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ORIGINAL RESEARCH

High Resting Coronary Flow Velocity by Echocardiography Is Associated With Worse Survival in Patients With Chronic Coronary Syndromes

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BACKGROUND: Resting coronary flow velocity (CFV) in the mid-distal left anterior descending coronary artery can be easily assessed with transthoracic echocardiography. In this observational study, the authors sought to assess the relationship between resting CFV, CFV reserve (CFVR), and outcome in patients with chronic coronary syndromes.

METHODS AND RESULTS: In a prospective multicenter study design, the authors retrospectively analyzed 7576 patients (age, 66±11 years; 4312 men) with chronic coronary syndromes and left ventricular ejection fraction ≥50% referred for dipyridamole stress echocardiography. Recruitment (years 2003–2021) involved 7 accredited laboratories, with interobserver variability <10% for CFV measurement at study entry. Baseline peak diastolic CFV was obtained by pulsed-wave Doppler in the mid-distal left anterior descending coronary artery. CFVR (abnormal value ≤2.0) was assessed with dipyridamole. All-cause death was the only end point. The mean CFV of the left anterior descending coronary artery was 31±12 cm/s. The mean CFVR was 2.32±0.60. During a median follow-up of 5.9±4.3 years, 1121 (15%) patients died. At multivariable analysis, resting CFV ≥32 cm/s was identified by a receiver operating curve as the best cutoff and was independently associated with mortality (hazard ratio [HR], 1.24 [95% CI, 1.10–1.40]; P<0.0001) together with CFVR ≤2.0 (HR, 1.78 [95% CI, 1.57–2.02]; P<0.0001), age, diabetes, history of coronary surgery, and left ventricular ejection fraction. When both CFV and CFVR were considered, the mortality rate was highest in patients with resting CFV ≥32 cm/s and CFVR ≤2.0 and lowest in patients with resting CFV <32 cm/s and CFVR >2.0.

CONCLUSIONS: High resting CFV is associated with worse survival in patients with chronic coronary syndromes and left ventricular ejection fraction ≥50%. The value is independent and additive to CFVR. The combination of high resting CFV and low CFVR is associated with the worst survival.

Key Words: coronary flow ■ diabetes ■ left anterior descending artery ■ vasodilatory stress

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CLINICAL PERSPECTIVE

What Is New?

- High resting coronary flow velocity is associated with all-cause death in patients with chronic coronary syndromes and normal resting left ventricular function, and the combination of high resting coronary flow velocity and low coronary flow velocity reserve is associated with the worst survival.

What Are the Clinical Implications?

- Because resting coronary flow provides important information on the physiology of the coronary circulation and has a high prognostic value, it seems reasonable to add the evaluation of coronary flow to the echocardiographic study at rest and not continue to consider it as an ancillary evaluation for coronary flow velocity reserve assessment.

Nonstandard Abbreviations and Acronyms

CCS	chronic coronary syndromes
CFV	coronary flow velocity
CFVR	coronary flow velocity reserve
RWMA	regional wall motion abnormality
SE	stress echocardiography
TTE	transthoracic echocardiography

The standard approach to risk stratification with stress echocardiography (SE) is based on regional wall motion abnormality (RWMA).[1,2] This approach misses the evaluation of coronary microcirculation, equally important as obstructive epicardial artery stenosis in determining symptoms and outcomes in chronic coronary syndromes (CCS) and several other conditions, including nonischemic dilated cardiomyopathy[3] and angina with normal coronary arteries.[4] With high-end instruments, coronary flow imaging with transthoracic echocardiography (TTE) can be easily obtained with pulsed-wave Doppler under color Doppler guidance.[4,5] The technical success rate is especially high (>95%) for the mid-distal left anterior descending coronary artery (LAD). TTE with vasodilator stress testing is used to assess coronary flow velocity reserve (CFVR), as indicated by current general cardiology guidelines with the class of recommendation 2b ("may be useful") for patients with chest pain and angiographically normal coronary arteries.[5,6] The assessment of CFVR also requires the evaluation of resting CFV. High resting CFV assessed with invasive or noninvasive methods is frequently associated with low CFVR after vasodilator stress[7,8] and might predict a worse outcome.[9–12] The current study hypothesis was that the combination of resting CFV and CFVR might identify different endotypes, with heterogeneous levels of risk, the highest for patients with high resting CFV and reduced CFVR. In this hypothesis-driven, retrospective analysis of prospectively acquired data,[13] we assessed the prognostic contribution of combined evaluation of CFVR and resting CFV in patients with CCS for known or suspected coronary artery disease (CAD) and left ventricular ejection fraction (LVEF) ≥50%, with or without resting or inducible RWMA.

METHODS

Patients

The initial population comprised 8402 patients prospectively enrolled by 7 certified laboratories in 3 countries from January 2003 to December 2021 as part of the international SE network started in 1990, with the add-on CFVR since 2003 and as a part of the Stress Echo 2030 study from March 2021 onward.[13] Exclusion criteria were LVEF ≤50%, significant valvular or congenital heart disease, and prognostically relevant noncardiac diseases (cancer, end-stage renal disease, or severe obstructive pulmonary disease). All patients underwent TTE including resting CFV and dipyridamole SE with an assessment of CFVR of mid-distal LAD. Of 8402 patients initially considered, 97 (1.2%) were excluded from analysis for inadequate acoustic window precluding satisfactory imaging of endocardial borders, 401 (4.8%) for inadequate acoustic window precluding satisfactory imaging of LAD flow Doppler (for CFV and CFVR assessment), 135 (1.7%) for side effects requiring premature test interruption, and 193 (2.5%) for missing follow-up data. Accordingly, 7576 (4312 [57%] men; mean±SD age, 66±11 years) with interpretable CFV and CFVR data and complete follow-up data formed the study group (Figure 1). Indications for SE in CCS were suspected CAD in 5008 (66%) and risk stratification of known CAD (ie, history of myocardial infarction, coronary revascularization, or angiographic evidence of ≥50% diameter coronary stenosis) in 2568 (34%) patients. Of the 7576 patients evaluated in the present study, 4351 (57%) were previously reported with a substantially shorter follow-up in a study on CFVR.[14]

Methylxanthine-containing drugs or beverages were discontinued at least 24 hours before testing. SE data were collected and analyzed by stress echocardiographers not involved in patient care.

