

Incremental Value of Transthoracic Doppler Echocardiography-Assessed Coronary Flow Reserve in Patients With Suspected Myocardial Ischemia Undergoing Myocardial Perfusion Scintigraphy

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Background—Adenosine-assisted transthoracic Doppler-derived coronary flow reserve (TDE-CFR) reflects coronary vascular function. The prognostic and incremental value of left anterior descending coronary artery TDE-CFR above myocardial perfusion scintigraphy in patients with suspected myocardial ischemia has not yet been studied.

Methods and Results—Three hundred seventy-one patients (mean age, 62.3 ± 8.7 years; 46.8% males) referred to myocardial perfusion scintigraphy attributed to suspected myocardial ischemia were included in the study. The TDE-CFR result was blinded to the referring physician. Patients were followed up regarding major cardiovascular events, defined as cardiovascular death, myocardial infarction, or acute revascularization during a median follow-up time of 4.5 years. A TDE-CFR value of ≤ 2.0 was considered reduced. Major cardiovascular events occurred during follow-up in 60 patients (16.2%). A reduced TDE-CFR was detected in 76 patients (20.5%). Patients with reduced TDE-CFR had an event rate of 36.8% compared to 10.8% in patients with normal TDE-CFR (unadjusted hazard ratio, 4.63; 95% CI, 2.78–7.69; $P < 0.001$). In a multivariate model, TDE-CFR remained a significant independent predictor of major cardiovascular events. The major cardiovascular events rate was 7.5% in patients without myocardial perfusion scintigraphy-detected myocardial ischemia and normal TDE-CFR ($n=200$), 24.2% in patients without ischemia but with reduced TDE-CFR ($n=33$), and 46.5% in patients with both myocardial perfusion scintigraphy-detected myocardial ischemia and a reduced TDE-CFR ($n=43$; $P < 0.001$).

Conclusions—Coronary microvascular dysfunction, as determined by TDE-CFR, is a strong independent predictor of cardiovascular events and adds incremental prognostic value compared with myocardial perfusion scintigraphy. The current study supports routine assessment of CFR in patients with suspected ischemic heart disease. (*J Am Heart Assoc.* 2017;6:e004875. DOI: 10.1161/JAHA.116.004875).

Key Words: adenosine • coronary blood flow reserve • echocardiography • myocardial perfusion imaging • prognosis

Myocardial perfusion scintigraphy (MPS) is a well-established method to diagnose the presence and extent of myocardial ischemia featuring, in particular, a useful high negative predictive value.¹ In fact, MPS-verified

myocardial ischemia is strongly related to the extent and severity of coronary artery disease (CAD) as verified by coronary angiogram.^{2,3} Coronary flow velocity reserve (CFR), assessed by transthoracic echocardiography Doppler (TDE-CFR), is an emerging diagnostic tool for CAD and has been used as a predictor of cardiovascular prognosis in different patient categories.^{4–9} TDE-CFR is known to reflect presence of macrovascular as well as microvascular disease in the coronary circulation with the advantages of being noninvasive, highly feasible, safe for patient and physician, and not associated with any radiation. Most frequently, the technique is used with a dipyridamole protocol in conjunction with a stress echocardiography examination.¹⁰

TDE-CFR is known to provide an independent prognostic value for prediction of cardiovascular events and provide incremental prognostic value on top of stress echocardiographic wall motion criteria in different clinical settings.⁶ However, MPS is based on relative perfusion measurement and reflects most likely only the degree of the lumen

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obstructive CAD status, which may cause heterogeneous flow distribution during exercise or pharmacological challenge. In cases of balanced 3-vessel disease or global microvascular dysfunction, MPS will have lower diagnostic and prognostic value. Moreover, we have previously reported a lack of correlation between the invasive assessment of CFR and noninvasive functional tests in patients without obstructive CAD.¹¹ Thus, the quantitative measurement of TDE-CFR may reflect more aspects of coronary vascular status and thereby provide an incremental value to MPS.

