Impaired Coronary Autoregulation Is Associated With Long-term Fatal Events in Patients With Stable Coronary Artery Disease

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Background—Abnormalities in the coronary microcirculation are increasingly recognized as an elementary component of ischemic heart disease, which can be accurately assessed by coronary flow velocity reserve in reference vessels (refCFVR). We studied the prognostic value of refCFVR for long-term mortality in patients with stable coronary artery disease.

Methods and Results—We included patients with stable coronary artery disease who underwent intracoronary physiological evaluation of ≥1 coronary lesion of intermediate severity between April 1997 and September 2006. RefCFVR was assessed if a coronary artery with <30% irregularities was present. RefCFVR >2.7 was considered normal. Patients underwent revascularization of all ischemia-causing lesions. Long-term follow-up was performed to document the occurrence of (cardiac) mortality. RefCFVR was determined in 178 patients. Kaplan–Meier estimates of 12-year all-cause mortality were 16.7% when refCFVR >2.7 and 39.6% when refCFVR ≤2.7 (P<0.001), whereas Kaplan–Meier estimates for cardiac mortality were 7.7% when refCFVR >2.7 and 31.6% when refCFVR ≤2.7 (P<0.001). After multivariable adjustment, refCFVR ≤2.7 was associated with a 2.24-fold increase in all-cause mortality hazard (hazard ratio, 2.24; 95% confidence interval, 1.13–4.44; P=0.020) and a 3.32-fold increase in cardiac mortality hazard (hazard ratio, 3.32; 95% confidence interval, 1.27–8.67; P=0.014). Impairment of refCFVR originated from significantly higher baseline flow velocity in the presence of significantly lower reference vessel baseline microvascular resistance (P<0.001), indicating impaired coronary autoregulation as its cause.

Conclusions—In patients with stable coronary artery disease, impaired refCFVR, resulting from increased baseline flow velocity indicating impaired coronary autoregulation, is associated with a significant increase in fatal events at long-term follow-up. **(*Circ Cardiovasc Interv*. 2013;6:329-335.)**

Key Words: coronary autoregulation ■ coronary flow velocity reserve ■ reference vessel

Abnormalities in the function and structure of the coronary microcirculation are increasingly recognized as an elementary component in the spectrum of ischemic heart disease. Coronary microvascular alterations may represent an important marker for risk or may contribute to the pathogenesis of myocardial ischemia[1] and may arise from a wide array of pathogenetic mechanisms.[1] Such alterations may contribute to adverse outcome in patients with stable coronary artery disease (CAD) and may, potentially, offer a target for risk stratification and evaluation of preventive treatment strategies.[2]

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In the absence of significant epicardial disease, the vasodilator response of coronary circulation, as measured by the coronary flow velocity reserve (CFVR), is determined by the functional status of the resistance vessels of coronary microcirculation and can, therefore, be considered a direct marker of microvascular function.[3] Defined as the ratio of hyperemic to basal average peak flow velocity,[4] impairment of reference vessel CFVR may originate from either an increased basal flow velocity or an impaired hyperemic flow velocity.

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WHAT IS KNOWN

- Abnormalities in the function and structure of coronary microcirculation play an important role in the spectrum of ischemic heart disease.
- The functional status of microcirculation may accurately be evaluated by means of coronary flow (velocity) measurements.
- Impaired coronary flow velocity reserve in unobstructed coronary arteries is associated with, predominantly nonfatal, adverse cardiac events.

WHAT THE STUDY ADDS

- Impaired coronary flow velocity reserved in unobstructed coronary arteries in patients with stable coronary artery disease likely originates from disturbance of the coronary autoregulatory mechanism.
- Such disturbance is associated with an increased risk for long-term fatal (cardiac) events.

Although there has been interest in the prognostic value of the vasodilatory function of coronary microcirculation,[2-5] selective evaluation of basal and hyperemic components of CFVR has not been performed in these investigations. Nonetheless, this discrimination may be particularly important to advance our understanding of processes underlying these vascular alterations and the consequent risk for adverse events.