Written informed consent was obtained from all patients before testing. The study protocol was reviewed

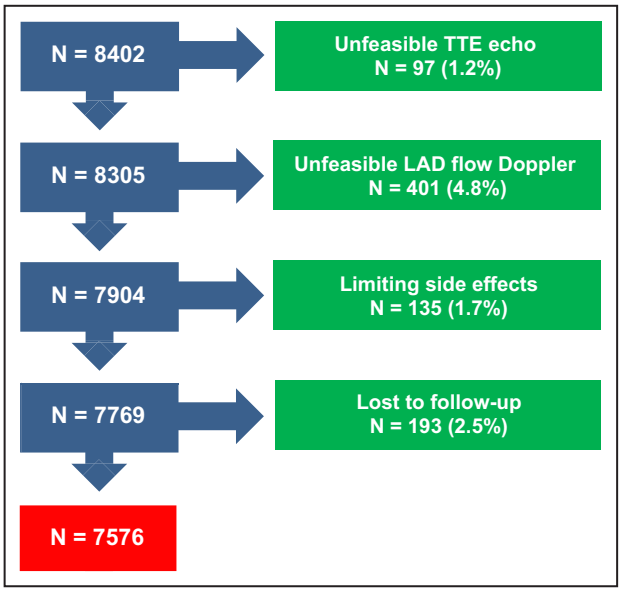


Figure 1. Consort diagram flow diagram showing how many individuals were excluded at each exclusion step.
LAD indicates left anterior descending artery; and TTE, transthoracic echocardiography.

and approved by the institutional ethics committees in its latest versions as part of the more comprehensive Stress Echo 2020 study (148-Comitato Etico Lazio-1, July 16, 2016; Clinical trials.Gov Identifier NCT 030.49995) and Stress Echo 2030 study 291/294/295 Comitato Etico Lazio-1, March 8, 2021; Clinical trials.Gov Identifier NCT 050.81115).

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Transthoracic Echocardiography

We used commercially available ultrasound machines equipped with multifrequency phased-array sector scan probes and second harmonic technology. All patients underwent comprehensive TTE at rest. All measurements were taken by certified cardiologists according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[15] Patients underwent SE with dipyridamole (0.84 mg/kg over 6 minutes) according to the recommended protocols.[16,17] ECG and blood pressure (BP) were monitored continuously. Criteria for interrupting the test were severe chest pain, diagnostic ST-segment shift, excessive BP increase (systolic BP ≥220 mm Hg and diastolic BP ≥120 mm Hg), limiting dyspnea, maximal predicted heart rate, significant arrhythmias, or limiting side effects. Echocardiographic imaging was performed from parasternal long- and short-axis views and apical 4-, 3-, and 2-chamber views, using conventional 2-dimensional echocardiography. Wall motion score index was calculated for each patient at baseline and peak stress, on a 4-point score ranging from 1 (normal) to 4 (dyskinetic) in a 17-segment model of the left ventricle. Pulsed-Doppler assessment of rest CFV and stress CFVR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities in the mid-distal LAD.[15] The procedure for acquisition between centers was standardized through a web-based learning module before starting data collection. All readers (1 for each center) underwent quality control as previously described with <10% variability for CFV measurements.[18]

SE Positivity Criteria

CFVR was considered abnormal when ≤2.0.[18] Inducible myocardial ischemia was identified with inducible RWMA and wall motion score index stress greater than rest (cutoff Δ ≥0.12), corresponding to the worsening of 1 grade in 2 of 17 segments or the worsening of 2 grades in 1 segment.

Follow-Up Data

Deaths were identified from the national health service database. Mortality was the only end point. To avoid misclassification of the cause of death,[19] overall mortality was considered. Coronary artery bypass surgery and angioplasty were also registered; however, follow-up was not censored at the time of revascularization.

Statistical Analysis

Continuous variables are expressed as mean±SD. Correlations between CFVR and rest CFV were estimated with Pearson coefficients. Resting CFV values were described with quintiles. We used ANOVA to examine potential differences in the means of independent variables (clinical and echocardiographic findings) at various quintiles of CFV of the LAD. If any interactions were significant, a post hoc comparison was performed using an unpaired Student *t* test with Bonferroni correction to detect differences between 2 groups. Independent predictors of increased CFV were assessed by multivariable logistic regression analysis considering the outcome variable the highest quintile versus all other quintiles. Variables included in the multivariable model included age, sex, diabetes, arterial hypertension, current smoker, prior myocardial infarction, resting LVEF, β-blocker therapy, resting heart rate, resting systolic, and diastolic BP. We used the Cox proportional hazards model to fit a multivariable regression that includes both the exposure variables (resting CFV and CFVR) and the identified confounding variables (ie, age, diabetes, hypertension, left bundle branch block, prior myocardial infartion, prior CABG, β-blocker therapy, LVEF, and resting and inducible RWMA). This

multivariable Cox proportional hazards model was employed to investigate the influence of various factors on the risk of the event (death). Proportionality of hazards was assessed using the Schoenfeld test. In addition, an adjusted model taking into account clinical and echocardiographic confounders was adopted for estimating mortality with Kaplan-Meier curves. The results of the multivariable-adjusted model was reported at the bottom of the survival curves. We confirmed the identified confounding variables using univariate regression with both exposure and outcome variables, and we selected as potential confounders those variables that were significantly associated with both exposure and outcome variables. For resting CFV, in the absence of historical data and recommendations in the literature, receiver operating characteristic analysis was used to obtain the best prognostic predictor. The primary end point was the time-to-event analysis by a multivariable Cox proportional hazards model. Hazard ratios (HRs) with the corresponding 95% CIs were estimated. Selection of independent predictors was performed both for the logistic and proportional hazards model with a backward approach using a *P* value of 0.10 as the threshold for inclusion in the model.