In the present study, we aim to evaluate the feasibility of adenosine-induced TDE-CFR in a patient population with suspected myocardial ischemia referred to MPS and hypothesize that TDE-CFR may convey additional prognostic values above MPS.

Methods

The CEVENT-Study

The CEVENT-study (Coronary flow reserve and cardiovascular EVENTS) was conducted at the Department of Clinical Physiology, Sahlgrenska University Hospital (Gothenburg Sweden) from February 2006 until November 2008. We consecutively enrolled 371 patients presenting with clinical chest pain referred for MPS examination attributed to suspected myocardial ischemia. All patients underwent both MPS and TDE-CFR examination and gave their informed and written consent to study participation. Inclusion criteria for TDE-CFR were (1) eligibility to adenosine stress echocardiography and (2) ability to understand informed consent. Exclusion criterion was unwillingness to participate. Measurement of TDE-CFR was performed within a week from MPS. In this clinical setting, the physician referring to the MPS examination was blinded to the result of the TDE-CFR, which, consequently, did not affect or guide the clinical decision process in this experimental study. Patients were later followed up annually regarding cardiovascular events by semistructured telephone interviews performed by a nurse, reviewing of medical records by a physician, and also by data collection from the Swedish National Board of Health Registry. The study was approved by the Regional Ethics Committee in Gothenburg, and all patients gave their written consent to study participation.

Echocardiography and Assessment of TDE-CFR

A basic transthoracic echocardiography protocol was performed according to recommendations.¹² The Sequoia C256 (Acuson Siemens, Mountain View, CA) ultrasound system was used with a 4-MHz probe. Our protocol has been described previously.¹³ Briefly, the mid to distal part of the left anterior descending coronary artery was identified using

3.5-MHz color Doppler in the interventricular sulcus in a modified 2-chamber view. Pulsed Doppler was used to sample flow velocity signals at rest and during adenosine infusion (140 $\mu\text{g}/\text{min}/\text{kg}$) over 5 minutes. During the whole procedure, blood pressure and ECG were monitored. All studies were digitally stored for offline reviewing and measurements. Coronary flow velocity data were analyzed offline using the ultrasound software Image Arena (Tomtec, Unterschlissheim, Germany). Mean diastolic flow velocity at baseline and during peak hyperemia was measured by manual tracing of the diastolic Doppler flow signals. CFR was calculated as the ratio between the hyperemic and baseline flow velocity values. A CFR ratio of ≤ 2 was considered reduced.¹⁴

Myocardial Perfusion Scintigraphy Examinations

Myocardial perfusion scintigram was performed by a 2-day stress/rest examination protocol according to a standard clinical protocol at the Department of Clinical Physiology, Sahlgrenska University Hospital. Our protocol has previously been described in detail.¹⁵ Briefly, stress provocation was performed by exercise test or pharmacological provocation. Radionuclide technetium (99mTc) sestamibi was administered and detected using single-photon emission computed tomography. Images were obtained using dual-head cameras (Infinia or Hawkeye; General Electric, Waukesha, WI) displaying perfusion and function of the left ventricle. Presence and extent of myocardial ischemia was determined by an experienced physician. Automatically generated variables from the software ECT toolbox (Syntermed, Atlanta, GA), such as reversibility stress score, was used as aid for clinical assessment. Severity of reversible ischemia was scored as no ischemia (0), mild (score 1), moderate (2), or severe (3), and extent of ischemia was scored as none (0), small (<10%, score 1), medium (10–19%, score 2), and large (>19%, score 3). No myocardial perfusion defects was defined as both severity and extent score=0.

Laboratory Analysis

Routine biochemical analyses were at the accredited coagulation laboratory at Sahlgrenska University Hospital. The laboratory participates in the ECAT foundation external quality assessment programme (www.ecat.nl). Triglycerides and cholesterol in serum were measured using reagent systems from Roche (Triglycerides/GB kit No. 12146029216; Cholesterol kit No. 2016630; Roche Diagnostics GMBH, Mannheim, Germany). Apolipoprotein A1 and B concentrations were measured with the turbidimetric technique, by use of polyclonal rabbit anti-human antibodies (Q 0496 and Q 0497; Dako Cytomation, Glostrup, Denmark).

