JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 74, NO. 18, 2019

PUBLISHED BY ELSEVIER

Functional, Anatomical, and Prognostic Correlates of Coronary Flow Velocity Reserve During Stress Echocardiography

Quirino Ciampi, MD, PhD,[a] Angela Zagatina, MD, PhD,[b] Lauro Cortigiani, MD,[c] Nicola Gaibazzi, MD, PhD,[d] Clarissa Borguezan Daros, MD,[e] Nadezhda Zhuravskaya, MD,[b] Karina Wierzbowska-Drabik, MD, PhD,[f] Jaroslaw D. Kasprzak, MD, PhD,[f] José Luis de Castro e Silva Pretto, MD,[g] Antonello D'Andrea, MD, PhD,[h] Ana Djordjevic-Dikic, MD, PhD,[i] Ines Monte, MD,[j] Iana Simova, MD, PhD,[k] Alla Boshchenko, MD, PhD,[l] Rodolfo Citro, MD, PhD,[m] Miguel Amor, MD,[n] Pablo Martin Merlo, MD,[o] Claudio Dodi, MD,[p] Fausto Rigo, MD,[q] Suzana Gligorova, MD,[r] Milica Dekleva, MD,[s] Sergio Severino, MD,[t] Fabio Lattanzi, MD,[u] Maria Chiara Scali, MD, PhD,[u] Alexander Vrublevsky, MD,[l] Marco A.R. Torres, MD, PhD,[v] Alessandro Salustri, MD,[w] Hugo Rodrìguez-Zanella, MD,[x] Fabio Marco Costantino, MD,[y] Albert Varga, MD, PhD,[z] Eduardo Bossone, MD,[aa] Paolo Colonna, MD, PhD,[bb] Michele De Nes, BSc,[cc] Marco Paterni, BSc,[cc] Clara Carpeggiani, MD,[cc] Jorge Lowenstein, MD,[o] Dario Gregori, PhD,[dd] Eugenio Picano, MD, PhD,[cc] on behalf of the Stress Echo 2020 Study Group of the Italian Society of Echocardiography and Cardiovascular Imaging

ABSTRACT

BACKGROUND The assessment of coronary flow velocity reserve (CFVR) in left anterior descending coronary artery (LAD) expands the risk stratification potential of stress echocardiography (SE) based on stress-induced regional wall motion abnormalities (RWMA).

OBJECTIVES The purpose of this study was to assess the feasibility and functional correlates of CFVR.

METHODS This prospective, observational, multicenter study initially screened 3,410 patients (2,061 [60%] male; age 63 ± 11 years; ejection fraction 61 ± 9%) with known or suspected coronary artery disease and/or heart failure. All patients underwent SE (exercise, n = 1,288; vasodilator, n = 1,860; dobutamine, n = 262) based on new or worsening RWMA in 20 accredited laboratories of 8 countries. CFVR was calculated as the stress/rest ratio of diastolic peak flow velocity pulsed-Doppler assessment of LAD flow. A subset of 1,867 patients was followed up.

RESULTS The success rate for CFVR on LAD was 3,002 of 3,410 (feasibility = 88%). Reduced (≤2.0) CFVR was found in 896 of 3,002 (30%) patients. At multivariable logistic regression analysis, inducible RWMA (odds ratio [OR]: 6.5; 95% confidence interval [CI]: 4.9 to 8.5; $p < 0.01$), abnormal left ventricular contractile reserve (OR: 3.4; 95% CI: 2.7 to 4.2; $p < 0.01$), and B-lines (OR: 1.5; 95% CI: 1.1 to 1.9; $p = 0.01$) were associated with reduced CFVR. During a median follow-up time of 16 months, 218 events occurred. RWMA (hazard ratio: 3.8; 95% CI: 2.3 to 6.3; $p < 0.001$) and reduced CFVR (hazard ratio: 1.5; 95% CI: 1.1 to 2.2; $p = 0.009$) were independently associated with adverse outcome.

CONCLUSIONS CFVR is feasible with all SE protocols. Reduced CFVR is often accompanied by RWMA, abnormal LVCR, and pulmonary congestion during stress, and shows independent value over RWMA in predicting an adverse outcome. (J Am Coll Cardiol 2019;74:2278–91) © 2019 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Cardiology Division, Fatebenefratelli Hospital, Benevento, Italy; [b]Cardiology Department, Saint Petersburg University Clinic, Saint Petersburg, Russian Federation; [c]Cardiology Department, San Luca Hospital, Lucca, Italy; [d]Cardiology Department, Parma University Hospital, Parma, Italy; [e]Cardiology Division, Hospital São José, Criciuma, Brazil; [f]Cardiology, Bieganski Hospital, Medical University, Lodz, Poland; [g]Hospital Sao Vicente de Paulo e Hospital de Cidade, Passo Fundo, Brazil; [h]Cardiology Department, Echocardiography Lab and Rehabilitation Unit, Monaldi Hospital, Second University of Naples, Naples, Italy; [i]Cardiology Clinic, Clinical Center of Serbia, Medical School, University of Belgrade, Belgrade, Serbia; [j]Cardio-Thorax-Vascular Department, Echocardiography Lab, "Policlinico Vittorio Emanuele," Catania University, Catania, Italy; [k]Head of Cardiology Department, Acibadem City Clinic Cardiovascular Center, University Hospital, Sofia, Bulgaria; [l]Cardiology Research Institute, Tomsk National Research Medical Centre of the Russian Academy of Sciences, Tomsk, Russian Federation; [m]Cardiology Department and Echocardiography Lab, University Hospital "San Giovanni di Dio e Ruggi d'Aragona," Salerno, Italy; [n]Cardiology

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2019.08.1046

Coronary flow velocity reserve (CFVR) in left anterior descending coronary artery (LAD) can be obtained during stress echocardiography (SE) as an add-on to inducible regional wall motion abnormalities (RWMA) during dipyridamole (1), adenosine (2), dobutamine (3), and exercise (4) stress. It offers an integrated assessment of epicardial coronary artery stenosis and coronary microcirculation, which are important for tailored risk stratification in patients with coronary artery disease (CAD) and/or heart failure (HF) with either reduced or preserved ejection fraction (EF) (5). Due to the unique physiology of the myocardium, which increases function, thickness, and also temperature with increased coronary flow (6), the heart with preserved CFVR can be referred to as a "warm heart," opposed to the "cold heart" with reduced CFVR (7,8).

Despite the large body of coherent and converging evidence supporting the usefulness of CFVR, especially for risk stratification in CAD and HF, and its endorsement in stress echocardiography recommendations by the European Society of Echocardiography (9), the use of the technique has remained largely confined so far to academic environments. Starting in 2016, CFVR related to the left anterior descending artery was adopted in the quadruple imaging protocol of the Stress Echo 2020 study as the new clinical standard of the technique, which includes B-lines and left ventricular contractile reserve (LVCR) (10).

SEE PAGE 2292

The study hypotheses were that a satisfactory success rate in CFVR could be obtained in consecutive patients referred for physical or pharmacological stress testing, and that patients with reduced CFVR may show more extensive coronary anatomic disease and greater functional impairment during stress, mirrored by more B-lines and blunted LVCR. To test these hypotheses, a combined assessment of stress-induced RWMA and CVFR was attempted in 3,410 consecutive patients with known or suspected CAD and/or HF, referred for clinically-indicated SE in 20 accredited laboratories of the network of the international, multicenter, prospective SE 2020 study.

METHODS

STUDY POPULATION. In this prospective study, we evaluated 3,410 patients (1,349 women, 2,061 men; mean age 63 ± 11 years; mean left ventricular EF 61 ± 9%) recruited by 20 laboratories in 8 countries (Argentina, Brazil, Bulgaria, Hungary, Italy, Poland, Russian Federation, Serbia).

The inclusion criteria were: 1) age >18 years; 2) referral for known or suspected CAD or HF, with any degree of resting left ventricular function (preserved or reduced); 3) no severe primary valvular or congenital heart disease; 4) wall motion imaging of acceptable quality at rest (<2 uninterpretable segments); and 5) willingness to give their written informed consent allowing scientific utilization of observational data, respectful of privacy rights.