All analyses were 2-sided. Statistical significance was set at $P<0.05$. All statistical calculations were performed using SPSS for Windows, release 20.0 (IBM).

RESULTS

TTE Findings

The resting echocardiographic LVEF in the entire study group was 60%±5%. The mean resting CFV of LAD was 31±12 cm/s. The mean CFVR of the LAD was 2.32±0.60. The acquisition time CVF was <3 minutes. The analysis time was <1 minute.

The univariate analysis showed that patients in the highest quintile of CFV were older, more frequently had diabetes, and showed lower LVEF, higher heart rate, and higher systolic and diastolic BPs compared with other groups; in addition, they had a greater prevalence of inducible ischemia and CFVR of the LAD ≤2 (Table 1).

The results of the multivariable regression analysis with various traits and the highest quintile of resting CFV as the outcome measure are shown in Table 2. Diabetes, increased resting heart rate, increased systolic BP, prior myocardial infarction, and CFVR of the LAD ≤2 were associated with an increased likelihood of increased CFV (Table 2).

SE Findings

No major complications occurred during the test. CFVR of the LAD ≤2.0 was found in 2164 (29%) patients. CFVR was weakly related to resting CFV ($r=0.27$, $P<0.0001$). A total of 1001 patients showed rest or stress-induced RWMA in the LAD territory. Of them, 672 (67%) also showed a reduced CFVR. Of the 605 patients without RWMA in the LAD territory, 133 (22%) had reduced CFVR.

Figure 2 shows an example of a patient with a normal response for CFVR (3.78) with resting CFV (27 cm/s) falling in the third quintile. Figure 3 shows an example of a patient with an abnormal response for CFVR (1.62) with resting CFV (45 cm/s) falling in the highest quintile.

Follow-Up Events

During a mean follow-up of 5.9±4.3 years, there were 1121 (15%) deaths. Moreover, 1170 (15%) patients underwent coronary revascularization (229 surgery, 941 angioplasty) and were not censored: 466 of 723 (64%) with and 704 of 6853 (10%) without inducible RWMA ($P<0.0001$).

Outcome Prediction

Resting CFV was considered abnormal when ≥32 cm/s, which is the optimal cutoff value to predict mortality established by a receiver operating characteristics analysis (area under the curve, 0.56 [95% CI, 0.55–0.57]; sensitivity 43%, specificity 68%).

A normal CFVR (n=5412; 71%) was associated with abnormal, high resting CFV in 1541 (20%) patients and with normal, low resting CFV in 3871 patients (51%). A reduced CFVR (n=2164; 29%) was associated with a normal, low CFV in 1169 (15%) patients and with an abnormal, high resting CFV in 995 (13%) patients.

The contingency table (Table 3) shows the distribution of patients across quintiles of resting CFV and their respective CFVR categories. From this table, it is evident that different quintiles of resting CFV are associated with varying proportions of patients with CFVR ≤2 (abnormal) and CFVR >2 (normal). The percentage values reveal these associations more clearly: for instance, in the lowest quintile of resting CFV, only 3% of patients have CFVR ≤2, while in the highest quintile, this percentage increases to 10%. Pearson χ^2 test confirms a significant association between resting CFV quintiles and CFVR categories ($P<0.001$), reinforcing the importance of considering these variables jointly rather than relying on fixed thresholds.

Univariable and multivariable prognostic predictors are reported in Table 4.

Multivariable indicators of all-cause death were age (HR, 1.09 [95% CI, 1.08–1.10]; $P<0.0001$), CFVR of the LAD ≤2.0 (HR, 1.78 [95% CI, 1.57–2.02]; $P<0.0001$), prior coronary surgery (HR, 1.58 [95% CI, 1.33–1.93]; $P<0.0001$), diabetes (HR, 1.37 [95% CI, 1.21–1.55]; $P<0.0001$), resting CFV ≥32 cm/s (HR, 1.24 [95% CI, 1.10–1.40]; $P<0.0001$), and LVEF (HR, 0.98 [95% CI, 0.97–1.00]; $P=0.03$). Resting CFV greater than the third quintile showed an HR of 1.16 (95% CI, 1.03–1.31)

Table 1. Clinical and Echocardiographic Findings According to Quintiles of Resting Flow Velocity of the LAD