Follow-up Data

Patients were followed up at least 4 years past study date by telephone interviews and medical records. The results of the TDE-CFR measurement was blinded to the MPS referring physicians and consequently did not affect further clinical investigations or decision making. Major cardiovascular events (MACE) were defined as a composite of cardiovascular death, acute myocardial infarction, and need for urgent coronary revascularisation with percutaneous coronary intervention or coronary artery bypass grafting. Cause of death was established by data from the Swedish National Board of Health registries. Acute myocardial infarction was defined as presence of typical symptoms, ST changes in ECG, and impact on cardiac enzymes.¹⁶ Revascularization was considered to be urgent when a patient was admitted to the hospital with persistent chest pain (with or without ST-segment or T-wave changes or elevated biomarker levels), and the revascularization procedure was performed during the same hospitalization.

Statistical Analysis

Continuous variables are presented as mean±SD and categorical variables as frequencies. Normal distribution of variables was assessed by the Shapiro–Wilk test. Differences between

groups in continuous normally distributed variables were tested with the Student *t* test. Differences in categorical variables were tested by chi-square test or Fisher's exact test. Independent predictors of MACE were identified using the Cox proportional hazards model. The following variables were included in the model: sex, age, diabetes mellitus, smoking, hypertension, hypercholesterolemia, ejection fraction, CFR, MPS ischemia area, and anti-ischemic treatment. Kaplan–Meier survival curves are shown for event-free survival. Hazard ratios with the corresponding 95% CI were calculated by Cox regression analysis. Two-sided *P*<0.05 was considered to be statistically significant. All data analysis were performed in the statistical software, SPSS (version 23.0; SPSS, Inc, Chicago, IL).

Results

TDE-CFR and Myocardial Perfusion Scintigraphy-Data

All examinations were performed successfully, and no major complications occurred. Baseline data are shown in Table 1. Of the 371 patients, 76 (20.5%) had reduced CFR (<2.0). MPS-detected myocardial ischemia was present in 138 cases (37.2%). Patients with presence of MPS-detected ischemia

Table 1. Clinical Characteristics in Patients With Reduced and Normal CFR (Mean±SD or Number [%])

	All Patients (n=371)	CFR ≤2.0 (n=76)	CFR >2.0 (n=295)	<i>P</i> Value
Age, y	62.2±8.7	64.5±10.0	61.7±8.3	0.027
Sex (male), n	174 (47)	46 (61)	128 (43)	0.008
BMI, m ² /kg	26.2±3.8	26.1±3.9	26.2±3.8	0.87
Diabetes mellitus, n	46 (12%)	13 (17%)	33 (11%)	0.17
Hypertension, n	47 (12%)	10 (13%)	37 (13%)	0.89
Smoking, n	181 (49%)	45 (59%)	136 (46%)	0.040
Hypercholesterolemia, n	184 (50%)	42 (55%)	142 (48%)	0.24
Ejection fraction, %	63±12	59±13	64±11	0.001
Laboratory data				
ApoB/ApoA1 ratio	0.7±0.2	0.7±0.2	0.7±0.2	0.80
Triglycerides, mmol/L	1.4±0.9	1.6±1.2	1.4±0.8	0.084
Total cholesterol, mmol/L	5.3±1.3	5.2±1.3	5.3±1.3	0.51
High-density lipoprotein, mmol/L	1.5±0.4	1.4±0.4	1.5±0.4	0.52
Medication				
β-blockers, n	191 (52%)	48 (63%)	143 (48%)	0.022
Statins, n	165 (45%)	39 (51%)	126 (43%)	0.18
ACE inhibitors, n	91 (25%)	26 (34%)	65 (22%)	0.028
Aspirin, n	195 (53%)	48 (63%)	150 (51%)	0.055
Clopidogrel, n	24 (7%)	5 (7%)	19 (6%)	0.97

ACE indicates angiotensin-converting enzyme; Apo, apolipoprotein; BMI, body mass index; CFR, coronary flow reserve.