In the selected group, all patients, by selection, had interpretable wall motion. The number of patients with unreadable regional wall motion was <2%, and they were excluded from the present study. All patients underwent SE testing as part of a clinically driven work-up and according to the referring physician's indications. Written informed consent was obtained from all patients before testing. The study protocol was reviewed and approved by the institutional ethics committees as a part of the SE 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; NCT03049995).

STRESS ECHOCARDIOGRAPHY. We used commercially available ultrasound machines. Left ventricular end-diastolic and end-systolic volumes (ESV) used to calculate EF were measured by modified biplane

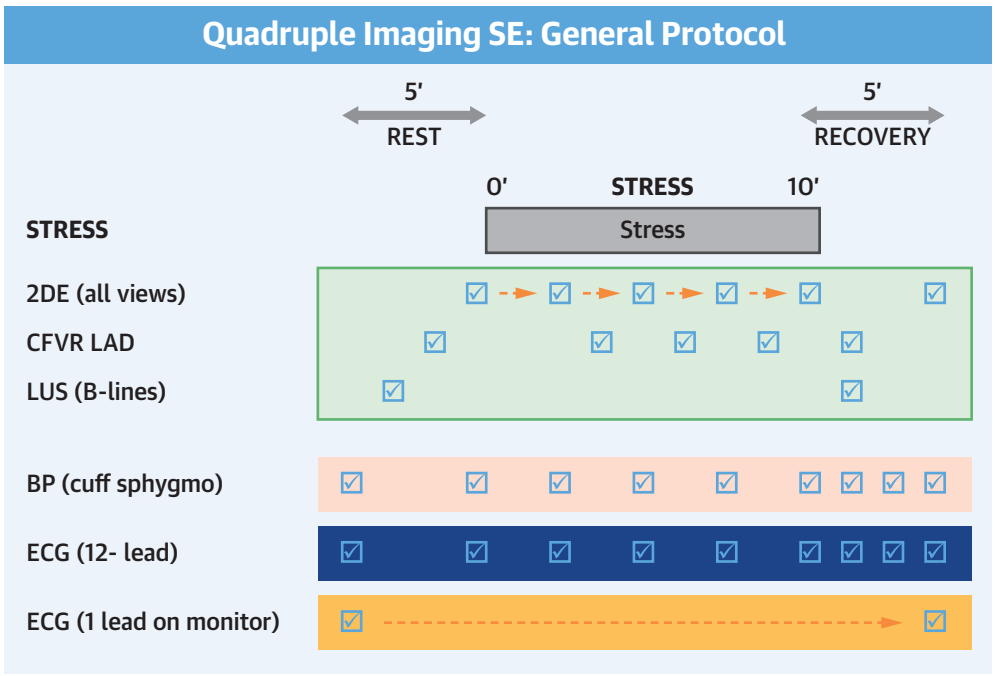
ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
EF = ejection fraction
ESV = end-systolic volume
HF = heart failure
LAD = left anterior descending
LVCR = left ventricular contractile reserve
RWMA = regional wall motion abnormalities
SE = stress echocardiography
WMSI = wall motion score index

Department, Ramos Mejia Hospital, Buenos Aires, Argentina; [o]Cardiodiagnosticos, Investigaciones Medicas, Buenos Aires, Argentina; [p]Casa di Cura Figlie di San Camillo, Cremona, Italy; [q]Cardiology Department, Ospedale dell'Angelo Mestre-Venice, Venice, Italy; [r]Cardiology Division Ospedale Casilino, Roma, Italy; [s]Clinical Cardiology Department, Clinical Hospital Zvezdara, Medical School, University of Belgrade, Belgrade, Serbia; [t]Cardiology Department, Coronary Care Unit, Monaldi Hospital, Second University of Naples, Naples, Italy; [u]Cardiothoracic Department, University of Pisa, Pisa, Italy; [v]Hospital de Clinicas de Porto Alegre-Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; [w]Non-invasive Cardiology, Heart Hospital, Hamad Medical Corporation, Doha, Qatar; [x]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico; [y]Cardiology Department, San Carlo Hospital, Potenza, Italy; [z]Institute of Family Medicine, University of Szeged, Szeged, Hungary; [aa]Azienda Ospedaliera Rilevanza Nazionale A. Cardarelli Hospital, Naples, Italy; [bb]Cardiology Hospital, Policlinico of Bari, Bari, Italy; [cc]CNR, Institute of Clinical Physiology, Biomedicine Department, Pisa, Italy; and the [dd]Biostatistics, Epidemiology and Public Health Unit, Padova University, Padova, Italy. Institutional funding for this study was provided by the CNR Institute of Clinical Physiology. Dr. Rodrìguez-Zanella has served on the Speakers Bureau of Siemens Healthineers. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 17, 2019; revised manuscript received August 8, 2019, accepted August 12, 2019.

FIGURE 1 The Combined RWMA-CFVR Stress Protocol



Intermittent imaging of left anterior descending artery (LAD) flow is performed at rest and peak stress with the same transducer used for continuous 2-dimensional imaging (2DE) of wall motion. BP = blood pressure; CFVR = coronary flow velocity reserve; ECG = electrocardiogram; LUS = lung ultrasound; RWMA = regional wall motion abnormalities; SE = stress echocardiography.

Simpson's method according to the American Society of Echocardiography and European Association of Cardiovascular Imaging (11).

All patients underwent exercise or pharmacological SE (9,12). Exercise SE was performed on supine bicycle steps of 2 min and increments of 25 W/step. We used a dipyridamole dose up to 0.84 mg/kg over 6 min, dobutamine starting from 5 up to 40 μg/kg/min with 3-min duration for each step (10, 20, 30, 40 μg/kg/min) and atropine coadministration up to 1 mg during the last 40-μg step, and adenosine up to 0.14 μg/kg/min over 6 min. The general SE protocol is shown in **Figure 1**.

QUADRUPLE IMAGING PROTOCOL. The "ABCD" protocol was used when each laboratory had completed the upstream quality control process (10). Step A included assessment of new or worsening RWMA. Wall motion score index (WMSI) was calculated in each patient at baseline and peak stress, in a 4-point score ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the left ventricle (12). Step B of the protocol included the assessment of B-lines with lung ultrasound and the 4-site simplified scan (10,13) and was performed in 2,445 patients. Step C of the protocol included the force-based assessment of LVCR as the stress/rest ratio of force, calculated as systolic blood pressure/ESV (10,14). SBP and ESV were obtained simultaneously at rest and at peak stress, and stress-specific, prognostically validated (10,14) cutoff values were considered abnormal (≤2.0 for exercise and dobutamine, ≤1.1 for adenosine and dipyridamole). CFVR (step D) was assessed during the standard SE examination using intermittent imaging of wall motion and LAD (14). Coronary flow in the mid-distal portion of the LAD was imaged from the low parasternal long-axis view and/or modified apical 2- , 3-, or 4-chamber view under the guidance of color Doppler flow mapping (14). At each time point, 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. CFVR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities (14). A CFVR value ≤2.0 was considered abnormal based on previously defined diagnostic and prognostic cutoff values. The acquisition time was <3 min at rest and usually less at peak stress. The analysis time was <1 min both at rest and at peak stress.

All readers (1 for each center) underwent a web-based training and quality control as previously described for RWMA (15), B-lines, ESV, and CFVR (10). As a part of the quality control process of the SE 2020-CFVR subproject, the accredited readers all had ≥90% concordance with core laboratory reading on measurement of peak diastolic flow velocity in a set of 20 clips selected from 8 different laboratories. The interobserver variability was <10% and the ICC coefficient was >90% for all accredited readers. The previously assessed intraobserver variability was <5% (10,14).

DATA STORAGE AND ANALYSIS. The results for each test were entered in the data bank at the time of testing by each recruiting center and sent monthly to the core lab with the electronic case report form with clinical data. After checking for internal consistency by trained technical staff, and double-checking with the center for data verification on possibly inconsistent input, the data were added to the data bank and frozen. The data were analyzed by personnel unaware of the study hypothesis.

CORONARY ANGIOGRAPHY. Invasive coronary angiography (n = 1,133) or noninvasive multidetector coronary angiography showing no CAD (n = 16) were available in 1,149 patients. Coronary angiography was decided by the referring physician based on symptoms, individual clinical characteristics, and noninvasive imaging results. Obstructive significant CAD was defined by a quantitatively assessed coronary diameter reduction ≥50% in the view showing the most severe stenosis. Images were read by experienced invasive cardiologists unaware of the results of SE.