	All patients (n=7576)	First quintile ≤22 cm/s (n=1242)	Second quintile 23–26 cm/s (n=1771)	Third quintile 27–29 cm/s (n=1249)	Fourth quintile 30–34 cm/s (n=1560)	Fifth quintile ≥35 cm/s (n=1754)	*P* value
Age, y	65.6±11.4	64.6±11.8	64.4±11.7	64.9±11.4	65.5±11.3	67.4±11.5	<0.0001
Male sex	4312 (57)	825 (66)	1021 (58)	669 (54)	837 (54)	960 (55)	<0.0001
Diabetes	2207 (29)	361 (29)	524 (30)	351 (28)	401 (26)	570 (33)	0.0007
Arterial hypertension	5061 (67)	873 (70)	1112 (63)	796 (64)	1045 (67)	1235 (70)	<0.0001
Hypercholesterolemia	4313 (57)	768 (62)	972 (55)	705 (56)	884 (57)	984 (56)	0.003
Current smoker	1925 (25)	325 (26)	416 (24)	304 (24)	396 (25)	484 (28)	0.06
Left bundle branch block	296 (4)	34 (3)	56 (3)	47 (4)	82 (5)	77 (4)	0.004
Prior myocardial infarction	1564 (21)	189 (23)	331 (19)	235 (19)	308 (20)	401 (23)	0.0005
Prior CABG	393 (5)	87 (7)	89 (5)	62 (5)	72 (5)	83 (5)	0.03
Prior PCI	1831 (24)	393 (32)	409 (23)	278 (22)	335 (22)	416 (24)	<0.0001
Known CAD	2568 (34)	512 (41)	558 (32)	385 (31)	495 (32)	618 (35)	<0.0001
Resting LVEF, %	59.7±4.9	60.3±5.1	60.1±4.8	59.6±4.5	59.6±4.8	59.1±5.1	<0.0001
Resting RWMA	1171 (15)	189 (15)	220 (12)	176 (14)	249 (16)	337 (19)	<0.0001
β-Blocker therapy	2640 (35)	506 (41)	598 (34)	430 (34)	527 (34)	579 (33)	0.0001
Calcium channel blocker therapy	1022 (13)	134 (11)	215 (12)	165 (13)	222 (14)	286 (16)	0.0001
Nitrate therapy	338 (4)	51 (4)	49 (3)	63 (5)	74 (5)	101 (6)	0.0004
At least 1 antianginal medication	3216 (42)	581 (47)	719 (41)	535 (43)	642 (41)	739 (42)	0.01
Resting heart rate, beats per min	68.0±11.4	64.8±9.9	67.1±11.5	68.8±11.3	69.3±11.2	71.0±11.8	<0.0001
Resting SBP, mmHg	135.5±17.4	131.7±17.3	133.4±16.8	135.2±17.4	137.4±16.7	140.1±17.9	<0.0001
Resting DBP, mmHg	78.9±8.9	77.2±8.9	78.2±9.0	79.4±8.9	79.8±8.7	80.0±9.0	<0.0001
Inducible RWMA	723 (9)	92 (7)	131 (7)	117 (9)	135 (9%)	248 (14)	<0.0001
CFV of LAD	30.7±11.8	19.7±2.0	24.6±1.1	28.0±0.8	31.6±1.4	45.8±15.5	<0.0001
CFVR of LAD	2.3±0.6	2.5±0.7	2.4±0.6	2.3±0.5	2.3±0.6	2.1±0.6	<0.0001
CFVR of LAD ≤2.0	2164 (29)	258 (21)	427 (24)	282 (23)	430 (28)	767 (44)	<0.0001

Data presented are mean value±SD or number (percentage) of patients. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; DBP, diastolic blood pressure; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RWMA, regional wall motion abnormality; and SBP, systolic blood pressure.

compared with an HR of 1.24 (95% CI, 1.10–1.40) of the CFV ≥32 cm/s derived from the receiver operating characteristic curve. Both resting and inducible RWMA were significant predictors of outcome at univariable but not at multivariable analysis.

The mortality rate increased progressively from the first to the fifth quintile of CFV (Figure 4). Similarly, the annualized mortality rate progressively increased with increasing quintiles of CFV, from 1.9% in the lowest up to 3.7% for the highest quintile (Figure 5). When both CFV and CFVR were considered, the mortality rate was highest in patients with high CFV and low CFVR and lowest in patients with low resting CFV and high CFVR (Figure 6).

In the subset of 1492 patients with nonsignificant (<50% stenosis) LAD disease with invasive coronary angiography or noninvasive computed tomography angiography, 892 patients showed normal or near-normal coronary arteries, 357 non-LAD diseases (circumflex artery stenosis in 110, right coronary artery stenosis in 176, both circumflex and right coronary artery stenosis in 71), and 243 native LAD disease corrected by myocardial revascularization with coronary artery bypass surgery (n=59) or percutaneous coronary interventions (n=184). In this subset of patients, there were 148 (10%) deaths. On multivariable analysis, resting CFV ≥32 cm/s (HR, 1.56 [95% CI, 1.12–2.16]; *P*=0.008) showed independent prognostic value, while CFVR ≤2.0 and inducible RWMA did not. In the subset of 357 patients with the non-LAD disease, 58 (16%) deaths occurred. In this subset, inducible RWMA, resting CFV ≥32 cm/s, and CFVR ≤2.0 failed to provide independent prognostic information.

DISCUSSION

In this study, we used TTE to assess resting CFV and dipyridamole stress for CFVR in patients with CCS and LVEF ≥50% followed-up for a mean of 6 years. We demonstrated that: (1) resting CFV and CFVR showed

Table 2. Predictors of the Highest Quintile of Resting CFV

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.02 (1.01–1.02)	<0.0001		
Male sex	0.89 (0.80–0.99)	0.04		
Diabetes	1.23 (1.10–1.38)	<0.0001	1.42 (1.19–1.69)	<0.0001
Arterial hypertension	1.24 (1.11–1.39)	<0.0001		
Hypercholesterolemia	0.96 (0.86–1.07)	0.42		
Current smoker	1.16 (1.03–1.31)	0.02		
Left bundle branch block	1.17 (0.90–1.53)	0.23		
Prior myocardial infarction	1.19 (1.04–1.35)	0.009	1.27 (1.02–1.58)	0.03
Prior CABG	0.93 (0.74–1.19)	0.58		
Prior PCI	0.99 (0.87–1.12)	0.86		
Resting LVEF	0.97 (0.96–0.98)	<0.0001		
Resting RWMA	1.42 (1.24–1.63)	<0.0001		
β-Blocker therapy	0.90 (0.80–1.01)	0.07		
Resting heart rate	1.03 (1.02–1.03)	<0.0001	1.03 (1.02–1.03)	<0.0001
Resting SBP	1.02 (1.01–1.02)	<0.0001	1.02 (1.01–1.02)	<0.0001
Resting DBP	1.02 (1.01–1.03)	<0.0001		
Inducible RWMA	1.85 (1.54–2.18)	<0.0001		
CFVR of LAD ≤2.0	2.46 (2.20–2.57)	<0.0001	3.45 (2.88–4.13)	<0.0001

CABG indicates coronary artery bypass graft; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; DBP, diastolic blood pressure; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; OR, odds ratio; PCI, percutaneous coronary intervention; RWMA, regional wall motion abnormality; and SBP, systolic blood pressure.

independent prognostic value, additive over resting LVEF, in patients with CCS with preserved global left ventricular function; (2) the worst outcome is associated with the combination of high resting CFV flow and reduced CFVR (graphical abstract); and (3) inducible RWMA is the cornerstone of conventional SE for risk stratification, but its value is lost when resting CFV and CFVR are considered, likely due to the clinical relevance of inducible RWMA with subsequent ischemia-driven revascularization as dictated by current guidelines.