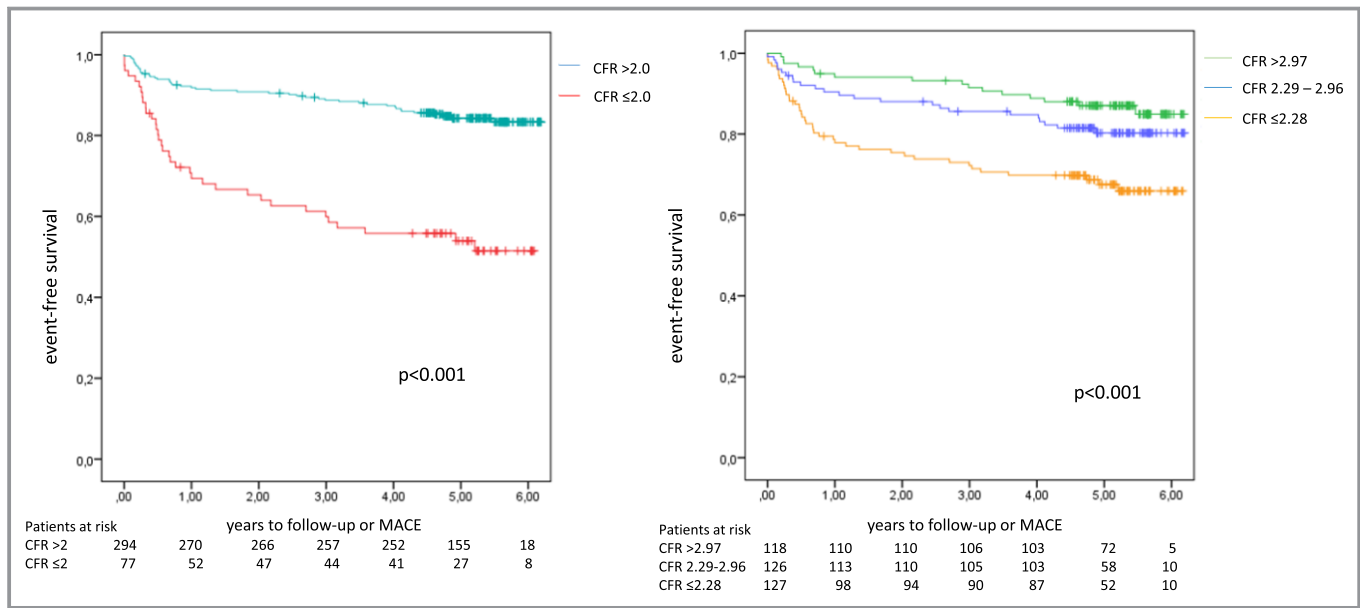


Figure 1. Left part of the image shows Kaplan–Meier event-free survival in patients with preserved and reduced coronary flow reserve (CFR). To the right, Kaplan–Meier event-free survival is shown by CFR tertiles. MACE indicates major cardiovascular events.

showed lower CFR values (2.50 ± 0.95 versus 2.80 ± 0.91 ; $P=0.003$). No difference in CFR was found between hypertensives and normotensives (2.56 ± 1.01 versus 2.74 ± 0.93 ;

Table 2. Cardiovascular and Cerebral Events in Patients With $CFR \leq 2.0$ or $CFR > 2.0$