Therefore, the aim of the present study was to evaluate the association between reference vessel CFVR and long-term fatal events in patients with stable CAD, as well as to document the relative contribution of baseline and hyperemic components in the impairment of reference vessel CFVR.

Methods

Study Population

Between April 1997 and September 2006, we evaluated patients with stable CAD whose diagnostic angiography showed ≥1 intermediate coronary artery lesion at visual assessment. These patients were enrolled in a series of study protocols,[6–9] and patient and procedural characteristics were entered into a dedicated database. We excluded patients with ostial lesions, ≥2 stenoses in the same coronary artery, severe renal function impairment (glomerular filtration rate calculated according to the Modification of Diet in Renal Disease formula <30 mL/min per 1.73 m^2), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks before screening), prior coronary artery bypass graft surgery, or visible collateral development to the perfusion territory of interest. The institutional ethics committee approved the study procedures, and all patients gave written informed consent.

Cardiac Catheterization Procedure

Coronary angiography was performed according to standard clinical practice, and angiographic images were obtained in a manner suitable for quantitative coronary angiography analysis. Quantitative coronary angiography analysis was performed offline to determine percent diameter stenosis with the use of a validated automated contour detection algorithm (QCA-CMS version 3.32; MEDIS, Leiden, The Netherlands).

Before percutaneous coronary intervention, intracoronary pressure was measured with a 0.014″ pressure sensor–equipped guidewire (Volcano Corp, San Diego, CA). Coronary blood flow velocity was subsequently measured with a 0.014″ Doppler crystal–equipped guidewire (Volcano Corp, San Diego, CA). Hyperemia was induced by an intracoronary bolus of adenosine (20–40 μg). Fractional flow reserve was defined as the ratio of mean distal coronary pressure to mean aortic pressure in the target vessels during maximal hyperemia. CFVR was defined as the ratio of hyperemic to baseline average peak blood flow velocity (APV) distal to the target lesions. CFVR was additionally assessed in an angiographically normal reference coronary artery, defined as a coronary artery with <30% irregularities on visual assessment, if present. A reference vessel CFVR >2.7 was considered normal.[10] From the recorded intracoronary hemodynamic data, both the hyperemic stenosis resistance index,[9] defined as the ratio between the pressure gradient across the stenosis and distal APV during maximal hyperemia, and the microvascular resistance index,[11] defined as mean distal coronary pressure divided by distal APV, were calculated. In the absence of significant epicardial disease, microvascular resistance index in the reference vessel was calculated as the mean aortic pressure divided by distal APV. In the presence of 2-vessel CAD, the most severe coronary lesion by hyperemic stenosis resistance index was depicted as the target lesion and was used for subsequent target vessel analyses.

Patients underwent percutaneous coronary intervention of all ischemia-causing lesions at the discretion of the operator. Decisions on further treatment and medication during follow-up were entirely left to the discretion of the treating cardiologist.

Long-term Follow-up

Long-term follow-up was performed by identifying patients in the Dutch national population registry to assess the occurrence of death. In addition, the cause of death was verified by evaluating hospital records or by contacting the general practitioner. Death was considered cardiac unless an unequivocal noncardiac cause was documented.[12]

Statistical Analysis

Cumulative event rates were estimated using the Kaplan–Meier method and were compared with the log-rank test. Event rates are presented as Kaplan–Meier estimates at 12-year follow-up. The association of reference vessel CFVR with long-term fatal events was evaluated in 2 sets of Cox proportional hazards models. A univariable analysis was performed to identify variables associated with all-cause mortality ($P<0.1$). Subsequent multivariable analysis was performed with adjustments for these variables. The multivariable analysis was subsequently repeated to evaluate the association of reference vessel CFVR with cardiac mortality. Variables are presented as mean (±SD), median with first and third quartiles (Q1–Q3), or frequency (percentage), where appropriate. Comparison between groups was performed using Student *t* test or Fisher exact test, where appropriate. A 2-sided α level of 0.05 was considered statistically significant.

