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Association of coronary artery Doppler-echocardiography diastolic-systolic velocity ratio at rest with obstructive coronary artery stenosis on the left main or left anterior descending coronary artery

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ABSTRACT

Background: We assessed whether the non-invasive measure of peak diastolic-systolic velocity ratio (rDSVR) at rest on the left anterior descending artery (LAD) using Doppler transthoracic echocardiography is associated with obstructive coronary artery disease (CAD) on the LAD and left main (LM) arteries. We compared rDSVR diagnostic accuracy with stress wall motion (WM) and coronary flow reserve (CFR-LAD), in a group of subjects who underwent contrast stress-echocardiography (cSE) and coronary angiography within 3 months.
Methods: 286 patients selected with a clinical indication to cSE, in which CFR-LAD was measured during the test who also underwent coronary angiography within 3 months were selected and diagnostic performance compared.
Results: Demographics and clinical variables were univariate predictors of LAD or LM >50% stenosis, but rDSVR < 1.7 outperformed other variables (OR 11.18, 95% CI 5.82–21.49, $p < 0.001$), comprising cSE variables such as reversible WM abnormalities (OR 1.53, 95% CI 0.94–2.49, $p = 0.087$) or CFR-LAD < 2 (OR 2.88, 95% CI 21.74–4.77, $p < 0.001$). The addition of rDSVR to multivariate logistic regression models (clinical or clinical + cSE variables) led to a marked increase in C-index (0.82, 95%CI 0.78–0.87) with significant improvement compared to all prior models ($p < 0.001$).
Conclusions: Our data suggest a strict association of reduced rDSVR with >50% coronary artery stenosis on the LM/LAD, superior to other standard clinical or cSE related indexes, such as WM assessment or CFR-LAD, and builds incrementally to them and clinical variables in multivariable logistic models for the prediction of CAD on LM and LAD coronaries.

1. Introduction

Stress-echocardiography (SE) is often considered a method with sub-optimal accuracy for the detection of coronary artery disease (CAD) [1].

Echocardiography remains the most frequently used imaging method in clinical cardiology, and its technological developments or the recent recommendations for more liberal use of ultrasound contrast [2], might revive its role for CAD detection. Furthermore, an additional diagnostic variable that could improve the limited diagnostic yield of echocardiography in stable CAD [3], proposed two decades ago [4,5], is the non-invasive measurement of peak diastolic-systolic velocity ratio (rDSVR) at rest of the left anterior descending (LAD) and left main (LM) coronary arteries [6]. Mid-distal LAD flow is measurable by standard Doppler transthoracic echocardiography [7,8], and it is almost fail-safe if taking advantage of ultrasound contrast enhancement [9,10]. The rationale to explain why rDSVR at rest corresponds to functional stenosis severity was demonstrated using intracoronary Doppler flow velocity and pressure measurements, and relates to higher impact of stenosis resistance on diastole than on systole with progressive worsening of functional stenosis severity [11]. We retrospectively measured rDSVR, to test its association with obstructive coronary artery stenosis on LM and LAD, relatively to either stress WM or coronary flow reserve (CFR-LAD) assessments, in a large group of subjects who underwent contrast stress-echocardiography (cSE) for suspected CAD, whom also underwent invasive coronary angiography (iCA).

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2. Methods

2.1. Patients

From our prospectively-collected cSE database, we selected 3770 patients with an indication to cSE for suspected CAD between 2013 and 2017, who had never undergone coronary artery bypass surgery prior to their cSE test; we selected 998 who underwent an invasive coronary angiogram, for any clinical reason within 3 months before or after the index cSE, with no coronary interventions in between. Finally, we selected only those 286 cSE tests in which CFR-LAD was actually measured during the test (depending on the preferences of the specific cardiologist performing the test), so that rDSVR would be available for offline measurement, using the rest LAD spectral Doppler cine-loops (or still-frames). Fig. 1 shows the diagram describing how patients/exams were selected.

Diabetes mellitus was defined as a fasting plasma glucose level >125 mg/dL or the need for insulin or oral hypoglycemic agents, hypercholesterolemia as total cholesterol >200 mg/dL or treatment with lipid lowering medications, hypertension as blood pressure >140/90 mm Hg or use of antihypertensive medication, obesity as BMI >30 kg/m^2. The study has been approved by the appropriate ethics committees and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