	CFR ≤ 2.0 (n=76)	CFR > 2.0 (n=295)	P Value (Chi-Square)
MACE	28 (37%)	32 (11%)	<0.001
All-cause death	10 (13%)	10 (3.4%)	<0.001
Cardiovascular death	8 (11%)	2 (0.7%)	<0.001
Myocardial infarction	6 (7.9%)	11 (3.7%)	0.121
Neurological events	6 (7.9%)	14 (4.7%)	0.28
Stroke	4 (5.3%)	4 (1.4%)	0.036
TIA	2 (2.6%)	10 (3.4%)	0.74
Revascularization	28 (37%)	42 (14%)	<0.001
PCI	19 (25%)	36 (12%)	0.005
Acute	7 (9.2%)	20 (6.8%)	0.47
Elective	12 (16%)	16 (5.4%)	0.002
CABG	9 (12%)	6 (2.0%)	<0.001
Acute	0	2 (0.7%)	0.47
Elective	9 (12%)	4 (1.4%)	<0.001
Episodes of unstable angina	7 (9.2%)	18 (6.1%)	0.34

Numbers and %. CABG indicates coronary artery bypass grafting; CFR, coronary flow reserve; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction, or acute revascularization); PCI, percutaneous coronary intervention; TIA, transient ischemic events.

$P=0.251$), patients with and without hypercholesterolemia (2.58 ± 0.96 versus 2.70 ± 0.93 ; $P=0.112$), and patients with and without a family history of cardiovascular diseases (2.65 ± 0.93 versus 2.66 ± 0.90 ; $P=0.911$). However, patients with a smoking habit showed decreased CFR (2.53 ± 0.85 versus 2.83 ± 0.98 ; $P=0.002$) as well as those with diagnosis of diabetes mellitus (2.40 ± 0.83 versus 2.73 ± 0.95 ; $P=0.015$). Patients with reduced CFR showed increased MPS ischemia score and area compared with patients with normal CFR (1.0 ± 1.1 versus 0.4 ± 0.8 ; $P<0.001$ and 0.9 ± 0.9 versus 0.4 ± 0.7 ; $P<0.001$, respectively). Also, patients in the reduced CFR group showed greater reversibility stress score (70.1 ± 124.0 versus 21.6 ± 60.6 ; $P=0.001$). Furthermore, patients with reduced CFR showed increased infarct score and area (0.24 ± 0.41 versus 0.11 ± 0.30 ; $P=0.015$ and 0.50 ± 0.98 versus 0.21 ± 0.62 ; $P=0.016$, respectively).

Follow-up Data

There was no loss to follow-up. During a median follow-up time of 4.5 years, 28 MACE events (cardiovascular death, myocardial infarction, and acute revascularization) occurred in the 76 patients with $CFR \leq 2.0$ (37%) and 32 events occurred in the 295 patients with $CFR > 2.0$ (11%; $P<0.001$). Event-free survival for the 2 groups is shown in Figure 1. Other important cardiovascular and neurological outcome variables in the 2 groups are presented in Table 2. Univariate and multivariate predictors of MACE are presented in Table 3. TDE-CFR predicted spontaneous cardiovascular events (hazard ratio, 4.1; CI, 2.67–6.33; $P<0.001$). Even after adjustment for all

Table 3. Univariate and Multivariate Predictors for MACE

	Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male sex	3.47 (1.89–6.36)	<0.001	3.14 (1.46–6.75)	0.003
Age	1.06 (1.02–1.10)	0.001	1.04 (1.00–1.08)	0.03
Diabetes mellitus	3.92 (1.99–7.75)	<0.001	3.21 (1.45–7.10)	0.004
Smoking	2.08 (1.16–3.70)	0.01	1.34 (0.68–2.65)	0.403
Hypertension	1.27 (0.58–2.78)	0.554		
Hypercholesterolemia	2.19 (1.21–3.97)	0.005	1.36 (0.68–2.70)	0.385
Ejection fraction	0.96 (0.94–0.98)	<0.001	1.00 (0.96–1.02)	0.519
TDE-CFR ≤ 2.0	4.79 (2.65–8.67)	<0.001	3.02 (1.51–6.04)	0.002
Scintigraphy ischemia area	1.99 (1.45–2.72)	<0.001	1.38 (1.01–1.89)	0.045

HR indicates hazard ratio; MACE, major adverse cardiovascular event; TDE-CFR, transthoracic Doppler-derived coronary flow reserve.

significant outcome predictors in the univariate analysis, TDE-CFR remained a significant independent predictor. Coronary flow at baseline and during hyperemia as well as TDE-CFR data are shown in Table 4 depending on presence or not of MACE.