OUTCOME DATA ANALYSIS. The original plan is to analyze all-cause mortality as the only endpoint. The recruitment will end in December 2020 with >5,000 patients, and follow-up will be completed by 2023 as per the original plan (10). The ad-interim analysis was provided with composite endpoints to corroborate the anatomic and functional data. Ad-interim outcome analysis was performed in 1,867 patients (of these, 1,436 had information on B-lines). Of this subset recruited in 8 centers who started enrollment before the other centers, 8 patients were lost to follow-up. The outcome status was verified until March 31, 2019. Follow-up data were obtained from at least 1 of 4 sources: 1) review of the patient's hospital record; 2) personal communication with the patient's primary care physician and review of the patient's chart; 3) a telephone interview with the patient conducted by trained personnel; and 4) a staff physician visiting the patients at regular 3-month intervals in the outpatient clinic. The composite primary endpoint was the occurrence of rehospitalization for acute HF (defined as new-onset or worsening, gradual or rapid, of signs and symptoms of HF that require urgent therapy and result in hospitalization), late (>3 months) myocardial revascularization, stroke, acute myocardial infarction, and all-cause death (1 composite endpoint per patient). Myocardial infarction was defined according to the 2007 Universal Definition. Stroke was defined as a sudden focal neurological deficit of cerebrovascular etiology persisting beyond 24 h and not due to another identifiable cause. Assessors were blinded to clinical and SE results.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD for continuous variables and as number (%) for categorical variables. Continuous variables were compared by paired-samples Student's *t*-test. Proportions were compared by chi-square statistics; the Fisher exact test was used when appropriate. The differences among different stressors were analyzed by analysis of variance (ANOVA). If any interactions were significant, post hoc comparison was performed using unpaired Student's *t*-test with Bonferroni correction to detect differences between 2 groups. Correlation between CFVR and LVCR, B-lines, or WMSI was estimated using Pearson's coefficients. All p values were adjusted for multiplicity to control the false discovery rate (i.e., the expected proportion of false discoveries amongst the rejected hypotheses) to keep power also in presence of test dependence (16). Independent predictors of reduced CFVR were assessed by multivariable logistic regression analysis. Odds ratios with the corresponding 95% confidence interval were estimated.

Univariable analyses by Cox proportional hazards models were performed to assess the association between each candidate variable and outcome. Nonproportionality of hazard was assessed using the Schoenfeld test. The primary endpoint was the time-to-first-event analysis by a multivariable Cox proportional hazards model. Hazard ratios with the corresponding 95% confidence interval were estimated.

Selection of independent predictors was performed both for logistic and proportional hazards model with a backward approach using a p value of 0.10 as threshold for inclusion in the model. A probability value of <0.05 was considered statistically significant. All statistical calculations were performed using SPSS for Windows, release 18.0 (Chicago, Illinois).

JACC VOL. 74, NO. 18, 2019
NOVEMBER 5, 2019:2278–91

TABLE 1 Clinical, Hemodynamic, Rest, and Stress Echocardiographic Findings

	Patients With Failed CFVR (n = 408, 12%)	Patients With CFVR ≤2.0 (n = 896, 26%)	Patients With CFVR >2.0 (n = 2,106, 62%)	p Value
Age, yrs	63 ± 11*†	65 ± 11	63 ± 11	0.0061
BMI, kg/m^2	27.6 ± 4.1	28.0 ± 4.4	28.0 ± 4.5	1.0000
Sex, M/F	273 (67)†/135 (33)	561 (63)/335 (37)	1,227 (58)/879 (42)	0.1438
Hypertension	307 (75)*†	733 (81)	1,601 (76)	0.2074
Diabetes	88 (22)	242 (27)	444 (21)	0.061
Previous PCI/CABG	122 (30)/24 (6)	285 (32)/63 (7)	606 (29)/141 (7)	0.0061
Known CAD	168 (42)	367 (41)	828 (39)	1.0000
Suspected CAD	175 (43)	384 (43)	996 (48)	
HFpEF	51 (12)	118 (13)	252 (12)	
HFrEF	14 (3)	27 (3)	30 (1)	
History of myocardial infarction	111 (27)*†	261 (29)	492 (23)	1.0000
History of dyspnea	65 (14)	145 (16)	282 (14)	0.0415
Beta-blockers	222 (54)	582 (65)	1,068 (51)	0.4524
Nitrates	97 (6)*†	50 (6)	47 (2)	0.0061
Calcium-channel blockers	73 (18)*†	168 (21)	281 (13)	0.0061
Statins	229 (56)	540 (60)	1,036 (38)	0.0061
ACE inhibitors	236 (58)	613 (68)	1,141 (54)	0.0061
Antiplatelet agents	244 (60)	586 (65)	931 (44)	0.0061
Heart rate rest, beats/min	71 ± 15*	70 ± 12	69 ± 12	0.0061
Heart rate stress, beats/min	116 ± 25*†	106 ± 24	106 ± 26	0.1552
DBP rest, mm Hg	78 ± 12	79 ± 11	79 ± 10	0.0061
DBP stress, mm Hg	85 ± 17*†	81 ± 16	80 ± 15	0.8768
SBP rest, mm Hg	133 ± 18*	134 ± 18	133 ± 17	0.0061
SBP stress, mm Hg	161 ± 34*†	152 ± 34	145 ± 33	0.1373
EF rest, %	58 ± 11*†	60 ± 10	61 ± 8	0.0061
EF stress, %	65 ± 13*†	64 ± 13	72 ± 10	0.0061
EDVi rest, ml/m^2	53 ± 25	54 ± 25	53 ± 23	0.0061
EDVi stress, ml/m^2	50 ± 25*†	52 ± 24	48 ± 21	0.8768
ESVi rest, ml/m^2	22 ± 13	22 ± 17	21 ± 12	0.002
ESVi stress, ml/m^2	18 ± 14*†	20 ± 16	14 ± 10	0.0061
Resting WMSI	1.18 ± 0.33	1.16 ± 0.31	1.08 ± 0.21	0.0061
Stress WMSI	1.27 ± 0.39*†	1.34 ± 0.43	1.08 ± 0.20	0.0061
ΔWMSI, stress-rest	0.06 ± 0.23*†	0.18 ± 0.34	0.01 ± 0.11	0.0061
B-lines rest	0.70 (0–28)	1.28 (0–35)	0.77 (0–22)	0.0061
B-lines peak	1.49 (0–28)	3.04 (0–40)	1.24 (0–27)	0.0061
LAD rest, cm/s	–	33.2 ± 12.9	26.1 ± 7.3	0.0061
LAD stress, cm/s	–	51.1 ± 18.7	65.6 ± 17.2	0.0061
CFVR	–	1.57 ± 0.35	2.57 ± 0.45	0.0061
Resting force, mm Hg/ml	3.9 ± 2.1	4.0 ± 2.1	4.0 ± 1.9	0.0061
Peak force, mm Hg/ml	6.9 ± 4.6*†	6.2 ± 4.6	7.7 ± 5.2	1.000
LVCR	1.9 ± 1.2	1.5 ± 0.8	2.0 ± 1.1	0.0061

