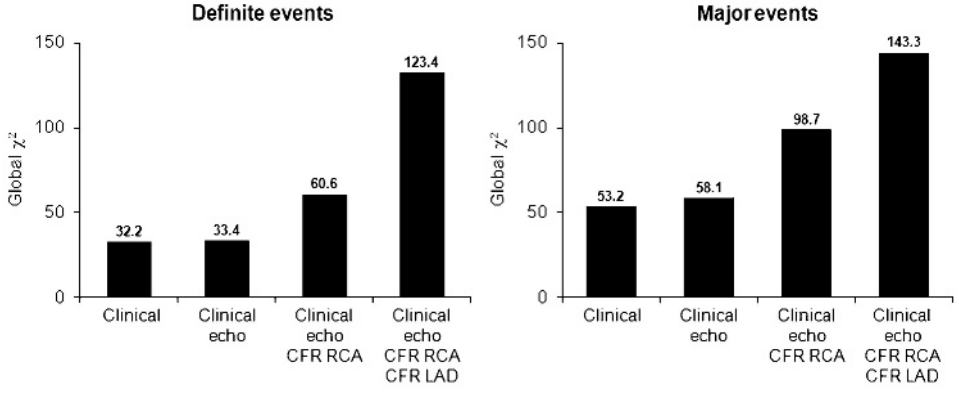

Figure 4 Global χ^2 value of significant predictor modelling of definite and major events according to an interactive procedure. In the model CFR still added significant information to clinical variables and stress echocardiographic parameters.

abnormalities include mild-to-moderate epicardial coronary artery stenosis,[25] left ventricular hypertrophy,[26] severe epicardial coronary artery stenosis in the presence of anti-ischaemic therapy[27–30] and severe microvascular coronary disease in the presence of patent epicardial coronary arteries.[31–36] All these conditions may adversely affect prognosis. In fact, a non-ischaemic test under anti-ischaemic therapy was found to be less prognostically benign in subjects with known or suspected CAD,[37] as well as in diabetic patients.[38] Accordingly, anti-ischaemic therapy at the time of testing was a multivariable predictor of future major events in our study. Moreover, the prognostic impact of microvascular coronary disease was previously documented in several clinical settings.[34 39–41]

The assessment of CFR by Doppler echocardiography has always been considered to be limited by the fact that it can be assessed only in one vessel, excluding the other two that may have a prognostic impact. There is a large body of evidence suggesting that microvascular disease is not related to a single vascular vessel, but when present, is the expression of a global dysfunction.[42 43] Nonetheless, the relative prognostic value of one vessel over the other has never been assessed during Doppler CFR suggesting that when the anterior and the posterior vessel have an impaired CFR, it is likely that microvascular disease is present. Our results have potential clinical implications. As a negative stress echo with preserved CFR on LAD and RCA confers a benign prognosis, no further investigation is required. On the contrary, angiographic evaluation and/or aggressive medical therapy can be considered, in spite of wall motion negativity, for relatively higher-risk patients with reduced CFR on either one, or both, LAD and RCA. From a practical viewpoint, the assessment of CFR only on LAD is more feasible and less technically demanding and its prognostic value remains unchanged even after RCA assessment.

Study limitations

One the main limitations of Doppler echocardiographically derived CFR on two coronary vessels is related to suboptimal feasibility in the RCA vessel. Accordingly, we found 95% feasibility for CFR on LAD and 60% for CFR on RCA. As test feasibility is heavily affected by the skill of the operator and advances in technology, it is likely that it may improve over time. Contrast agents have not been employed in all cases, which may have theoretically improved the feasibility on the right coronary artery, because of costs and safety concerns. In the present study, we adopted central core laboratory reading, allowing us to minimise inter-operator variability.[22]

The Doppler technique needs a maximal vasodilation in order to compare resting and peak diastolic velocities, whereas the resting velocities may exert a prognostically significant meaning only when measured in a quantitative way as happens with positron emission tomography.[44] Dipyridamole was the stressor of choice because it allows the assessment of wall motion and CFR in the same session. Its sensitivity is comparable to that of dobutamine when high-dose protocols are employed.[45]

CONCLUSIONS

The present results add an important piece of information in the stratification of patients at low risk, such as those with a negative stress echo by wall motion criteria. Assessment of CFR integrates and complements classic stress echocardiography founded on regional wall motion analysis.[7 46] With the addition of CFR, measured in the anterior and posterior vessels, to wall motion, the stress echocardiography response can be stratified into a severity code mirroring the ischaemic cascade. On one end of the spectrum, there is the totally normal pattern, with hyperdynamic left ventricular function and preserved CFR both on LAD and RCA, which is highly predictive of normal coronary anatomy and normal physiological response of coronary micro-circulation and macro-circulation. The CFR impairment on one single vessel is more relevant when it occurs on the anterior one. At the other end of the spectrum, the reduction of CFR on both vessels identifies patients at risk of becoming ill in the long run.

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Competing interests: None.

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