In Figure 2, cumulative event-free survival in patients with reduced or preserved TDE-CFR and presence of ischemia on scintigraphy are depicted. Incidence of MACE was significantly higher in patients with reduced TDE-CFR both in patients without scintigraphy-verified ischemia (24% versus 8%; $P=0.003$) and in those with ischemia (47% versus 18%; $P<0.001$). In patients with negative scintigraphy, there were also significant differences between reduced and preserved TDE-CFR in the incidence of all-cause death, cardiovascular death, stroke, total revascularizations, and elective coronary artery bypass grafting (Table 5). In patients with scintigraphy-verified ischemia, there was, besides MACE, also significant differences between reduced and preserved TDE-CFR in the incidence of total revascularizations and elective coronary artery bypass grafting (Table 5).

Discussion

In this study, we examined TDE-CFR in patients undergoing MPS investigation attributed to suspected myocardial

Table 4. Coronary Flow Data in Patients With and Without MACE

	MACE (n=60)	No MACE (n=311)	P Value
Baseline, cm/s	0.34±0.18	0.30±0.10	0.23
Hyperaemia, cm/s	0.70±0.28	0.79±0.24	0.01
Coronary flow reserve	2.36±1.14	2.75±0.88	0.003

MACE indicates major adverse cardiovascular events.

ischemia. Reduced TDE-CFR was a significant predictor of MACE in this patient group. Moreover, after adjustment for significant cardiovascular variables in the univariate analysis, TDE-CFR remained a significant independent predictor of MACE. More important, TDE-CFR showed an incremental prognostic value to myocardial ischemia determined by MPS. The current study further supports the role and need for assessment of the coronary microcirculation for risk stratification in patients with suspected CAD.

The prognostic value of TDE-CFR has previously been demonstrated with dipyridamole-induced hyperemia in conjunction with a stress echocardiography examination. A reduced TDE-CFR is known to predict an impaired cardiovascular prognosis in several patient groups, including patients with diabetes mellitus, hypertension, ischemic cardiomyopathy, normal coronary arteries, and CAD.^{4,6-9,14,17} Furthermore, TDE-CFR has also been suggested as an additive prognostic marker to stress-induced wall motion defects, which also has been demonstrated in multicenter studies.^{4,6} Recently, TDE-CFR, assessed by adenosine protocol, has been shown to predict cardiovascular prognosis in a post-acute coronary syndrome population.¹⁸ To our knowledge, this study is the first to evaluate prognostic value of the adenosine TDE-CFR protocol in an experimental setting independent of the routine diagnostic route. Attributed to rapid onset and short half-life of adenosine, the protocol has the advantages of being easily manageable, patient safe, and no antidote is required.

To date, MPS is the standard method for diagnosis of myocardial ischemia and to predict cardiovascular outcome.¹⁹ The standard interpretation of MPS is based on assessment of relative myocardial perfusion defects and refers to the region with the best perfusion as normal. Consequently, diagnostic problems arise in the case of multivessel disease or diffuse microvascular disease.^{20,21} The results of the present study