Mechanism of the Reduced CFVR and Increased Resting Flow

A reduced CFVR can be due to a reduction of the maximal vasodilatory capacity or an increase in the resting coronary flow. The increased resting CFV is the final common pathway of several, not mutually exclusive, possible mechanisms: metabolic, myocardial, hydraulic epicardial, coronary microvascular, aortic, and neural.

A high resting flow is correlated with insulin resistance in patients with type 2 diabetes, suggesting that a cellular reduction in glucose uptake may result in a metabolic shift toward increased fatty acid oxidation, with a consequent decrease of adenosine triphosphate produced per molecule of oxygen consumed, leading to the need for higher resting coronary blood flow.[20] The increased resting CFV can be due to a secondary increase in oxygen consumption for increased myocardial function, left ventricular hypertrophy, heart rate, or systolic BP, driving an increase in flow that follows the increased myocardial oxygen demand through metabolic vasodilation.[21] For simply hydraulic reasons, any reduction of the coronary lumen will lead to an increase in CFV to keep the volumetric coronary flow or myocardial perfusion constant in a finely autoregulated district. In the progression of the atherosclerotic process, after the initial compensatory phase of abluminal dilation through the Glagov mechanism is exhausted, lumen encroachment occurs and resting CFV may increase.[22] Coronary microvascular dysfunction is also possible as a primary target of disease, with lumen reduction for structural abnormalities such as smooth muscle hypertrophy or purely functional abnormalities of the coronary small vessels in the absence of any structural disease.[23] Large artery stiffening is associated with increased systolic BP and pulse pressure with loss of the efficient cushioning function of the healthy aorta, which protects the coronary microvasculature from potentially harmful fluctuations in pressure.[24] An abnormal sympathetic innervation can also be present in the early stages of diabetes and may determine an increase in resting CFV with abnormal microcirculatory function.[25] All of these factors may contribute to the increased CFV, which was associated

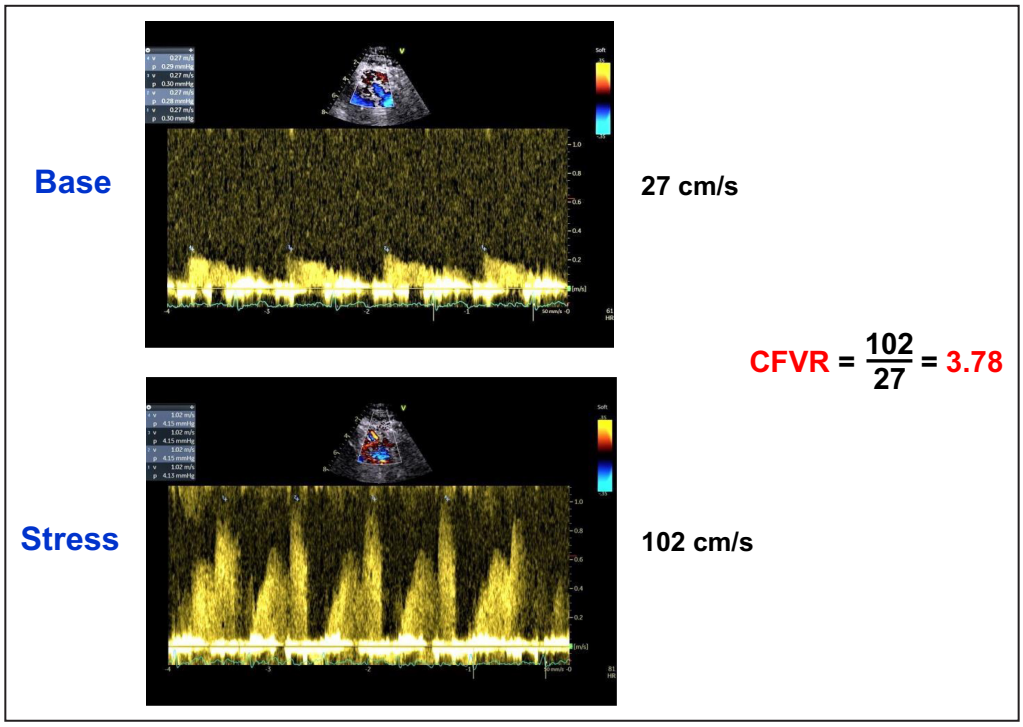


Figure 2. **The normal response for CFVR with normal resting CFV. CFV indicates coronary flow velocity; and CFVR, coronary flow velocity reserve.**

in our population with advanced age, diabetes, high resting heart rate, and increased systolic BP (Table 1). The atherosclerotic-hydraulic, cellular-metabolic, and neural-sympathetic mechanisms are different endotypes that may all converge in an identifiable phenotype of increased resting CFV.