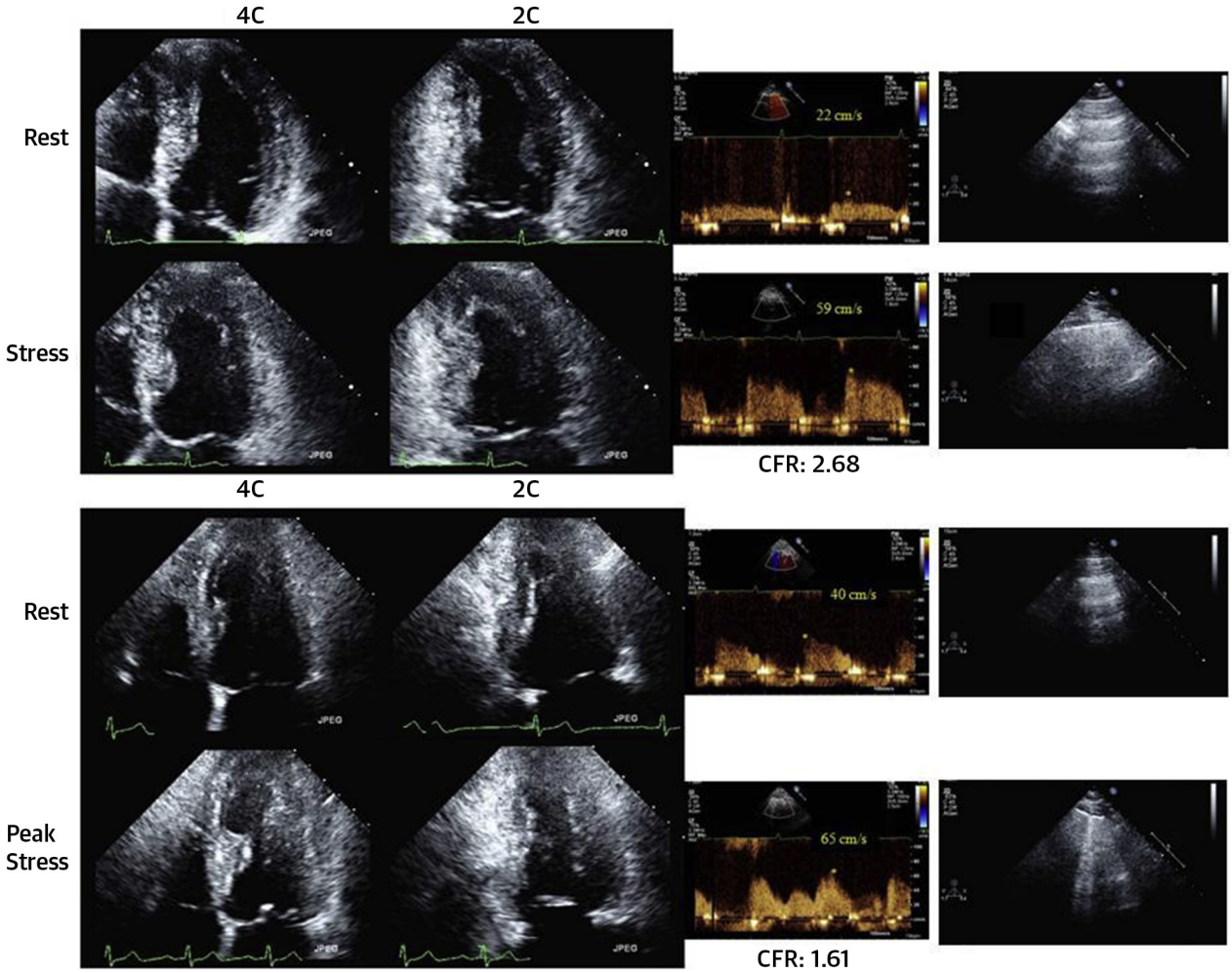
Values are mean ± SD, n (%), or median (range). The p values (adjusted by multiplicity of testing) refer to an overall difference among the 3 groups. *p < 0.05 vs. CFVR ≤2. †p < 0.05 vs. CFVR >2.

ACE = angiotensin-converting enzyme; BMI = body mass indes; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CFVR = coronary flow velocity reserve; DBP = diastolic blood pressure; EDVi = end-diastolic volume index; EF = ejection fraction; ESVi = end-systolic volume index; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reserved ejection fraction; LAD = left anterior descending artery; LVCR = left ventricular contractile reserve; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; WMSI = wall motion score index.

RESULTS

Of the 3,410 patients initially screened with SE, 408 were excluded due to unfeasible and/or uninterpretable CFVR tracing at rest or during stress. The utilized stress was exercise in 1,288 or pharmacological testing in 2,122 patients (vasodilator stress with dipyridamole, n = 1,842, and adenosine, n = 18; dobutamine, n = 262). Contrast agents were used in >80% of studies in 1 center, sometimes (5% to 20% of cases) used in 4 centers and rarely (<5%) or never used in the remaining centers. The main clinical, hemodynamic, rest, and SE findings in the 3,410 patients initially

FIGURE 2 An Example of a Cold and a Warm Heart



A nonischemic patient with normal regional wall motion **(top left)** compared with an ischemic patient with abnormal septoapical regional wall motion **(bottom left)**. The peak diastolic flow velocity increases during stress at least 2-fold in the warm heart **(top right)** and <2-fold in cold heart **(bottom right)**. In the **right** panels, the lung ultrasound study shows A-lines at rest and during stress at the **top** ("dry lung") of a warm and nonischemic heart; A-lines at rest and 3 B-lines during stress ("wet lung") in the **bottom** of a cold and ischemic heart. 4C = 4-chamber view; 2C = 2-chamber view; CFR = coronary flow reserve.

considered are shown in Table 1. Representative examples of 2 patients with either a warm (preserved CFVR) or cold (reduced CFVR) heart are shown in Figure 2.

FEASIBILITY OF CFVR. The overall success rate for CFVR on LAD was 3,002 of 3,410 (feasibility = 88%): 1,025 of 1,288 for exercise (80%), 1,766 of 1,860 (95%) for dipyridamole/adenosine (vasodilator stress), and 211 of 262 (81%) for dobutamine ($p < 0.001$ vs. dipyridamole/adenosine, p = NS vs. exercise). We examined the characteristics of patients who were excluded before starting the study on the basis of unfeasible Doppler signal of coronary flow velocity at rest or during stress (n = 408). The 408 patients with unfeasible coronary flow velocity signal were more frequently with occluded LAD vessel at subsequent angiographic verification (11 of 173 vs. 23 of 1,149; 6% vs. 2%; $p = 0.001$).

The hemodynamic, resting, and stress echocardiographic findings of the different stressors used are reported in Table 2.

THE FUNCTIONAL CORRELATES OF CFVR. A reduced CFVR (≤2.0) was found in 896 patients (30% of those with interpretable studies). Patients with reduced CFVR showed a higher prevalence of previous PCI or CABG, diabetes, inducible RWMA,

JACC VOL. 74, NO. 18, 2019
NOVEMBER 5, 2019:2278–91

TABLE 2 Hemodynamic, Rest, and Stress Echocardiographic Findings With Different Stresses

	Exercise (n = 1,025)	Vasodilator (n = 1,766)	Dobutamine (n = 211)	p Value
Heart rate rest, beats/min	71 ± 12*†	68 ± 12†‡	66 ± 11*‡	0.004
Heart rate stress, beats/min	127 ± 21*	92 ± 17	125 ± 21*	0.004
DBP rest, mm Hg	79 ± 10†	80 ± 10†	73 ± 11	0.004
DBP stress, mm Hg	89 ± 15	75 ± 13‡	75 ± 16‡	0.004
SBP rest, mm Hg	130 ± 17	135 ± 17‡	129 ± 17*	0.004
SBP stress, mm Hg	181 ± 30*†	129 ± 21†‡	136 ± 26*‡	0.004
EF rest, %	63 ± 9*†	60 ± 8†‡	59 ± 12*‡	0.004
EF stress, %	69 ± 13	70 ± 11‡	68 ± 14*	0.004
EDVi rest, ml/m^2	52 ± 19*†	55 ± 26†‡	47 ± 21	0.004
EDVi stress, ml/m^2	49 ± 17	51 ± 23	34 ± 22*‡	0.004
ESVi rest, ml/m^2	20 ± 10	23 ± 15‡	20 ± 16	0.004
ESVi stress, ml/m^2	16 ± 10	16 ± 13	12 ± 15*‡	0.004
Resting WMSI	1.11 ± 0.24	1.09 ± 0.24	1.14 ± 0.32*	0.004
Stress WMSI	1.26 ± 0.40	1.10 ± 0.24‡	1.12 ± 0.27‡	0.004
ΔWMSI, stress-rest	0.16 ± 0.32	0.03 ± 0.11‡	-0.17 ± 0.14‡	0.004
B-Lines at rest	1.05 (0-35)	0.90 (0-34)	0.47 (0-12)‡	0.092
B-Lines at peak	2.56 (0-40)	1.36 (0-33)‡	0.90 (0-12)‡	0.004
ΔB-lines	281/940 (29)	156/1,307 (12)‡	24/198 (12)‡	0.004
LAD rest, cm/s	29.4 ± 11.1	28.8 ± 9.5‡	26.5 ± 7.8‡	0.004
LAD stress, cm/s	58.6 ± 19.8*†	63.6 ± 18.3†‡	54.5 ± 16.0*‡	0.004
CFVR	2.11 ± 0.71*	2.38 ± 0.55	2.18 ± 0.55*	0.004
CFVR <2.0	448 (44)*	363 (21)	85 (40)*	0.004
Resting force, mm Hg/ml	4.1 ± 1.9*†	3.9 ± 2.0‡†	4.5 ± 2.5*‡	0.004
Peak force, mm Hg/ml	8.6 ± 5.6*†	6.0 ± 3.9†‡	10.3 ± 7.8*‡	0.004
LVCR	2.1 ± 1.2*†	1.6 ± 0.7†‡	2.4 ± 1.7*‡	0.004

Values are mean ± SD, median (range), n/N (%), or n (%). The p values (adjusted by multiplicity of testing) refer to an overall difference among the 3 groups. *p < 0.05 compared with vasodilator group. †p < 0.05 compared with dobutamine group. ‡p < 0.05 compared with exercise group.