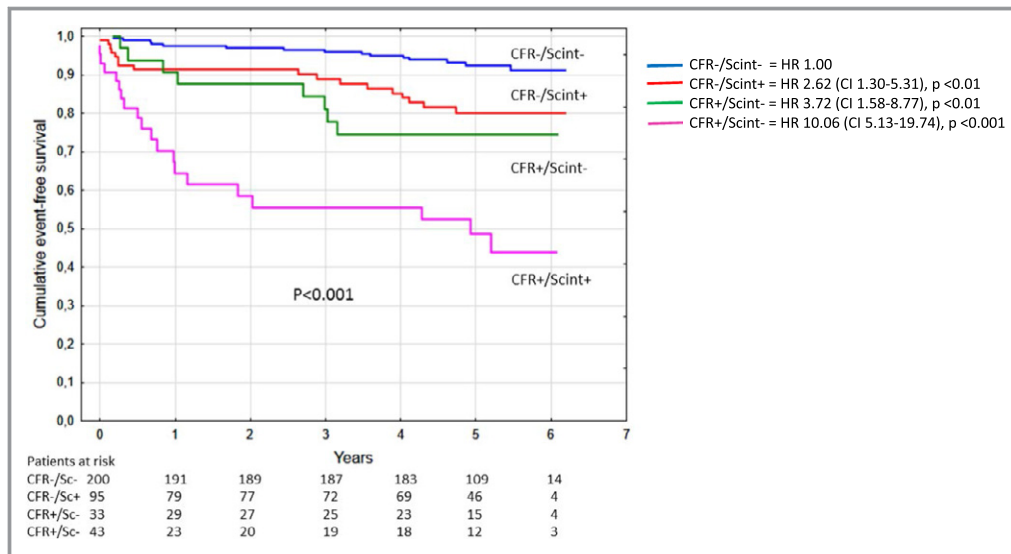


Figure 2. Kaplan–Meier event-free survival in patients with reduced or preserved coronary flow reserve (CFR) in patients with or without ischemia on scintigraphy. There were significant differences between the CFR <2.0 and scintigraphy-negative group, and all other groups and between the CFR ≤2.0 and scintigraphy-positive group. In contrast, there was no significant difference between the CFR ≤2.0 and scintigraphy-negative group and the CFR >2.0 and scintigraphy-positive group. HR indicates hazard ratio.

indicate that TDE-CFR, as an integrated measure, might be comparable and independent in its prognostic value for future cardiovascular events, most likely attributed to its quantitative

nature, as well as reflection of microvascular function. In this clinical setting, we demonstrate TDE-CFR to provide incremental value to MPS detected ischemia.

Table 5. Cardiovascular and Cerebral Events in Different Groups of Patients With CFR ≤2.0 or CFR >2.0 and Scintigraphy Indicating Ischemia or Not

	CFR ≤2.0 Scint Pos (n=43)	CFR ≤2.0 Scint Neg (n=33)	CFR >2.0 Scint Pos (n=95)	CFR >2.0 Scint Neg (n=200)	P Value (Chi-Square)
MACE	20 (47%)	8 (24%) [†]	17 (18%)	15 (7.5%)	<0.001
All-cause death	5 (12%)	5 (15%) [‡]	6 (6.3%)	4 (2.0%)	<0.001
Cardiovascular death	4 (9.3%)	4 (12%) [‡]	2 (2.1%)	0	0.006
Myocardial infarction	5 (12%)	1 (3.0%)	5 (5.2%)	6 (3.0%)	0.097
Neurological events	2 (4.7%)	4 (12%)	5 (5.2%)	9 (4.5%)	0.35
Stroke	1 (2.3%)	3 (9.1%) [†]	1 (1.1%)	3 (1.5%)	0.037
TIA	1 (2.3%)	1 (3.0%)	4 (4.2%)	6 (3.0%)	0.93
Revascularization	21 (49%) [§]	7 (21%)*	26 (27%)	16 (8.0%)	<0.001
PCI	16 (37%)	3 (9.1%)	22 (23%)	14 (7.0%)	<0.001
Acute	6 (14%)	1 (3.0%)	12 (13%)	8 (4.0%)	0.012
Elective	10 (23%) [§]	2 (6.1%)	10 (11%)	6 (3.0%)	<0.001
CABG	5 (12%)	4 (12%) [‡]	4 (4.2%)	2 (1.0%)	<0.001
Acute	0	0	2 (2.1%)	0	0.12
Elective	5 (12%)	4 (12%) [‡]	0	2 (1.0%)	<0.001
Unstable angina	7 (16%)	0	9 (9.5%)	9 (4.5%)	0.01