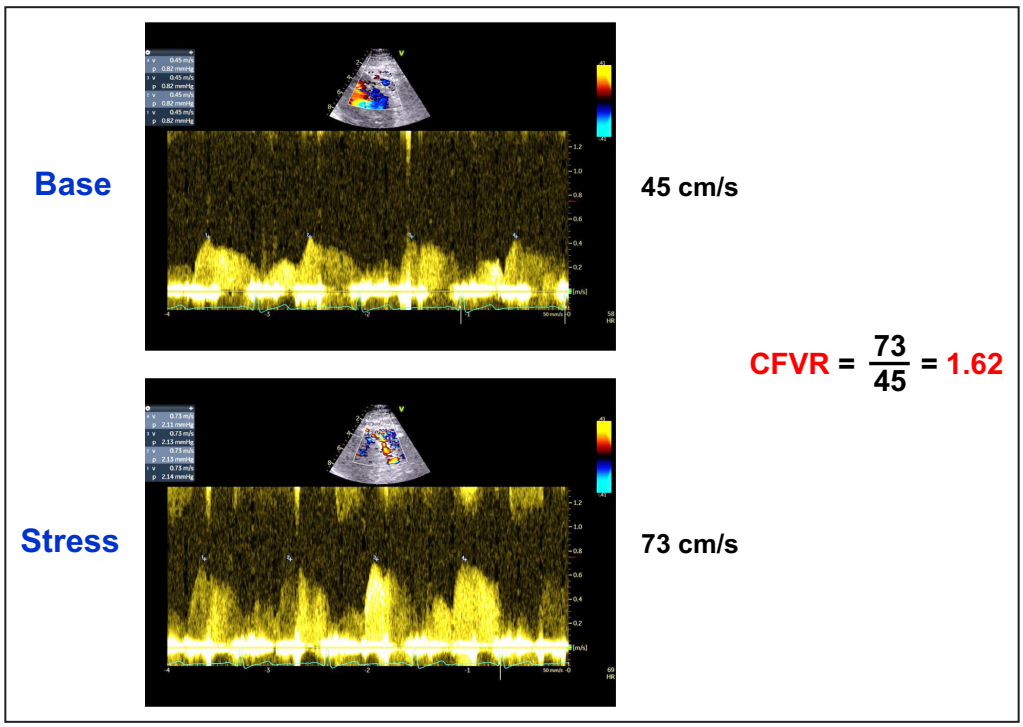


Figure 3. **The abnormal response for CFVR with high resting CFV. CFV indicates coronary flow velocity; and CFVR, coronary flow velocity reserve.**

Table 3. Quintiles of Resting CFV and Abnormal CFVR

	CFVR >2	CFVR ≤2
First quintile of CFV	984 (13)	258 (3)
Second quintile of CFV	1344 (18)	427 (6)
Third quintile of CFV	967 (13)	282 (4)
Fourth quintile of CFV	1130 (15)	430 (6)
Fifth quintile of CFV	987 (13)	767 (10)

Data presented are number (percentage) of patients. CFV indicates coronary flow velocity; and CFVR, coronary flow velocity reserve.

Comparison With Previous Studies

The data of the present work are consistent with extensive evidence that CFVR can help cardiologists in the challenging task of risk stratification in patients with CCS. A reduced CFVR is a strong predictor of all-cause mortality in CCS, independent and incremental over RWMA, as also documented by a meta-analysis including over 7174 patients from 9 SE studies showing a >4-fold increased risk of mortality with abnormal CFVR.[26] The present study also highlights the value of resting CFV, which is a preliminary step in the assessment of CFVR, and is necessary to differentiate different endotypes underlying the same reduction in CFVR.[8] Suppogu et al studied 259 women with suspected ischemia and no obstructive CAD and showed that women with higher baseline CFV had lower CFVR.[9] Zagatina et al reported the additive prognostic value of high baseline flow velocity to LVEF in a single-center prospective study with TTE in 747 patients followed for a median of 3 years.[10] A positron emission tomography study in 1283 patients has also suggested that higher resting coronary flow is associated with low coronary flow reserve and elevated cardiovascular mortality risk.[11] Phase-contrast cine cardiovascular magnetic resonance in 693 patients showed that a high resting coronary flow showed a prognostic value similar to coronary flow reserve.[12] Compared with previous experiences, the present study has unique features, due to the large sample size, long follow-up, inclusion of all-cause deaths as the only outcome measure, and multicenter design with direct reading of the data at the time of testing from the peripheral reader, as requested by a real-world study design. All previous studies were based on a single-center experience. Compared with the largest cohort published to date with absolute measurements of resting flow by positron emission tomography,[11] the present study has a 6-fold larger sample size (7576 patients compared with 1283 patients), >2-fold longer follow-up (mean of 5.9 years compared with a mean of 2.3 years), and a 16-fold higher number of events (1121 deaths compared with 70 deaths).

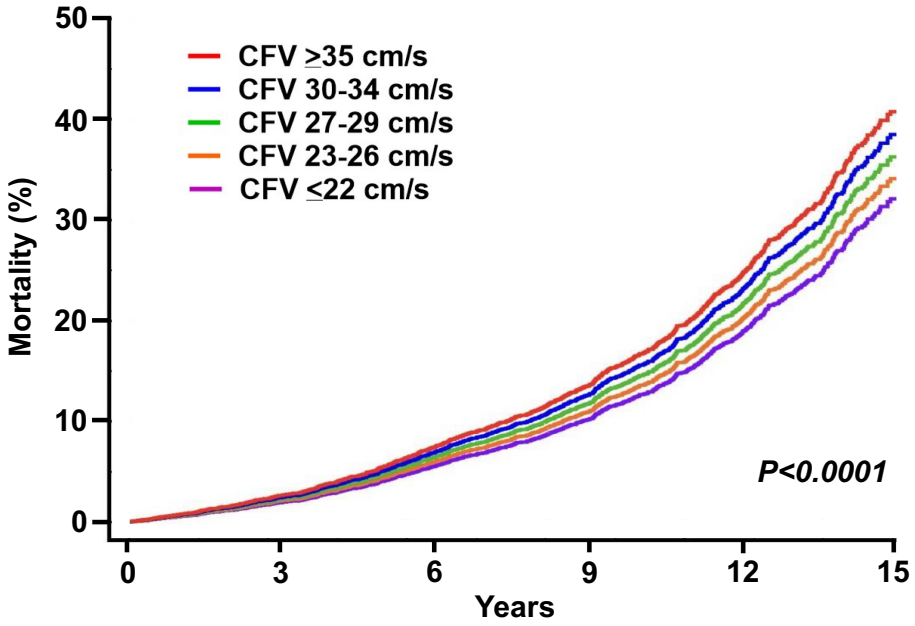
Clinical Implications

The resting TTE assessment of patients with CCS can be easily integrated with the evaluation of resting CFV, when possible, associated with CFVR with vasodilator stress as already indicated by the general cardiology guidelines of the European Society of Cardiology in 2019 and the American College of Cardiology/