Results

Baseline and Procedural Characteristics

Reference vessel CFVR was measured in a total of 178 patients. Long-term follow-up was obtained in all these patients. Mean age of the study population was 59±13 years. Most patients had moderate-to-severe stable anginal complaints (15% Braunwald class I, 58% Canadian Cardiovascular Society class 3, 21% Canadian Cardiovascular Society class 2, and 6% Canadian Cardiovascular Society class 1). Two-vessel CAD was present in 69% of patients (123 of 178 patients). In 36% of patients (64 of 178 patients), the coronary lesion of interest was treated during the index procedure. All baseline clinical and procedural characteristics are presented

Table 1. Clinical and Procedural Characteristics of Study Population, and Stratified According to Patients With a Normal or Abnormal Reference Vessel CFVR (n=178)

		Reference CFVR		
		Normal	Abnormal	
	All	>2.7	≤2.7	*P* Value*
No. of patients	178	101	77	
Age, y	59±13	57±9	61±16	0.04
Male sex	128 (72)	77 (76)	51 (66)	0.18
Risk factors				
Hypertension	70 (39)	38 (37)	32 (42)	0.64
Hyperlipidemia	102 (57)	67 (66)	35 (45)	0.01
Family history of CAD	86 (48)	50 (50)	36 (47)	0.76
Smoking	61 (34)	36 (36)	25 (32)	0.75
Diabetes mellitus	27 (15)	14 (14)	13 (17)	0.68
Prior myocardial infarction	65 (37)	36 (36)	29 (38)	0.88
Prior percutaneous coronary intervention	25 (14)	14 (14)	11 (14)	1.0
Medication at hospital admission				
β-Blocker	141 (79)	80 (79)	61 (79)	1.00
Calcium antagonist	112 (63)	65 (64)	47 (61)	0.75
ACE inhibitor	34 (19)	20 (20)	14 (18)	0.85
Nitrates	120 (67)	66 (65)	54 (70)	0.52
Lipid-lowering drugs	102 (57)	62 (61)	40 (52)	0.22
Aspirin	159 (89)	92 (91)	67 (87)	0.47
Ventricular function				
Abnormal left ventricular function (EF <50%)	14 (8)	5 (5)	9 (12)	0.16
Left ventricular hypertrophy	9 (5)	4 (4)	5 (6)	0.73
Hemodynamics during measurements				
Baseline				
Heart rate, bpm	68±11	67±11	69±10	0.24
Mean arterial pressure, mm Hg	98±13	96±11	101±14	0.03
Hyperemia				
Heart rate, bpm	68±11	67±11	70±10	0.14
Mean arterial pressure, mm Hg	94±13	93±11	97±14	0.06
Functional parameters before PCI/deferral				
Two-vessel coronary artery disease	123 (69)	69 (68)	54 (70)	0.80
Diameter stenosis of most severe lesion (%)	57±10	57±10	57±11	0.74
Reversible ischemia on MPS	61 (34)	37 (37)	24 (31)	0.52
CFVR	2.2±0.8	2.4±0.8	1.9±0.6	<0.001
Baseline APV target vessel, cm/s	17±8	15±6	20±10	<0.001
Hyperemic APV target vessel, cm/s	36±17	35±16	38±19	0.41
FFR	0.73±0.17	0.73±0.17	0.73±0.18	0.98
Reference vessel CFVR	2.9±0.7	3.4±0.4	2.3±0.3	
Baseline APV reference vessel, cm/s	18±7	16±5	21±7	<0.001
Hyperemic APV reference vessel, cm/s	50±17	52±18	48±16	0.23
HSR, mm Hg/cm per second	1.33±2.28	1.16±1.66	1.54±2.88	0.30
Reference vessel diameter, mm	2.9±0.6	2.9±0.6	2.9±0.7	0.72
Microvascular resistance				
Target vessel				
Baseline MR, mm Hg/cm per second	6.01±3.04	6.49±2.61	5.40±3.44	0.02
Hyperemic MR, mm Hg/cm per second	2.29±1.21	2.18±0.78	2.42±1.60	0.22
Reference vessel				
Baseline MR, mm Hg/cm per second	6.16±2.30	6.92±2.42	5.21±1.73	<0.001
Hyperemic MR, mm Hg/cm per second	2.14±1.02	2.07±1.19	2.22±0.76	0.35
PCI of target lesion	64 (36)	35 (35)	29 (38)	0.75