Abbreviations as in Table 1.

higher values of peak WMSI, lower peak Force, and more B-lines (Table 1). Linear regression analysis demonstrated an inverse relationship between CFVR and stress-rest change in WMSI ($r = -0.362$; $p < 0.001$) (Figure 3), and a direct relationship between CFVR and LVCR ($r = 0.2335$; $p < 0.001$) (Figure 4). There was an inverse relationship between CFVR and stress-rest increase in B-lines, evaluated in 2,445 patients ($r = 0.2331$; $p < 0.001$) (Figure 5).

An ischemic (RMWA) response with reduced CFVR was found in 384 patients (13%), an ischemic response with preserved CFVR in 137 (4%), a nonischemic response with reduced CFVR in 512 patients (17%), and a nonischemic response with preserved CFVR in 1,969 (66%) ($p < 0.001$) (Figure 6).

At multivariable analysis, advanced age, presence of diabetes, RWMA, abnormal values of LVCR, and increased number of stress B-lines were associated with an increased likelihood of reduced CFVR (Table 3).

Compared with patients off beta-blockers (n = 1,352), patients on beta-blockers (n = 1,650) showed lower heart rate values both at rest (70.6 ± 12.0 beats/min vs. 67.8 ± 11.8 beats/min) and at peak stress (112.0 ± 26.6 beats/min vs. 103.6 ± 24.6 beats/min). Beta-blocker therapy was more frequently present in patients with reduced compared with those with preserved CFVR (65% vs. 51%; $p < 0.001$). Antianginal therapy was a significant predictor of reduced CFVR at univariable but not at multivariable analysis (Table 3).

ASSOCIATION OF CFVR WITH CORONARY ANGIOGRAPHIC FINDINGS. Angiographic findings in patients with known or suspected CAD were obtained by invasive or noninvasive coronary angiography in 1,149 patients, with no CAD in 455 patients and CAD in 694 patients; of these, 432 patients had 1-vessel, 167 2-vessel, and 95 3-vessel disease. Left anterior descending CAD was present in 166 of the 432 patients (38%) with 1-vessel and in 118 of the 167 patients (71%) with 2-vessel disease. In the subset with significant LAD disease and quantitative coronary angiography, CFVR was lowest in patients with stenosis >90% (n = 79, CFVR: 1.79 ± 0.66; $p < 0.001$) compared with those with 70% to 90% (n = 90, CFVR: 1.90 ± 0.66; $p < 0.001$) and 50% to 70% stenosis (n = 90, CFVR: 2.05 ± 0.62).

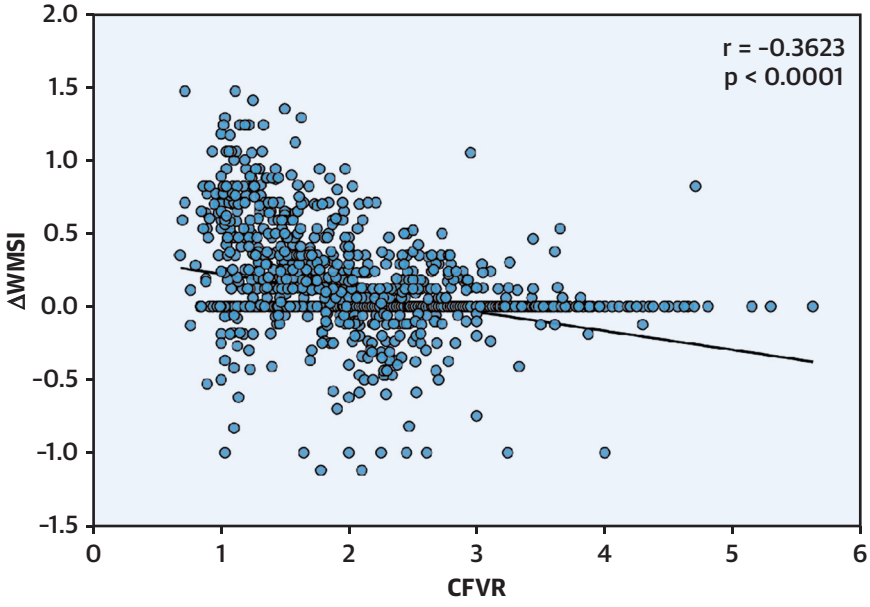
At the individual patient analysis, a reduced CFVR was present in 103 of 455 patients (23%) with no CAD, 119 of 432 (27%) with 1-vessel, 72 of 167 (43%) with 2-vessel, and 62 of 95 (65%) with 3-vessel disease ($p < 0.001$ by ANOVA for trend). At group analysis, the mean value of CFVR was 2.31 ± 0.49 in no-CAD, 2.26 ± 0.54 in 1-vessel, 2.13 ± 0.73 in 2-vessel, and 1.91 ± 0.81 in 3-vessel disease ($p < 0.001$ by ANOVA for trend).

OUTCOME DATA RESULTS. During a median follow-up time of 16 months (interquartile range: 13 to 22 months) in 1,867 patients, 22 patients died, 22 had a nonfatal myocardial infarction, 7 experienced a stroke, 55 were rehospitalized for acute heart failure, and 112 had late myocardial revascularizations. The event rate was lower in patients with preserved CFVR compared with patients with reduced CFVR (Figure 7). At multivariable proportional hazards analysis, rest-stress change in wall motion score index and reduced CFVR were independent predictors of events, together with LVCR and B-lines (Table 4).

DISCUSSION

Dual imaging of RWMA and CFVR during SE is feasible with a high success rate, requiring only a moderate increase in imaging time (<3 min) and even

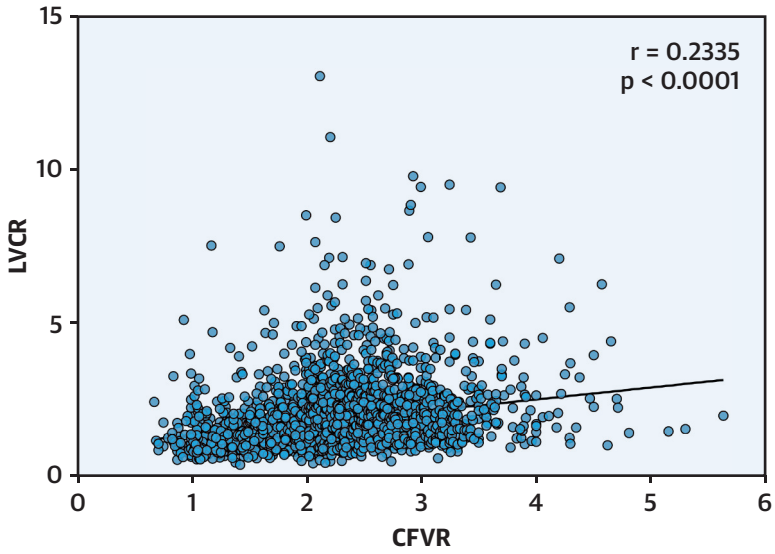
FIGURE 3 The Correlation Between CFVR and Δ-WMSI



x-axis = coronary flow velocity reserve (CFVR); y-axis = stress-rest variation (Δ) of wall motion score index (WMSI).