Table 4. Univariate and Multivariate Predictors of Mortality

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.10 (1.09–1.10)	<0.0001	1.09 (1.08–1.10)	<0.0001
Male sex	1.06 (0.94–1.19)	0.38		
Diabetes	1.50 (1.33–1.69)	<0.0001	1.37 (1.21–1.55)	<0.0001
Arterial hypertension	1.41 (1.24–1.61)	<0.0001		
Hypercholesterolemia	0.94 (0.83–1.05)	0.26		
Current smoker	1.05 (0.92–1.20)	0.47		
Left bundle branch block	1.44 (1.03–1.77)	0.03		
Prior myocardial infarction	1.54 (1.35–1.75)	<0.0001		
Prior CABG	1.89 (1.55–2.30)	<0.0001	1.58 (1.33–1.93)	<0.0001
Prior PCI	1.08 (0.95–1.23)	0.26		
β-Blocker therapy	1.24 (1.10–1.41)	0.001		
LVEF	0.95 (0.94–0.97)	<0.0001	0.98 (0.97–1.00)	0.03
Resting RWMA	1.64 (1.42–1.89)	<0.0001		
Inducible RWMA	1.34 (1.10–1.64)	0.004		
Resting CFV of LAD ≥32 cm/s	1.63 (1.45–1.84)	<0.0001	1.24 (1.10–1.40)	<0.0001
CFVR of LAD ≤2	2.80 (2.49–3.15)	<0.0001	1.78 (1.57–2.02)	<0.0001

CABG indicates coronary artery bypass graft; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; HR, hazard ratio; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and RWMA, regional wall motion abnormality.



Covariate	b	SE	Wald	HR	95% CI	p value
Age	0.08644	0.003147	754.6358	1.09	1.08-1.10	<0.0001
Diabetes	0.3075	0.06284	23.9372	1.36	1.20-1.54	<0.0001
Prior_CABG	0.4961	0.1015	23.9048	1.64	1.35-2.00	<0.0001
LVEF	-0.02997	0.007005	18.3015	0.97	0.96-0.98	<0.0001
CFVR ≤2	0.566	0.06307	80.6093	1.76	1.56-1.99	<0.0001
Quintiles of CFV	0.07587	0.20166	12.2675	1.08	1.03-1.13	0.005

Figure 4. Adjusted reverse Kaplan-Meier survival curves.
Death rate according to the resting CFV in the 5 quintiles. CABG indicates coronary artery bypass graft; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

American Heart Association in 2021 in patients with ischemia and angiographically normal coronary arteries.[5,6] It is now reasonable to extend this indication to patients with CCS without inducible ischemia, adding resting CFV also as a meaningful parameter and not only as an ancillary evaluation for CFVR assessment. These simple parameters outperform stress-induced RWMA, and are potentially useful in all-comers with CCS and preserved LVEF, including those with CAD and with normal coronary arteries, although further studies in angiographically defined patients' subsets are needed.

Study Limitations

The study design was observational, with a retrospective data analysis. CFV (cm/s) is not synonymous with myocardial perfusion (mL/min per g) or volumetric coronary flow (mL/min), and resting CFV is lower in the presence of larger coronary lumen size, for instance, in athletes.[27] Ongoing antianginal therapy at the time of enrollment was present in 42% of patients (Table 1), but not controlled, and in principle might have affected the results. Resting coronary blood flow can be increased by nitrates (used in 4% of patients) but remains unchanged with calcium channel blockers.[27] Resting myocardial blood flow can be decreased by β-blockers through a reduction in myocardial oxygen consumption[28] and by novel antidiabetic drugs such as sodium-glucose cotransporter-2 inhibitors independently of changes in myocardial oxygen consumption.[29] We analyzed death as the hardest and most reliable end point derived from national administrative database, easily accessible from all centers. In addition, the coronary microvascular dysfunction assessed with resting and stress CFV may affect cardiovascular and even noncardiovascular death,[30,31] which we did not consider separately in the present study. A more