2.2. Contrast stress-echocardiography

Philips ie33 (Philips Medical Systems) was used with the standard S5 transducer. Our protocol for accelerated high-dose dipyridamole cSE has been described elsewhere [12]; briefly, it consists in rest and peak vasodilation assessments of the following three imaging parameters: WM, myocardial perfusion and spectral Doppler CFR-LAD for peak diastolic velocity stress/rest ratio, after repeated boluses of 0,5 mL ultrasound contrast (SonoVue®, Bracco, Milan). Stress acquisition is performed after dipyridamole administration of 0,84 mg/kg infused in 6 min. WM analysis is the only mandatory assessment during the protocol, myocardial perfusion imaging and/or CFR-LAD being instead optional and assessed only when deemed technically feasible, also based on the specific operator skills. The left ventricle is divided in 17 segments according to the recommendations of the American and European Societies of Echocardiography [13]. Myocardial perfusion is visually assessed, normal myocardial perfusion after dipyridamole is assigned if myocardium is fully replenished 2 s after the end of the flash impulse, normal myocardial replenishment at rest is defined as complete replenishment within 4 s after the flash impulse. Segmental wall motion is graded as follows: normal = 1; hypokinetic = 2; akinetic = 3; and dyskinetic = 4, Reversible ischemia was defined as the occurrence of a stress-induced new dyssynergy or worsening of rest hypokinesia in ≥1 segment. CFR-LAD < 2 is considered abnormal.

We used bolus instead of continuous infusion of contrast administration for several reasons, among which the lower cost due to lower quantity of contrast needed and a rapid and immediate administration of contrast when it is needed for perfusion imaging or CFR-LAD assessment.

2.3. Rest diastolic to systolic peak velocity ratio measurement (rDSVR)

The transthoracic Doppler measurement of CFR-LAD during SE is widely utilized and recommended by European guidelines [14]. Since CFR-LAD is the stress/rest ratio of peak diastolic velocities, it requires sampling mid-distal LAD coronary velocity both at rest and at peak stress, so that if CFR-LAD has been measured during the test, the rest LAD velocity profile is available for off-line measurement rDSVR. Mid-distal LAD imaging and Doppler sampling requires to follow few steps to achieve the highest success rate (see how to description in the "Supplementary Data" in the online appendix), feasibility being generally high in the literature using standard ultrasound, but significantly increased by the use of ultrasound contrast [9,10,15,16].

2.4. Intra, inter-observer and test-rest variability

Since rDSVR measurement might be perceived by operators not used to perform such measure as technically difficult and dependent on the observer, we designed a comprehensive reproducibility assessment: the same rDSVR images of 50 random tests were read and measured by 2 different observers independently (inter-observer variability) and read by the same observer twice (at least a week later) (intra-observer variability).

We also performed test-retest assessment, measuring rDSVR in 50 patients who had two separate cSE tests performed within 10 months, with no coronary interventions in between (Test-retest variability).

2.5. Invasive coronary angiography

Angiograms were performed by standard technique via radial or femoral approach. Obstructive CAD was primarily defined as a maximal diameter stenosis >50% in any major epicardial coronary artery, although the alternative diameter stenosis >70% definition was also initially tested and compared with the primary definition. Left main trunk with at least 50% stenosis was always considered as obstructive CAD. Invasive coronary angiography wad graded by visual inspection of the cath-lab physician performing the diagnostic procedure.

2.6. Statistics

This was an observational retrospective study of data collected in clinical practice.

For rDSVR measurement inter- and intra-observer reliability and agreement were evaluated using the Lin's concordance correlation coefficient, ρ_c [17] and the Bland and Altman's limits-of-agreement [18]; reliability was evaluated using the Spearman rank correlation coefficient. ROC analysis was used to determine the accuracy of rDSVR and other conventional stress-echocardiography parameters to detect significant CAD, and the area under curve (AUC) with its 95% confidence interval was calculated to compare the diagnostic performance of the different parameters. A cut-off value of <1.7 was considered reduced rDSVR according to prior studies [6,11].

Baseline characteristics were described as number of subjects and frequencies in case of categorical variables and considering mean and standard deviation for continuous variables. The distribution of variables between the patients with and without significant CAD were compared using independent sample *t*-test and Chi-square test.

Logistic regression was used to assess the association between demographic, clinical and echocardiographic parameters with CAD. All variables with $p < 0.10$ at univariable analysis were considered for multivariable models. Multivariable models were adapted considering different steps, first a clinical model was developed, then the model was updated adding in further steps WM abnormalities, CFR-LAD < 2 and rDSVR < 1.7. Performance of the different models to accurately detect CAD were evaluated using AUC and compared using the C-statistic. $p < 0.05$ was considered statistically significant.

3. Results

Of the overall 286 patients included, 109 (38%) had no or <50% coronary artery stenosis on the LM and/or LAD (no CAD group) (and 75 of them-69%- had no stenosis >50% in any coronary artery), while 177 (62%) had at least one >50% coronary artery stenosis on the LM and/or LAD (CAD group); the distribution of demographics, clinical risk factors, and rest echocardiography or cSE variables in the CAD and no CAD