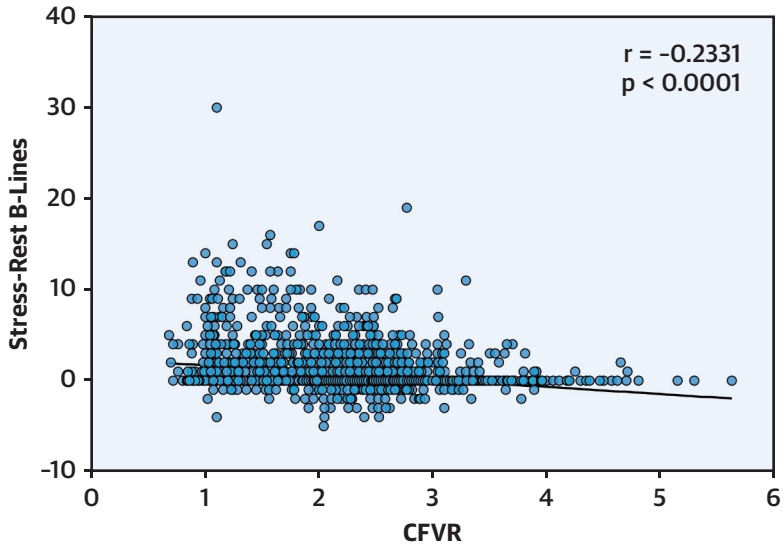
more limited increase in analysis time (<1 min). The success rate is higher with vasodilator than with dobutamine or exercise tests, yet it is satisfactory even with these 2 stresses that are more challenging for signal acquisition due to higher heart rate, hyperventilation, and hypercontractility of the heart, which all may interfere with signal capture during stress. CFVR and RMWA are concordantly abnormal in 13% of patients, concordantly normal in 66% of patients, and discordant in 21% of patients (4% with

FIGURE 4 The Correlation Between CFVR and LVCR



x-axis = coronary flow velocity reserve (CFVR); y-axis = left ventricular contractile reserve (LVCR).

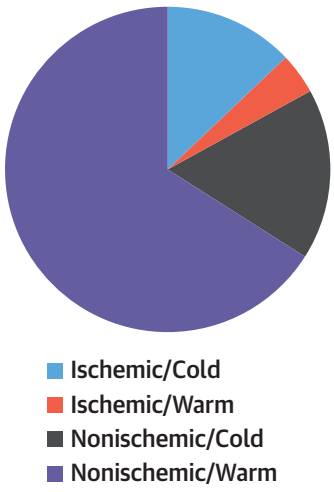
FIGURE 5 The Correlation Between CFVR and Δ-B-Lines



The correlation between CFVR (x-axis) and stress-rest variation (Δ) of B-lines (y-axis).

RWMA and preserved CFVR, 17% with no RWMA and reduced CFVR). Reduced CFVR is more prevalent in the patients with inducible RWMA or extensive CAD but also can be found in patients with normal coronary arteries.

FIGURE 6 Pie Graph of Response Patterns



The distribution of the 4 response patterns on the basis of RWMA (ischemic or nonischemic heart) and CVFR (warm or cold heart). The ischemic heart has epicardial stenosis, absent in nonischemic heart. The cold heart has altered coronary microcirculation in the LAD territory, absent in warm heart. Abbreviations as in Figure 1.

The cold heart with a reduced CFVR is a marker of altered coronary microvascular function and/or epicardial artery stenosis, which integrates and complements stress-induced RWMA that are more specific for a reduction of CFVR due to epicardial artery stenosis. The integration of CFVR and RWMA provides a better insight into the heterogeneous pathophysiology of myocardial ischemia within and beyond coronary artery disease (17,18) and allows a better risk stratification than each of the 2 parameters separately considered. The risk is lowest for patients with preserved CFVR and no RWMA, and highest for patients with RWMA and reduced CFVR (**Central Illustration**).

COMPARISON WITH PREVIOUS STUDIES. The results of the present study are consistent with a large and growing body of evidence that in the last 20 years showed the high feasibility of CFVR with different stressors and various patients' subsets, with the highest success rate and better-quality signal with vasodilator stresses (9,19,20) and slightly lower success rate and worse signal quality with exercise (80%) or dobutamine (81%) (3,4,9).

It has also been repeatedly described that a reduced CFVR can be found in a consistent percentage of patients with normal coronary arteries (21) or in conditions outside of CAD, such as HF (18). In the population of the present study, the reduction in CFVR was also more common in the presence of advanced age or diabetes (21,22). The common link

TABLE 3 Predictors of Reduced CFVR

	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis		Observed Event Rate
	OR (95% CI)	p Value	OR (95% CI)	p Value	Positive/Negative, n (%)
Age, yrs	1.022 (1.014–1.030)	<0.001	1.024 (1.014–1.034)	<0.001	
Male	1.200 (1.022–1.409)	0.021			330 (29)/198 (26)
Hypertension	1.527 (0.931–2.504)	0.094			454 (30)/74 (20)
Beta-blocker therapy	1.801 (1.533–2.118)	<0.001			363 (31)/165 (26)
Dyspnea at history	1.238 (0.996–1.540)	0.054			93 (36)/435 (27)
Diabetes	3.128 (1.956–5.004)	<0.001	2.093 (1.103–3.974)	0.017	121 (31)/407 (28)
Peak SBP, mm Hg	1.005 (1.003–1.008)	<0.001			
Peak heart rate, beats/min	1.000 (0.997–1.003)	0.927			
ΔWMSI	10.779 (8.668–13.404)	<0.001	6.854 (5.227–8.989)	<0.001	264 (75)/264 (17)
Abnormal LVCR	5.957 (5.024–7.063)	<0.001	3.433 (2.758–4.272)	<0.001	294 (59)/234 (17)
ΔStress-rest B-lines	3.187 (2.586–3.927)	<0.001	1.520 (1.173–1.969)	0.002	156 (51)/257 (23)

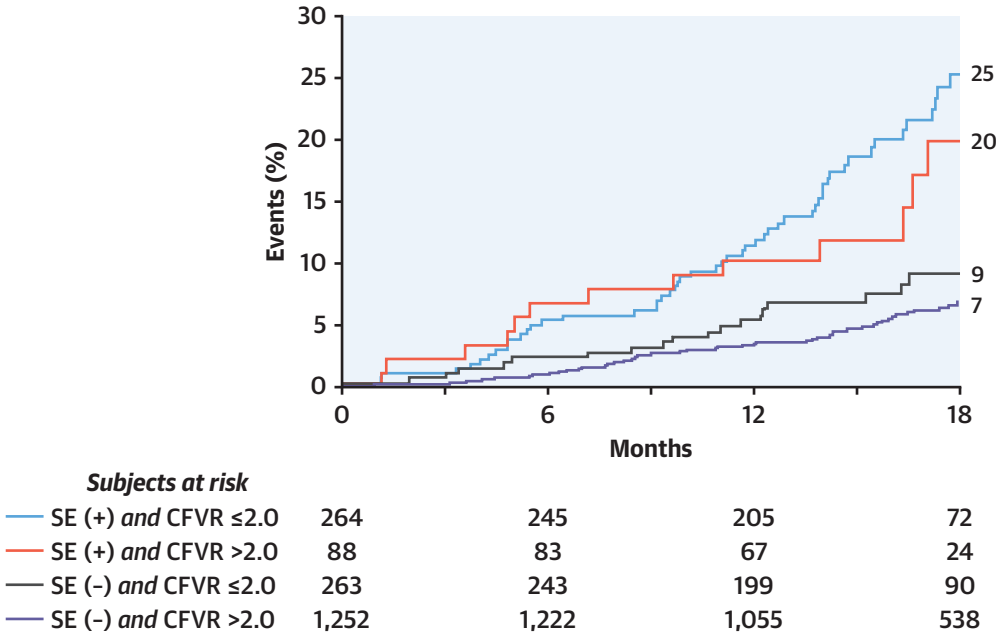
OR for continuous variables are computed with reference to unit change in the explanatory variable. Abnormal values of LVCR were considered ≤2.0 (≤1.1 for vasodilators); abnormal values of B-lines were considered with stress > rest for ≥2 points. Δ indicates stress-rest variation.

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

across these different clinical conditions is the presence of coronary microvascular disease, which could develop independently of epicardial CAD.