Numbers and %. CABG indicates coronary artery bypass grafting; CFR, coronary flow reserve; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction, or acute revascularization); PCI, percutaneous coronary intervention; TIA, transient ischemic events.
 *P<0.05; †P<0.01; ‡P<0.001 for CFR ≤2.0 and scint neg vs CFR >2.0 and scint neg; §P<0.05; ||P<0.001 for CFR ≤2.0 and scint pos vs CFR >2.0 and scint pos.

It is now evident that CFR comprises a composite measure of coronary macrovascular and microvascular status.²² Besides lumen-narrowing epicardial stenosis, intact endothelial function by nitric oxide pathway is required for maximal CFR response.²³ In addition to vasodilation, healthy endothelium is also crucial for the atheroprotective and thromboprotective properties of the vascular wall. Thus, impaired coronary vasodilation in response to ischemic stress, in combination with dysfunctional protective mechanisms in the vascular wall, may be responsible for the poor outcome observed in patients with impaired CFR. CFR is known to relate to angiographic findings, and our group has previously shown CFR to be an independent predictor of the extent and severity of CAD in all 3 major coronary arteries as determined from coronary angiogram.²⁴ In our study, the relatively high event rate during the first year of follow-up may be explained by diffuse CAD or balanced 3-vessel disease not detected by MPS. However, patients with CFR >2 still had an event rate of 10.8% over ≈5 years of follow-up. Other important factors for cardiovascular events, such as blood viscosity and hypercoagulability, may contribute in acute situations concerning coronary plaque instability/rupture and thrombus formation, which is not is foresight by CFR per se.

CFR can be assessed by many imaging modalities. Concerning noninvasive techniques, positron emission tomography is considered golden standard.²⁵ Positron emission tomography has the ability to study both ischemia extent, coronary blood flow, and CFR. Rubidium/positron emission tomography–assessed CFR has shown similar incremental predictive values as TDE-CFR above myocardial ischemia and other cardiac indexes.²⁶ Positron emission tomography can also be performed, together with high-resolution computed tomography, to provide further structural information.²⁷ Furthermore, contrast computed tomography may be a new modality for myocardial perfusion imaging.²⁸ However, the above-mentioned techniques provide radiation, are more expensive, and have less clinical availability compared to a simple echocardiographic examination. Magnetic resonance imaging is a nonradioactive method, which also can assess CFR, but is relatively costly and time-consuming. TDE-CFR stands as attractive with the advantages of being safe for patient and physician, inexpensive, available, and feasible. Furthermore, its ability to predict cardiovascular prognosis appears to be similar to the more-complex mentioned techniques.

Study Limitations

Attributed to the limited size of our patient population, a combined end point (MACE) with cardiovascular death, myocardial infarction, and acute revascularization was chosen as the outcome measure. Larger study populations are

needed to analyze the role of TDE-CFR for prediction of the individual MACE components. Also, the number of patients in the subgroups in Figure 2 are quite few. However, our study demonstrates the potential clinical role of TDE-CFR alone in an independent unbiased setting on top of MPS-derived data. In the current study, the CFR assessment was restricted to the left anterior descending distribution; it may be speculated that the assessment of TDE-CFR in all 3 vessels will add diagnostic accuracy.

Conclusions

Our study demonstrates that coronary microvascular dysfunction, as was assessed by TDE-CFR, is an independent and strong predictor of spontaneous cardiovascular events in patients with suspected myocardial ischemia. More important, in this clinical study, TDE-CFR provides incremental prognostic value to MPS-detected ischemia. The current study underscored the significance of the assessment and potential to develop future therapeutic intervention for microvascular dysfunction.

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Disclosures

Dr Gan is employed by AstraZeneca. All other authors have nothing to disclose.

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