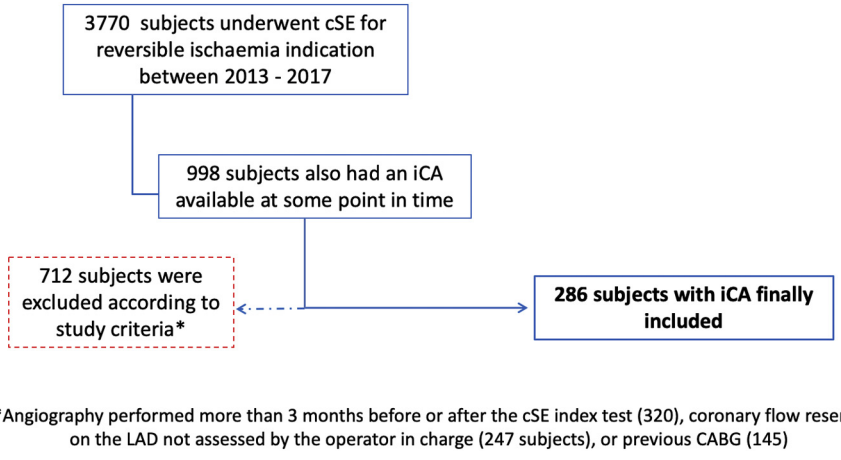


Fig. 1. Diagram describing how patients/exams were selected for the study.

groups are shown in Table 1. Demographics and most clinical risk factors (including a reported prior myocardial infarction) were significantly different between the CAD (higher age, male gender or more prevalent risk factors) and no CAD groups, with only obesity and family history of CAD apparently not differently distributed between the two groups (p = ns). The presence of reversible WM abnormalities (63% vs 53%, $p < 0.087$, of only borderline significance) and reduced CFR-LAD < 2 (74%% vs 50%, $p < 0.001$) were more prevalent in the CAD group than in the no CAD group. A rDSVR<1.7 was the least evenly distributed echocardiography variable, with a prevalence of 60% vs 12% ($p < 0.001$) in the CAD and no CAD groups, respectively.

Table 2 shows univariate predictors of >50% CAD on the LM and/or LAD. Demographics and clinical variables were confirmed as univariable predictors; rDSVR<1.7 outperformed all other variables (OR 11.18, 95% CI 5.82–21.49, $p < 0.001$), comprising standard cSE variables, such as reversible WM abnormalities (OR 1.53, 95% CI 0.94–2.49, $p = 0.087$) or CFR-LAD < 2 (OR 2.88, 95% CI 1.74–4.77, $p < 0.001$).

Table 3 shows the performance of multivariate logistic regression models, starting from a multivariable clinical model comprising age, gender, smoker state, diabetes mellitus, hypercholesterolemia and prior myocardial infarction, then adding available data from cSE, such as the detection of reversible WM abnormalities and/or CFR-LAD < 2, and finally adding the newly measured variable rDSVR < 1.7. C-index of the clinical model was not improved significantly by the addition of reversible WM (0.66, 95%CI 0.60–0.73 vs 0.67, 95%CI 0.60–0.73, $p = 0.612$) while the addition of CFR-LAD led to a significantly higher C-index of the model (0.70, 95%CI 0.64–0.77 $p = 0.081$) with respect to the clinical + reversible WM model. The final addition of rDSVR to the prior models led to a C-index of 0.82, 95%CI 0.78–0.87, with a significant improvement ($p < 0.001$) when compared to all 3 prior models. Model A + only rDSVR demonstrated a significantly higher C-index of 0.82 (0.78–0.87) compared with C-index = 0.70 (0.64–076) of Model A + only CFR-LAD ($p < 0.001$). Data were similar when alternatively defining LAD disease more restrictively as maximal diameter stenosis of >70% (see Fig. 2 graphically comparing ROC curves of all the models when alternatively defining obstructive CAD for LAD as >50% or >70% diameter stenosis).

Fig. 3 shows the ROC curve for rDSVR in the detection of >50% stenosis on the LM and/or LAD in the 286 patients population demonstrating an AUC = 0.830 (95%CI 0.828–0.902). Fig. 4 shows the diagnostic data in the 286 patient population, for the presence of reversible WM abnormalities or CFR-LAD < 2 during cSE and for rDSVR using the prespecified <1.7 cut-off; rDSVR < 1.7 demonstrates an AUC of 0.741

Table 1
Baseline demographics, clinical, rest and stress-echocardiography variables and rDSVR data in the entire population and in the subgroups with or without obstructive coronary artery stenosis on the left main trunk or LAD.

	No CAD ($N = 109$)	CAD ($N = 177$)	Total ($N = 286$)	p-Value
Age	63.2 ± 11.4	67.4 ± 9.8	65.8 ± 10.6	0.001
Male	66 (60.6%)	129 (73.3%)	195 (68.4%)	0.024
Family history of CAD	35 (32.1%)	44 (25%)	79 (27.7%)	0.192
Smoker	50 (45.9%)	96 (54.6%)	146 (51.2%)	0.155
Hypercholesterolemia	63 (57.8%)	114 (64.8%)	177 (62.1%)	0.238
Diabetes	15 (13.8%)	48 (27.3%)	63 (22.1%)	0.008
Hypertension	71 (65.1%)	137 (77.8%)	208 (73%)	0.019
Obesity	22 (20.2%)	39 (22.2%)	61 (21.4%)	0.693
Previous PCI	27 (24.8%)	46 (26.1%)	73 (25.6%)	0.797
Previous MI	19 (17.4%)	45 (25.6%)	64 (22.5%)	0.11
LVEF < 50%	23 (21.5%)	42(24.3%)	65 (23.2%)	0.592
Inducible WM abnormalities*	57 (52.8%)	111 (63.1%)	168 (59.2%)	0.087
Fixed WM abnormalities*	47 (43.5%)	90(51.1%)	137 (48.2%)	0.212
CFR-LAD	54 (49.5%)	130 (73.9%)	184 (64.6%)	<0.001
rDSVR < 1.7	13 (11.9%)	106 (60.2%)	n(41.8%)	<0.001