CFVR showed a weak correlation with LVCR and B-lines. This is not surprising because different parameters explore different variables, and the potential for their complementary information and additive use is exactly in their different focus and underlying pathophysiological target. B-lines are an index of extravascular lung water that are only mildly correlated with coronary flow reserve and are also sensitive to diastolic function, afterload mismatch, and severe mitral insufficiency (13). CFVR evaluates the subendocardial and also subepicardial coronary

FIGURE 7 Survival Curves Based on CFVR and RWMA



Event rate in patients stratified according to the presence of reduced CFVR and ischemia with inducible RWMA (worse survival), either 1 parameter abnormal (intermediate survival), and preserved CFVR without inducible ischemia (better survival). Abbreviations as in Figure 1.

TABLE 4 Predictors of Follow-Up Events

	Univariable Logistic Regression Analysis		Multivariable Logistic Regression Analysis		Observed Event Rate
	HR (95% CI)	p Value	HR (95% CI)	p Value	Positive/Negative, n (%)
Age	0.998 (0.985–1.011)	0.781			
Sex	1.047 (0.779–1.406)	0.762			106 (58)/77 (42)
Diabetes	0.792 (0.568–1.104)	0.168			48 (12)/135 (9)
Rest LVEF	1.002 (0.983–1.021)	0.846			15 (10)/168 (10)
ΔWMSI	5.611 (3.750–8.396)	<0.001	3.883 (2.379–6.336)	<0.001	72 (20)/11 (7)
Abnormal CFVR	2.376 (1.770–3.188)	<0.001	1.598 (1.123–2.275)	0.009	79 (15)/104 (8)
ΔB-Lines	2.068 (1.478–2.894)	<0.001	1.578 (1.102–2.261)	0.013	52 (17)/99 (9)
LVCR	2.929 (2.176–3.941)	<0.001	1.265 (1.050–1.525)	0.014	83 (17)/100 (7)

Δ indicates stress-rest variation.
HR = hazard ratio; other abbreviations as in Tables 1 and 3.

flow reserve, but only the former actively contributes to regional wall motion and pressure development (1,17).

CLINICAL IMPLICATIONS. As with all aspects of echocardiographic and SE diagnosis, the CFVR technique also does not tolerate improvisation. A standardized web-based module and credentialing process is helpful in the training phase, and should be accompanied or followed by a practical hands-on learning and validation of competence, no different from what has been described and endorsed by European and North American training guidelines for regional wall motion assessment (i.e., a hands-on training with an expert supervisor of approximately 100 cases) (9,12). In a systematic assessment of the effect of training specifically on CFVR quality, Michelsen et al. (19) found that the rate of unfeasible and/or poor-quality studies dropped to 11% for echocardiographers with experience of >100 studies, compared with 30% for echocardiographers with 0 to 10 studies. All of our recruiting centers underwent a web-based credentialing process and had established experience in CFVR before starting recruitment.

CFVR can be added to RWMA to increase the information obtained with SE within and beyond CAD. The simple combination of RWMA and CFVR readily identifies 4 separate patterns, from the more functionally benign negativity of RWMA and preserved CFVR, to intermediate responses (with either one positivity), up to the less functionally benign dual positivity of RWMA and reduced CFVR. The combination of RWMA and CFVR has the clear potential to expand the spectrum of prognostic stratification achieved by SE in CAD and HF patients, as indicated by the ad-interim analysis of outcome data showing the more benign prognosis in patients with dual negativity and the less benign prognosis in patients with dual positivity. In particular, the greatest value of the incremental information of the CFVR probably resides in the 21% of patients with discordant RWMA-CFVR findings. In patients without RWMA, an impaired CFVR is indicative of impaired coronary microcirculation. In patients with RWMA in a non-LAD territory, a preserved CFVR is indicative of a preserved coronary microcirculation. Prognostic data of the present study suggest that coronary microvascular disease and CFVR are important independently of epicardial coronary stenosis and RWMA in determining the outcome.

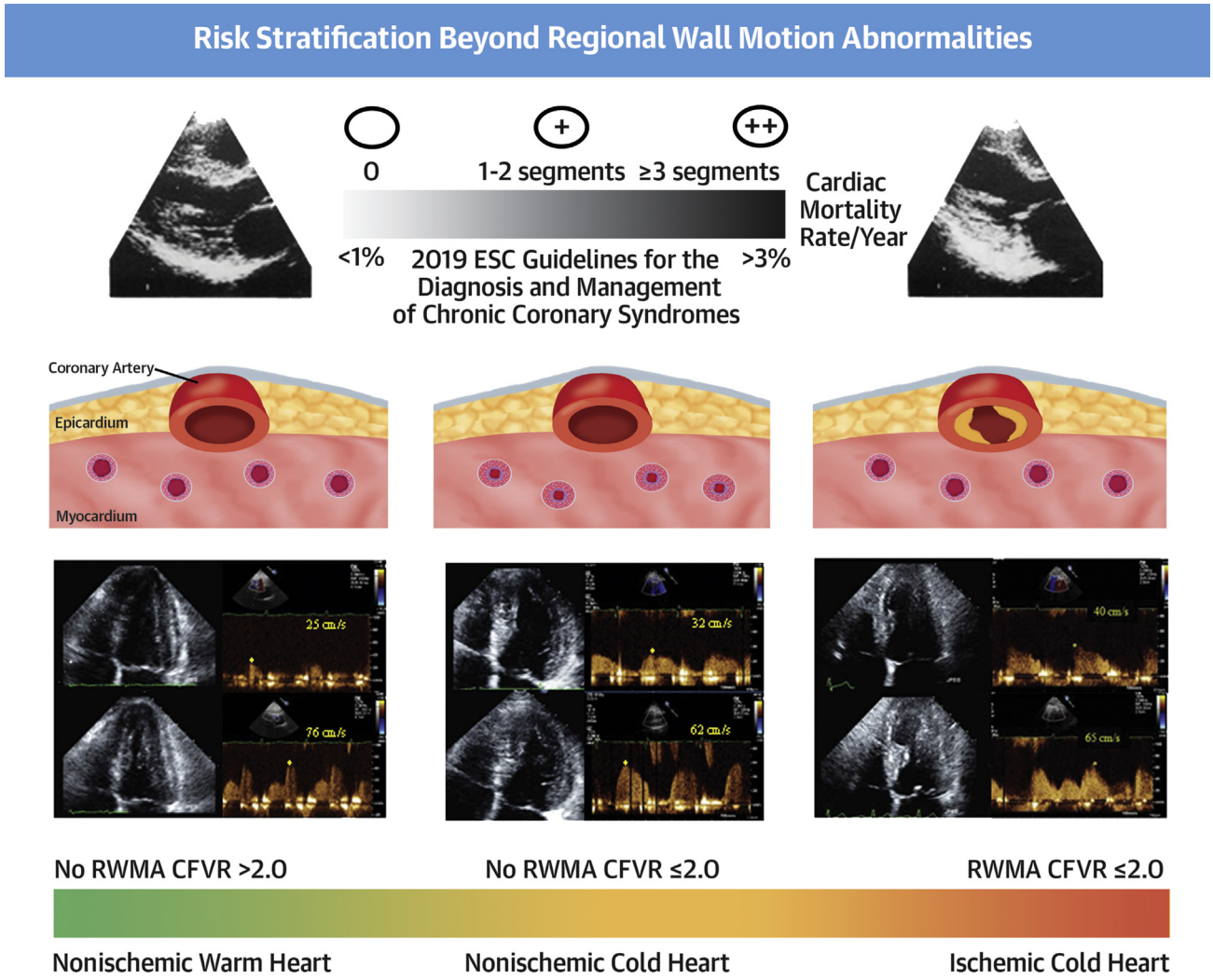
STUDY LIMITATIONS. We selected a consecutive population of patients arriving to the SE laboratory with known or suspected CAD and/or HF, and with the whole spectrum of underlying resting left ventricular function, from normal to severely reduced. The substantial heterogeneity of enrolled patients is likely to reflect the variety of patients met in real-world conditions.

Most patients were studied under anti-ischemic therapy, which may affect test results. Anti-ischemic therapy may exert an asymmetric effect on SE response and is more protective on RWMA than CFVR (9,10); this variable could not be controlled in our study due to the observational design.

We left the use of contrast agents to the experience of the recruiting center. We did not recommend it by protocol because it is not reimbursed in most participating countries. It clearly improves the flow profile in some patients but may also be potentially problematic in others due to blooming artifacts (exaggerated enhancement) of the LAD Doppler signal.