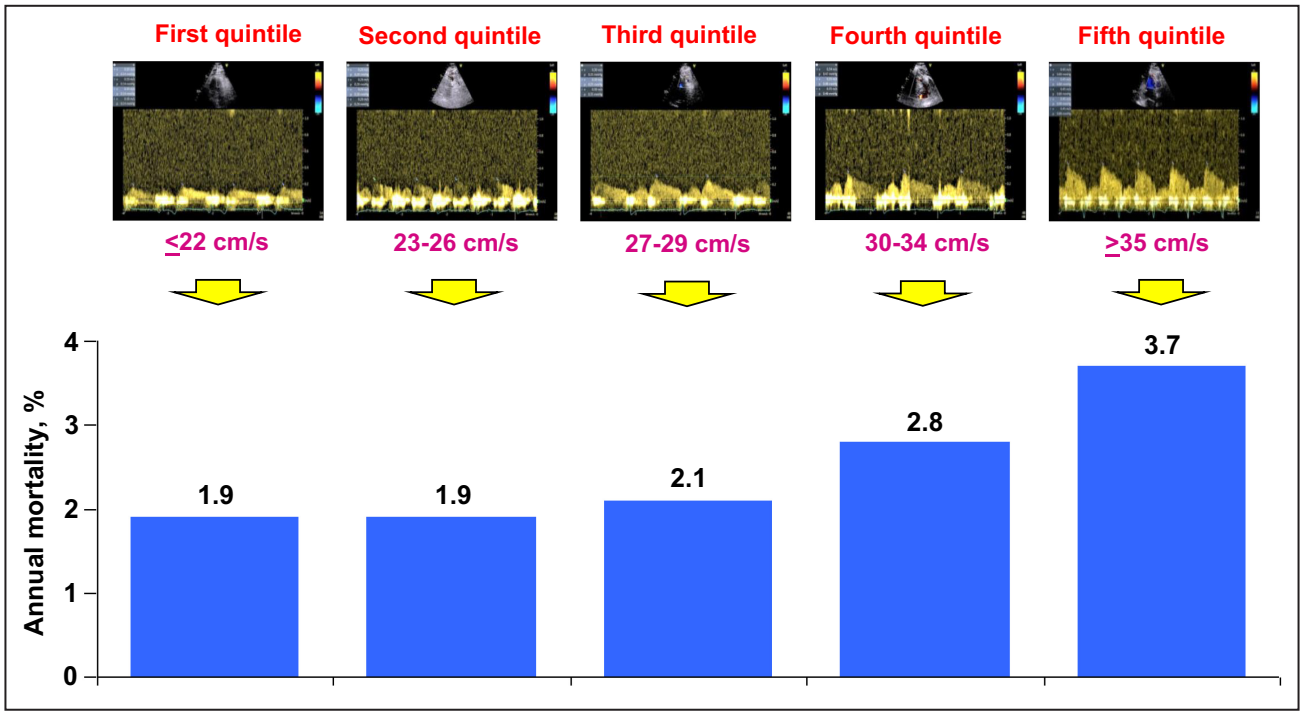
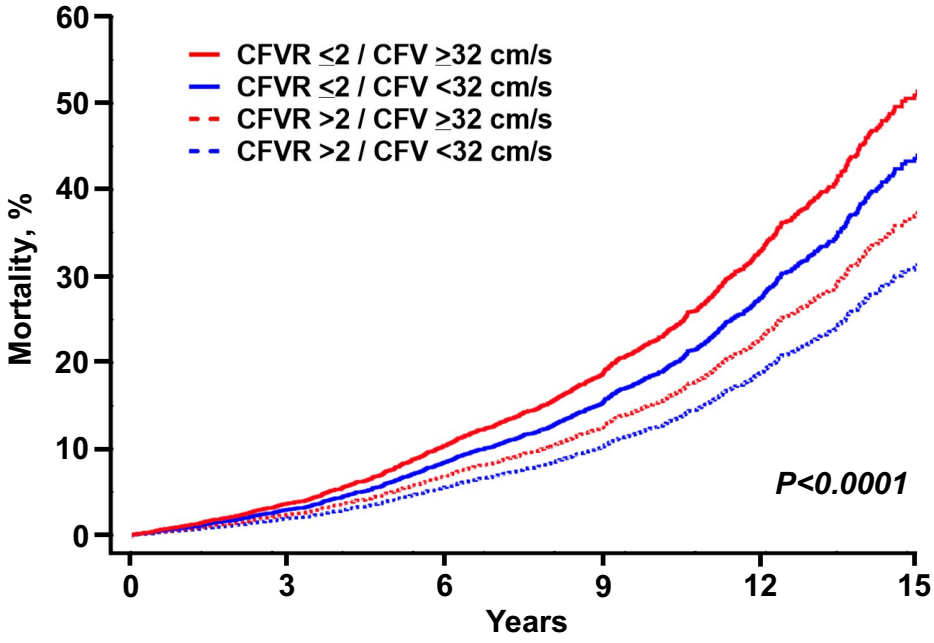


Figure 5. **Annual mortality according to the resting coronary flow velocity in the 5 quintiles.**

comprehensive assessment of all prognostic end points (including cardiac mortality) is part of the data collection strategy of the ongoing Stress Echo 2030 study.[13] The value of CFV evaluated as a binary variable is relatively modest and this may be due to several confounders, including the variability of sampling size. Sampling was always in the mid-distal segment of the LAD, but middle segments show slightly higher values than distal segments, and this may introduce a nonsystematic bias.[32] In addition, slight (beat-by-beat) changes in heart rate, systolic BP, and contractility affect CFV for any given sampling site. As already observed for other parameters such as CFVR or peak wall motion score index, the value of CFV is stronger when the stratification considers quintiles, because the risk continuously increases for increasing CFV values. We enrolled patients with CCS who had preserved LVEF. The results of the present study cannot be generalized to patients with CCS with depressed LVEF and in conditions beyond CAD, such as hypertrophic cardiomyopathy or dilated cardiomyopathy. In addition, it remains to be established the potential independent prognostic value of CFV compared with other, more recent TTE parameters not available in the data set of this study, such as global longitudinal strain from deformation imaging and B-lines by lung ultrasound. Patients enrolled in the present study were all referred for SE testing and studied by early adopters of the CFVR technique. However, the potential target of the technique is the entire general population referred to resting TTE for known or suspected CCS, because the success rate for imaging resting CFV is extremely high in contemporary consecutive unselected populations studied with high-end instruments, dedicated coronary flow setting, and ultrasound enhancing agents when needed. Virtually all patients can be studied, with high feasibility (>90%) and reproducibility of measurements (>90% when the peak diastolic flow velocity is considered) even in obese patients.[4] The cutoff value of CFV derived from this cohort should now be tested in an external, prospective cohort for validation. Subset analyses within specific demographic or clinical subgroups may be constrained by low event counts, potentially limiting the strength of associations observed. We acknowledge that these subset analyses may have lower statistical power and, therefore, should be interpreted with caution. In addition, future studies with alternative methodologies may be warranted to further explore these associations in depth.

CONCLUSIONS

No stress and no hazard are needed to obtain information on resting CFV, which is useful in CCS and outperforms resting or inducible RWMA. High resting CFV



Covariate	b	SE	Wald	HR	95% CI	p value
Age	0.08958	0.003091	839.8971	1.09	1.09-1.10	<0.0001
Diabetes	0.3449	0.06248	30.4621	1.41	1.25-1.60	<0.0001
Prior_CABG	0.4679	0.1015	21.2657	1.60	1.31-1.95	<0.0001
LVEF	-0.03150	0.007012	20.1831	0.97	0.96-0.98	<0.0001
CFV / CFVR	0.2177	0.02528	74.1456	1.24	1.18-1.31	<0.0001

Figure 6. Adjusted reverse Kaplan-Meier survival curves.
Death rate according to the resting CFV and CFVR. CABG indicates coronary artery bypass graft; CFV, coronary flow velocity; CFVR, coronary flow velocity reserve; HR, hazard ratio; and LVEF, left ventricular ejection fraction.

and reduced CFVR with TTE in the mid-distal LAD show additive and independent values in predicting worse survival in patients with CCS who have LVEF ≥50%. The combination of high resting CFV and low CFVR is associated with the worst survival.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1

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