CAD = coronary artery disease, defined as >50% diameter stenosis specifically on the left main trunk and/or left anterior descending coronary artery, PCI = percutaneous coronary intervention, MI = myocardial infarction, LVEF = left ventricle ejection fraction, WM = wall motion, CFR-LAD = coronary flow reserve of the left anterior descending coronary artery, rDSVR = peak diastolic-systolic velocity ratio on the left anterior descending coronary artery. *WM abnormalities refers to the presence of abnormalities specifically in the LAD territory.

Table 2
Univariate association of demographic data, clinical, rest and stress-echocardiography variables and rDSVR data with obstructive coronary artery stenosis on the left main trunk or LAD.

	OR	95%CI	p-Value
Age	**1.039**	**(1.015–1.063)**	**0.001**
Male	**1.788**	**(1.075–2.975)**	**0.025**
Family history of CAD	0.705	(0.416–1.194)	0.193
Smoker	1.416	(0.877–2.287)	0.155
Hypercholesterolemia	1.343	(0.822–2.192)	0.239
Diabetes	**2.350**	**(1.242–4.448)**	**0.009**
Hypertension	**1.880**	**(1.106–3.197)**	**0.020**
Obesity	1.126	(0.626–2.026)	0.693
Previous PCI	1.627	(0.893–2.964)	0.112
Previous MI	1.075	(0.62–1.862)	0.797
LVEF < 50%	1.171	(0.657–2.086)	0.592
Inducible WM abnormalities	1.528	(0.94–2.485)	0.087
Fixed WM abnormalities	1.358	(0.839–2.199)	0.213
CFR-LAD	**2.878**	**(1.739–4.765)**	**0.000**
rDSVR < 1.7	**11.182**	**(5.819–21.488)**	**0.000**

CAD = coronary artery disease, defined as >50% diameter stenosis specifically on the left main trunk and/or left anterior descending coronary artery, PCI = percutaneous coronary intervention, MI = myocardial infarction, LVEF = left ventricle ejection fraction, WM = wall motion, CFR-LAD = coronary flow reserve of the left anterior descending coronary artery, rDSVR = peak diastolic-systolic velocity ratio on the left anterior descending coronary artery. WM abnormalities refers to the presence of abnormalities specifically in the LAD territory.

Table 3
Multivariate models and their diagnostic performance after the addition of stress-echocardiography variables and rDSVR.

Multivariate models	OR	p-Value	95%CI	C-index
Clinical (Model A)				
Age	1.036	0.004	(1.011–1.062)	
Male	2.038	0.009	(1.194–3.476)	
Diabetes	2.172	0.025	(1.104–4.275)	
Hypertension	1.338	0.320	(0.753–2.377)	
				0.66 (0.60–0.73)
Clinical + WM (Model B)				
Age	1.035	0.007	(1.009–1.06)	
Male	1.985	0.012	(1.16–3.398)	
Diabetes	2.183	0.027	(1.094–4.357)	
Hypertension	1.326	0.337	(0.745–2.36)	
Inducible WM abnormalities	1.342	0.260	(0.804–2.238)	
				0.67 (0.60–0.73)
Clinical + WM + CFR (Model C)				
Age	1.028	0.035	(1.002–1.054)	
Male	2.015	0.013	(1.163–3.493)	
Diabetes	2.174	0.031	(1.072–4.412)	
Hypertension	1.315	0.365	(0.727–2.379)	
Inducible WM Abnormalities	1.137	0.638	(0.667–1.936)	
CFR-LAD	2.518	0.001	(1.469–4.316)	
				0.70 (0.64–0.77)
Clinical + WM + CFR + rDSVR				
Age	1.034	0.020	(1.005–1.064)	
Male	2.925	0.001	(1.524–5.614)	
Diabetes	1.913	0.102	(0.878–4.167)	
Hypertension	1.398	0.338	(0.705–2.773)	
Inducible WM abnormalities	1.057	0.854	(0.584–1.914)	
CFR-LAD	1.629	0.117	(0.886–2.996)	
rDSVR < 1.7	11.866	0.000	(5.791–24.315)	
				0.82 (0.78–0.87)

WM = wall motion, CFR-LAD = coronary flow reserve of the left anterior descending coronary artery, rDSVR = peak diastolic-systolic velocity ratio on the left anterior descending coronary artery. WM abnormalities refers to the presence of abnormalities specifically in the LAD territory.