We pooled the data of 4 different stress modalities: semisupine exercise, dipyridamole, adenosine, and dobutamine. The study design did not interfere with the individual choice of the referring physician, which is a matter of personal experience, awareness of the individual patient indications and contraindications to specific stressors, and local practice (9,10).

CENTRAL ILLUSTRATION **Coronary Flow Velocity Reserve During Stress Echocardiography**



Ciampi, Q. et al. J Am Coll Cardiol. 2019;74(18):2278–91.

The combination of regional wall motion abnormalities (RWMA) and coronary flow velocity reserve (CFVR) expands the spectrum of prognostic stratification, with lowest risk associated with a nonischemic warm heart without RWMA and preserved CFVR (**green** in the risk bar) and highest risk associated with ischemic cold heart with RWMA and reduced CFVR (**red** in the risk bar). **(Left lower panel)** Normal pattern (no RWMA and preserved CFVR); **(middle lower panel)** coronary microvascular disease pattern (no RWMA and impaired CFVR); and **(right lower panel)** epicardial stenosis pattern (RWMA and impaired CFVR). For each pattern, the components of the normal heart are shown: epicardial coronary arteries, myocardium, and small vessels.

We only assessed CFVR in the LAD, but this approach has inherent limitations, because CAD commonly develops in the right coronary artery or left circumflex. The multiple coronary assessment of CFVR is feasible and useful to refine the diagnostic and prognostic potential of the technique but is too technically demanding and time-consuming to be proposed for general application at the present stage of technology (23).

CFVR has been available for >15 years (1,2), with demonstration of its prognostic impact for >10 years (22), yet it is not widely used in clinical practice. In fact, we need an effectiveness study prior to unrestricted dissemination of the technique, and Stress Echo 2020 is aimed at providing the missing evidence (10).

The recruitment of the study as outlined in the published protocol will be completed on December

31, 2020 (last patient in) with outcome data available on December 31, 2023 for the full ABCD imaging protocol (on RWMA, B-lines, LVCR, and CFVR), integrated with the nonimaging E step, based on EKG assessment of chronotropic reserve as peak/rest heart rate evaluating cardiac autonomic function (24).

CONCLUSIONS

CFVR, focused on peak diastolic flow velocity of LAD, is now incorporated in the standard quadruple imaging ABCDE protocol, with A for Asynergy in RWMA, B for B-lines, C for left ventricular Contractile reserve, D for Doppler-based CFVR, and E for EKG-based heart rate reserve. In this way, SE gains insight into the variables of coronary microcirculation, of paramount importance within and beyond CAD, and overcoming the limitations of an approach monolithically based on RWMA, which is well established with a central role in contemporary evidence-based cardiology guidelines (25) but only detects the physiologically critical coronary artery stenosis.

ADDRESS FOR CORRESPONDENCE: Dr. Eugenio Picano, CNR Research Campus-Institute Clinical Physiology, Building C- Room 130, Via Moruzzi, 1, 56124 Pisa, Italy. E-mail: picano@ifc.cnr.it. Twitter: @eupic58.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: CFVR can be calculated as the ratio of stress/rest diastolic pulsed-Doppler peak flow velocity in the LAD artery during exercise or pharmacological stress echocardiography. A blunted increase in CFVR has independent value over inducible RWMA for prediction of adverse events.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to determine whether patients at higher risk identified by CFVR benefit from interventions such as statins or angiotensin-converting enzyme inhibitors that improve coronary microcirculatory function.

REFERENCES

1. Rigo F, Richieri M, Pasanisi E, et al. Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography. Am J Cardiol 2003;91:269–73.

2. Djordjevic Dikic A, Tesic M, Boskovic N, et al. Prognostic value of preserved coronary flow velocity reserve by noninvasive transthoracic doppler echocardiography in patients with angiographically intermediate left main stenosis. J Am Soc Echocardiogr 2019;32:74–80.

3. Lowenstein JA, Caniggia C, Rousse G, et al. Coronary flow velocity reserve during pharmacologic stress echocardiography with normal contractility adds important prognostic value in diabetic and nondiabetic patients. J Am Soc Echocardiogr 2014;27:1113–9.

4. Zagatina A, Zhuravskaya N. The additive prognostic value of coronary flow velocity reserve during exercise echocardiography. Eur Heart J Cardiovasc Imaging 2017;18:1179–84.

5. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014;35:1101–11.

6. Robicsek F, Masters TN, Svenson RH, et al. The application of thermography in the study of coronary blood flow. Surgery 1978;84:858c64.

7. Opie L. Stunning, Hibernation and Calcium in Myocardial Ischemia and Reperfusion. Introduction. New York: Springer Verlag, 1992:1–3.

8. Picano E, Ciampi Q, Wierzbowska-Drabik K, Urluescu ML, Morrone D, Carpeggiani C. The new clinical standard of integrated quadruple stress echocardiography with ABCD protocol. Cardiov Ultrasound 2018;16:22.

9. Sicari R, Nihoyannopoulos P, Evangelista A, et al., on behalf of the European Association of Echocardiography. Stress echocardiography expert consensus statement. European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2008;9:415–37.

10. Picano E, Ciampi Q, Citro R, et al. Stress echo 2020: The international Stress Echo study in ischemic and non-ischemic heart disease. Cardiovasc Ultrasound 2017;15:3.

11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantitation by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.

12. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007;20:1021–4.

13. Scali MC, Zagatina A, Ciampi Q, et al. Stress Echo 2020 study group of the Italian Society of Echocardiography and Cardiovascular Imaging (SIECVI). The functional meaning of B-profile during stress lung ultrasound. J Am Coll Cardiol Img 2019;12:928–30.

14. Cortigiani L, Huqi A, Ciampi Q, Bombardini T, Bovenzi F, Picano E. Integration of wall motion, coronary flow velocity, and left ventricular contractile reserve in a single test: prognostic value of vasodilator stress echocardiography in patients with diabetes. J Am Soc Echocardiogr 2018;31:692–701.

15. Ciampi Q, Picano E, Paterni M, et al., on behalf of Stress Echo 2020 study group of the Italian Society of Cardiovascular Echography. Quality control of regional wall motion analysis in Stress Echo 2020. Int J Cardiol 2017;249:479–85.

16. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Statistical Society 1995;57:289–300.

17. Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. Eur Heart J 2014;35:1033–40.

18. Lancellotti P, Pellikka PA, Budts W, et al. Recommendations for the clinical use of stress echocardiography in non-ischemic heart disease: joint document of the European Association of Cardiovascular imaging and the American Society of Echocardiography. Eur Heart J Cardiov Imaging 2016;17:1191–229.

19. Michelsen MM, Pena A, Mygind ND, et al. Coronary flow velocity reserve assessed by transthoracic Doppler: the iPOWER study: factors influencing feasibility and quality. J Am Soc Echocardiogr 2016;29:709–16.

20. Takeuchi M, Lodato JA, Furlong KT, Lang RM, Yoshikawa J. Feasibility of measuring coronary flow velocity and reserve in the left anterior descending coronary artery by transthoracic Doppler echocardiography in a relatively obese American population. Echocardiography 2005;22:225–32.

21. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. Am J Cardiol 2009;103:626–31.

22. Cortigiani L, Rigo F, Gherardi S, Sicari R, Galderisi M, Bovenzi F, Picano E. Additional prognostic value of coronary flow reserve in diabetic and nondiabetic patients with negative dipyridamole stress echocardiography by wall motion criteria. J Am Coll Cardiol 2007;50:1354–61.

23. Cortigiani L, Rigo F, Bovenzi F, Sicari R, Picano E. The prognostic value of coronary flow velocity reserve in two coronary arteries during vasodilator stress echocardiography. J Am Soc Echocardiogr 2019;32:81–9.

24. Cortigiani L, Carpeggiani C, Landi P, Raciti M, Bovenzi F, Picano E. Usefulness of blunted heart rate reserve as an imaging-independent prognostic predictor during dipyridamole-echocardiography test. Am J Cardiol 2019;124:972–7.

25. Knuuti J, Wijns W, Saraste A, et al. The task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology. Eur Heart J 2019 Aug 31 [E-pub ahead of print].

KEY WORDS **coronary artery disease, coronary flow velocity reserve, heart failure, lung ultrasound, stress echocardiography**