Values presented as n (%) or mean±SD. ACE indicates angiotensin-converting enzyme; APV, average peak flow velocity; CAD, coronary artery disease; CFVR, coronary flow velocity reserve; EF, ejection fraction; FFR, fractional flow reserve; HSR, hyperemic stenosis resistance index; MPS, myocardial perfusion scintigraphy; MR, microvascular resistance; and PCI, percutaneous coronary intervention.

**P* value for comparison between normal and abnormal reference vessel CFVR groups.

in Table 1. The location of the reference vessel relative to the target vessel is presented in Table 2.

Clinical Characteristics of Patients With Normal Versus Abnormal Reference Vessel CFVR

Clinical and procedural characteristics stratified by normal or abnormal reference vessel CFVR (>2.7, and ≤2.7, respectively) are presented in Table 1. On average, patients with an abnormal reference vessel CFVR were older at the time of cardiac catheterization and less frequently had hyperlipidemia. All other clinical characteristics were balanced between the 2 groups. Lesion characteristics and epicardial lesion severity assessed either angiographically or by fractional flow reserve or hyperemic stenosis resistance index were similar between groups. Accordingly, percutaneous coronary intervention of the lesion of interest was performed equivalently between groups. Nevertheless, CFVR in the target vessel was significantly lower among patients with an impaired reference vessel CFVR.

Coronary Flow Velocity Parameters

Reference vessel APV under baseline conditions was significantly higher, and microvascular resistance under baseline conditions was significantly lower among patients with an abnormal reference vessel CFVR (Table 1). Contrariwise, reference vessel hyperemic flow velocity and reference vessel hyperemic microvascular resistance were similar between both groups (Table 1).

In addition, target vessel APV under baseline conditions and baseline microvascular resistance were also significantly different between the normal and abnormal reference vessel

Table 2. Reference Vessel Location Relative to the Target Vessel

	Reference Vessel		
Target Vessel	LAD	LCX	RCA
LAD	…	79 (44)	13 (7)
LCX	25 (14)	…	11 (6)
RCA	22 (12)	28 (16)	…

Data presented as n (%). LAD indicates left anterior descending coronary artery, LCX, left circumflex coronary artery; and RCA, right coronary artery.

CFVR groups, whereas hyperemic APV and microvascular resistance in the target vessel did not differ significantly (Table 1).

Reference Vessel CFVR and Long-term Fatal Events

Median follow-up amounted to 11.6 years (Q1–Q3: 10.1–13.2 years). Twelve-year Kaplan–Meier estimates of cumulative all-cause mortality amounted to 16.7% in patients with a normal reference vessel CFVR and to 39.6% in patients with an abnormal reference vessel CFVR (P<0.001; Figure A), whereas 12-year Kaplan–Meier estimates of cumulative cardiac mortality amounted to 7.7% in patients with a normal reference vessel CFVR and to 31.6% in patients with an abnormal reference vessel CFVR (P<0.001; Figure B).