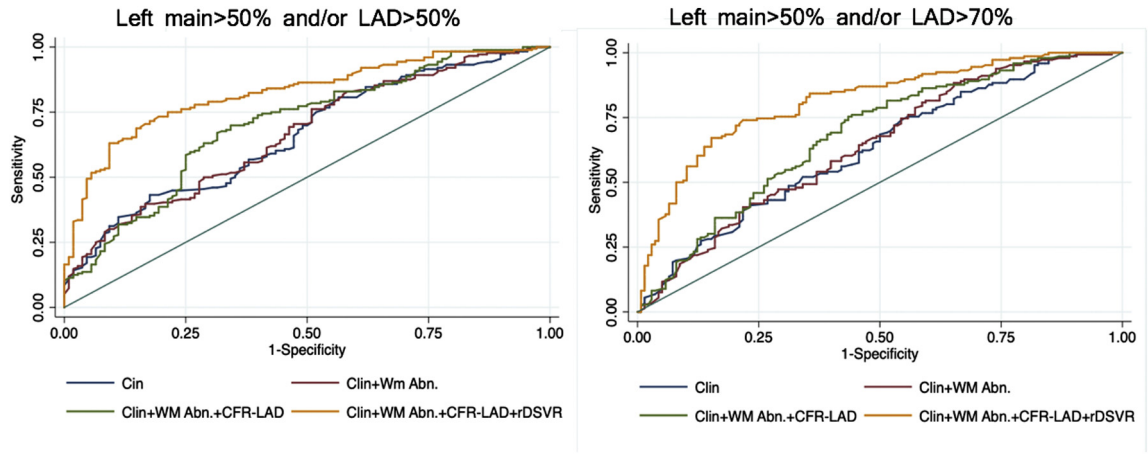


Fig. 2. ROC curves of all the models when defining CAD on the LAD as >50% or alternatively >70% diameter stenosis.

(0.693–0.789), with a sensitivity of 60% and a specificity of 88%, which in the current study population corresponds to 89% (95%CI 83%–93%) positive predictive value and 57.5% (95%CI 53%–62%) negative predictive value.

Fig. 5 graphically depicts the distribution of rDSVR values, as a box & whisker plot for cases of angiographically isolated >50% stenosis of the LM, isolated >50% stenosis of the proximal, mid or distal LAD, and also for no significant LM/LAD stenosis, showing that such rDSVR is reduced in presence of >50% stenosis of LM or LAD, but less markedly in cases of distal LAD stenosis, as expected from its lower functional impact.

3.1. rDSVR measurements agreement and reliability

Fig. 6 graphically shows the agreement data in the form of Lin's concordance correlation coefficient and Bland & Altman average difference, and reliability, calculated using Spearman rho. Test-retest (correlation coefficient = 0.933, 95%CI 0.897–0.969) and first-second read by a single observer (intra-observer) (correlation coefficient = 0.891, 95%CI 0.841–0.940) showed optimal agreement, while the same data could be classified as only "moderate" in case of two different readers of the same tracings (inter-observer) (correlation coefficient = 0.639, 95%CI 0.480–0.799), when compared with the good agreement data for test-retest or intra-observer reproducibility.

In this study we excluded 247 patients from the overall cohort satisfying initial enrollment criteria because CFR-LAD was not assessed by the operator in charge, mainly due to personal preference or expected technical difficulties (for example when using dobutamine or exercise instead of dipyridamole as a stressor).

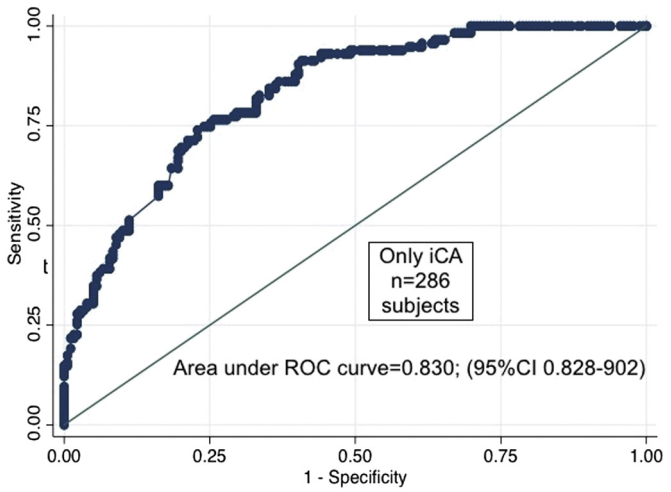


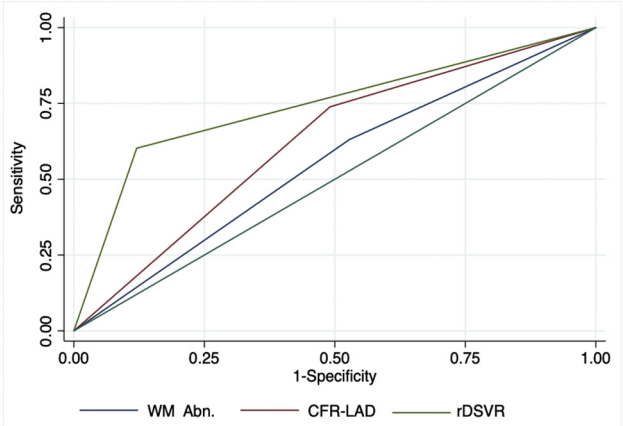
Fig. 3. ROC curve for rDSVR in the detection of >50% stenosis on the LM and/or LAD in the 286 patients population.

4. Discussion

Our study demonstrates that a reduced ratio between diastolic and systolic peak velocity (pre-defined <1.7 cut-off) non-invasively measured on the mid-distal LAD *in resting condition* using ultrasound spectral Doppler is significantly associated with the presence of anatomically obstructive CAD on the LAD or/and LM coronary arteries. The strength of such association and the high positive predictive value of this variable for CAD on the LAD/LM are remarkable compared with existing non-invasive parameters which can be measured either at rest or during stress echocardiography.

rDSVR index is measured during rest echocardiography and contrast is not necessarily required for rDSVR measurement (landmark studies assessing CFR-LAD during SE in fact did not use contrast at all) [19]. Fig. 7 shows typical examples of velocity patterns with calculated diastolic/systolic ratio and corresponding angiograms.

This is the first study able to compare rDSVR with standard stress-related diagnostic indexes, such as WM or CFR-LAD assessment, for the detection of >50% diameter coronary artery stenosis on the LM/



	AUC (95% CI)	Sensitivity	Specificity
Reversible WM Abn	55.2% (49.2%-61.1%)	63%	47%
CFR-LAD	62.4% (56.6%-68.1%)	74%	51%
rDSVR<1.7	74.1% (69.3%-78.9%)	60%	88%

Fig. 4. Shows the diagnostic data in the 286 patient population, for the presence of reversible WM abnormalities or CFR-LAD<2 during cSE and for rDSVR using the pre-specified <1.7 cut-off.

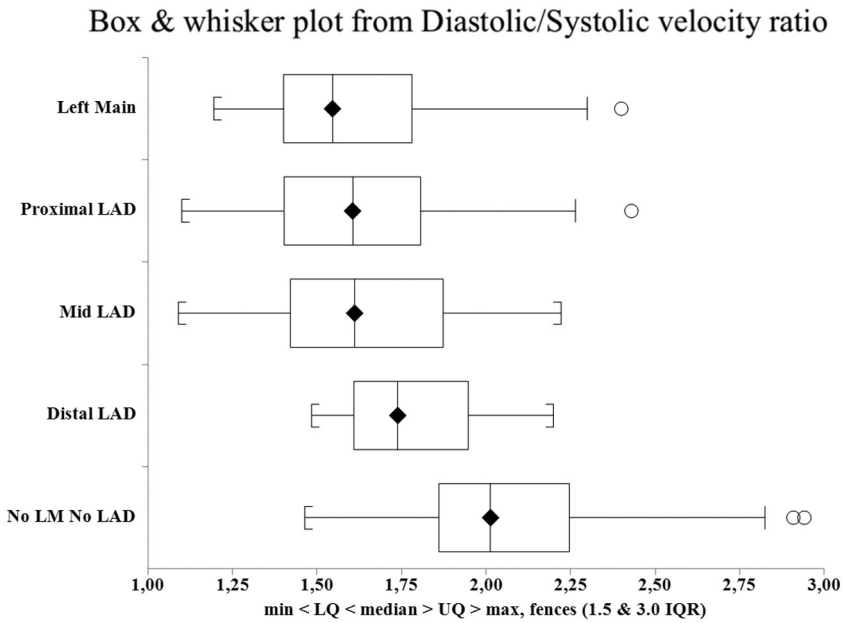


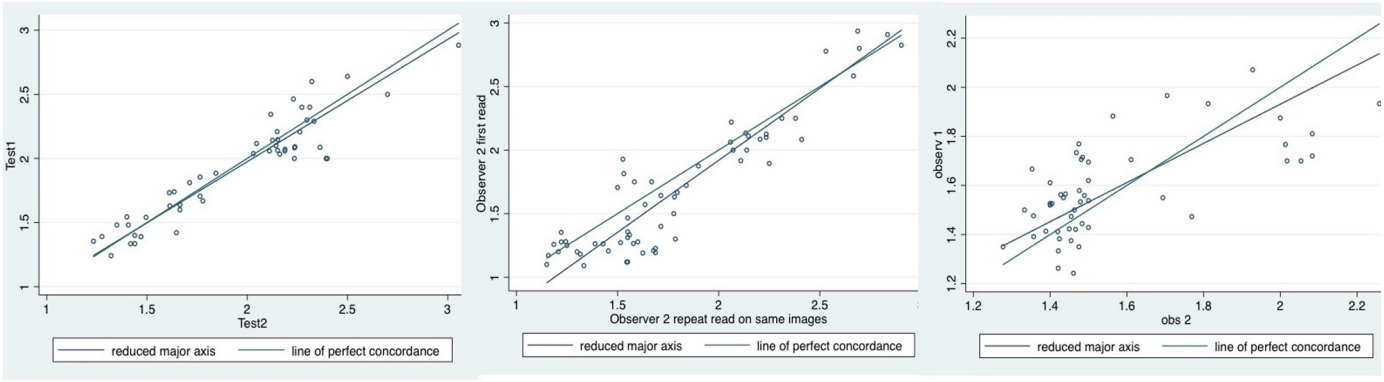
Fig. 5. Distribution of rDSVR values, as a box & whisker plot for cases of angiographically isolated >50% stenosis of the LM, isolated >50% stenosis of the proximal, mid or distal LAD.

LAD; the diagnostic accuracy of rDSVR was markedly superior to other tested parameters, either as a standalone variable or incrementally to clinical and cSE variables in multivariable logistic models.

4.1. Rest echocardiography to detect coronary artery stenosis?

There are only few cardiac or vascular ultrasound parameters that can be clinically assessed in resting patients, which have also been associated with severe and/or diffused CAD in the literature. Among such variables, a reduced rest global longitudinal strain [20], a high cardiac calcium score [21], or the presence of carotid/femoral plaques do associate with CAD [22], but generally with the downside of varying cutoffs, dependence on the clinical setting, and with positive predictive values not high enough to influence clinical decision making. The definition of the pre-defined cutoff of reduced rDSVR used in this study (<1.7) is based on prior echocardiography studies, but also intracoronary pressure and fractional flow reserve comparison studies [6,11]. The positive predictive value for LAD and/or LM >50% stenosis was very high, so that it would not appear unconceivable to indicate angiography (maybe CTA) in a patient with intermediate risk of CAD, in whom a clearly reduced rDSVR is found. The current study does not validate this behavior though, since it is retrospective and only hypothesis-generating; prospective and multicenter studies are needed to validate such a strategy.

The rDSVR variable gives the additional information not available using the aforementioned ultrasound variables at rest. The technical difficulty to interrogate the posterior coronary circulation (the feasibility of sampling the circumflex o right coronaries is too low) is a clear limitation of this method, which is useful only to interrogate the LM and



	Single Observer, 2 tests Test-retest,		Single Observer first-second read Intraobserver		Two different observers Interobserver	
Linn' concordance correlation coef (Agreement)	0.933(0.897-0.969)		0.891 (0.841-0.940)		0.639 (0.480-0.799)	
Bland & Altman Average diff (95% CI)	-0.023 (-0.311;0.264)		-0.108 (-0.507;0.291)		0.019 (-0.341;0.378)	
Spearman rho (reliability)	0,869	<0.001	0,835	<0.001	0,648	<0.001

Fig. 6. Agreement data in the form of Lin's concordance correlation coefficient and Bland & Altman average difference, and reliability, calculated using Spearman rho.

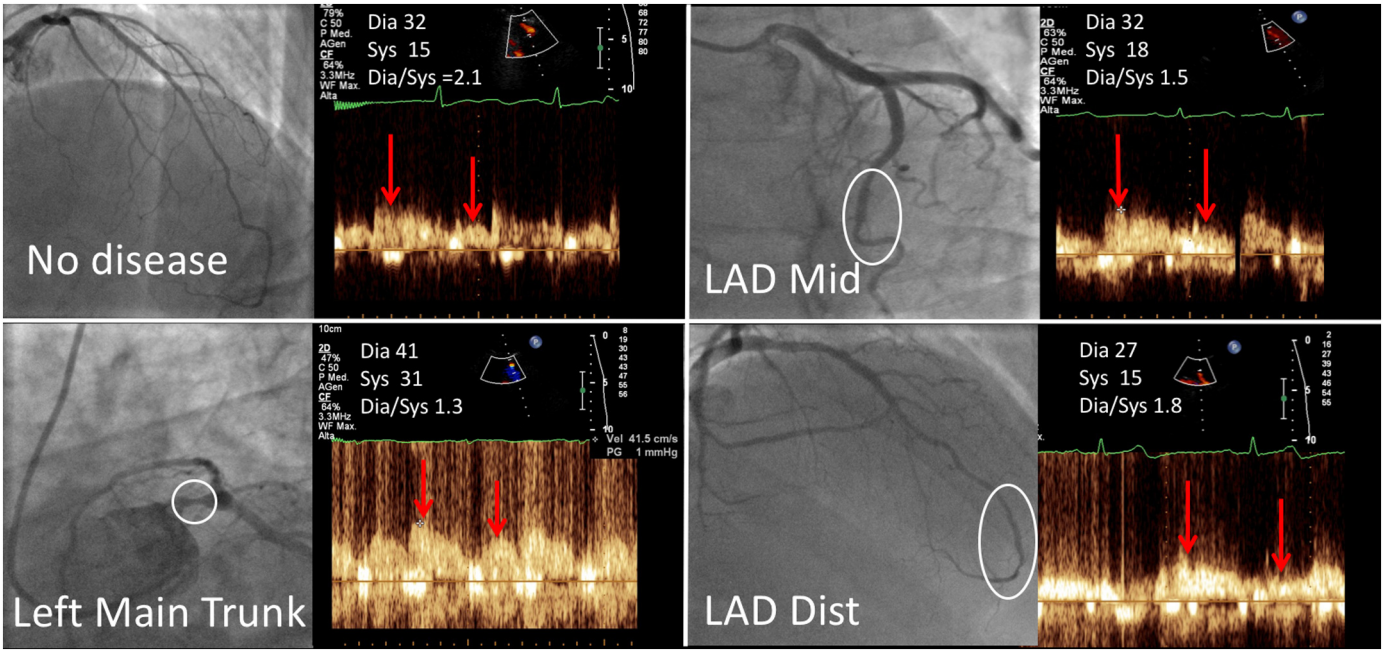


Fig. 7. Examples of velocity patterns with calculated diastolic/systolic ratio and corresponding angiograms.

LAD coronary arteries, but they are the most frequently diseased coronary arteries [23] and the most relevant for prognosis and clinical decision-making. [24]

The potential use that we foresee for rDSVR is in the setting of rest echocardiography, for example in intermediate risk subjects, but its use as an additional variable available before cSE, as was retrospectively calculated in the current study, is also a potential clinical application, due to the significantly increased C-index resulting by the addition of rDSVR data on top of clinical data, reversible WM abnormalities and CFR-LAD.

4.2. Study population in the current study

Patients undergoing cSE for suspected CAD, who also underwent iCA for some indication, represent a selected population, expected to be intrinsically high-risk for obstructive CAD because of a high prevalence of positive cSE and anatomically obstructive CAD, but in our study cohort we found "only" 53% of subjects with >50% stenosis on the LAD and/or LM, and 63% with at least one >50% stenosis on at least one coronary artery. These figures qualify our population as one at intermediate prevalence of CAD, which is the population that should ideally undergo provocative testing. Only 50% of patients had a positive cSE for reversible WM abnormalities: the reason lies probably in the practice of multi-parametric cSE, assessing not only WM, but also myocardial perfusion and CFR-LAD when technically feasible, making WM the strongest, but only one among other variables considered to indicate coronary anatomy tests. This improves cSE overall sensitivity for CAD, at the price of lower specificity compared with standard SE practice based only on robust (but low-sensitivity) WM assessment. WM sensitivity for obstructive CAD during cSE may appear low, compared with historical highly referral-biased studies, but is perfectly in line with more recent, less biased multicenter data [5].

Referral bias may apply to diagnostic data from cSE variables, which may have been partially used to indicate coronary anatomy tests. Referral bias apparently does not apply to rDSVR, which was additionally assessed retrospectively only for the aim of the current study; this "differential referral bias" may have underestimated the positive predictive value of cSE variables compared with rDSVR.

4.3. Contrast or not

While in the current study rDSVR was routinely measured with the use of ultrasound contrast, this was done because it was the only possibility for data collection, that is, in the context of our existing cSE registry; in this prospective registry, rest and stress LAD Doppler tracings are routinely recorded after contrast has been injected for other reasons (left ventricle opacification and myocardial perfusion assessment), and not purposefully injected to facilitate LAD measurement. When using current technology however the use of contrast is not deemed necessary for this purpose, rather it may mildly degrade the spectral Doppler tracing quality and this may have been a limitation for rDSVR inter-observer agreement in our study.

4.4. Limitations

This is a retrospective and single-center study and our results need to be replicated in a prospective and multicenter validation cohort. Visual coronary artery stenosis assessment was used for classification of CAD, and not fractional flow reserve, which may be perceived as more appropriate, although this measurement is used mostly if not only in visually intermediate lesions in the daily clinically routine and consequently was rarely measured in our retrospectively-selected population. The prevalence of significant CAD in this selected population is high, due to the per-protocol need of an available iCA; this may influence the results and the reported accuracies may not be reproduced in a population with a more typically lower prevalence of CAD.

5. Conclusions

Our data suggest that rDSVR is a reproducible variable, strongly associated with obstructive CAD either (or both) on the LM or LAD, easily measurable during rest echocardiography. While the presence of a normal rDSVR >1.7 is not informative (due to low sensitivity), a reduction below this value is instead associated with a very high likelihood that the LM or/and LAD are truly stenosed >50% at coronary angiography. Interestingly, the association of rDSVR with the presence of coronary stenosis in such prognostically key coronary arteries is significantly

stronger than it is for clinical variables, but also stronger than wall motion abnormalities or reduced CFR-LAD at stress-echocardiography.

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Competing interests

All authors declare that they have no conflict of interests.

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