Of all clinical and procedural characteristics (Table 1), reference vessel CFVR ≤2.7, age >65 years, impaired left ventricular function (left ventricular ejection fraction <50%), the presence of left ventricular hypertrophy, and history of angiotensin-converting enzyme inhibitor use were found to be associated with long-term all-cause mortality in this study population (P<0.1). After multivariable adjustment, reference vessel CFVR ≤2.7 was associated with a 2.24-fold increase in mortality hazard at long-term follow-up (hazard ratio, 2.24; 95% confidence interval, 1.13–4.44; P=0.020). Furthermore, after multivariable adjustment, reference vessel CFVR was associated with a 3.32-fold increase in cardiac mortality hazard at long-term follow-up (hazard ratio, 3.32; 95% confidence interval, 1.27–8.67; P=0.014). Additional adjustment for index procedure treatment strategy did not alter these findings (hazard ratio for all-cause mortality, 2.23; 95% confidence interval, 1.13–4.42; P=0.021 and hazard ratio for cardiac mortality, 3.34; 95% confidence interval, 1.28–8.73; P=0.014).

Discussion

In our study population, we observed that an abnormal reference vessel CFVR of ≤2.7 was associated with a 2.24-fold increase in hazard for long-term all-cause mortality after multivariable adjustment. Twelve-year Kaplan–Meier estimates of all-cause mortality amounted to 16.7% when reference vessel CFVR was normal, in contrast to 39.6% in the

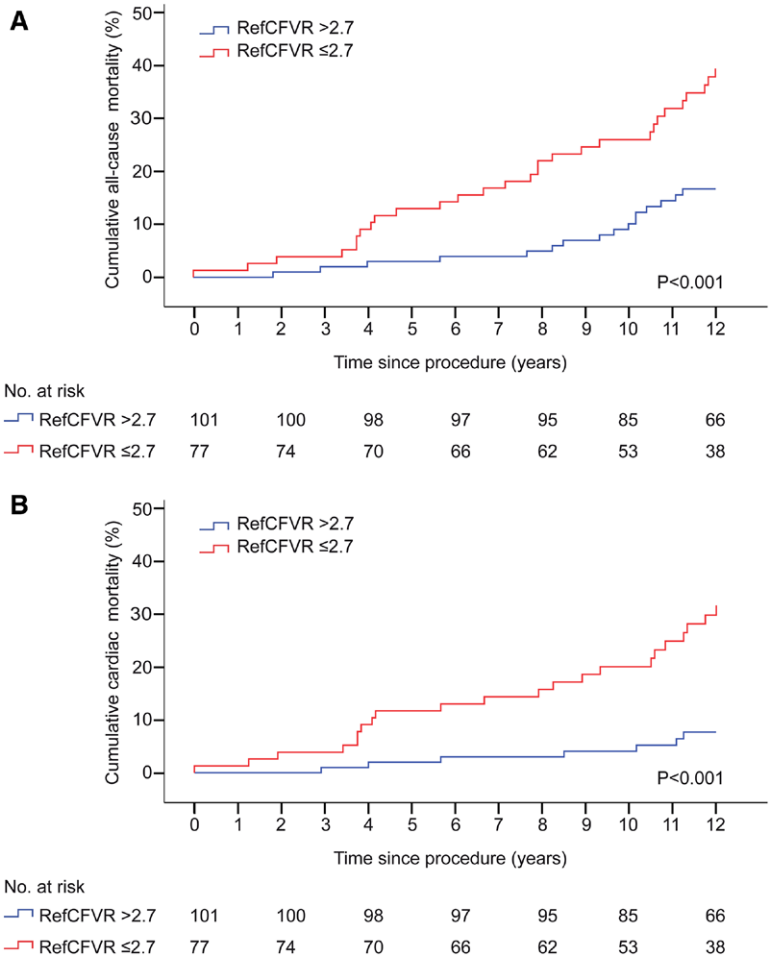

Figure. Kaplan–Meier estimates and log-rank comparison of cumulative fatal events. Log-rank comparison of Kaplan–Meier estimates resulted in a significant difference in (**A**) all-cause mortality, as well as (**B**) cardiac mortality, between normal and abnormal reference vessel coronary flow velocity reserve. RefCFVR indicates coronary flow velocity reserve in reference vessels.

presence of an abnormal reference vessel CFVR. In addition, abnormal reference vessel CFVR was associated with a 3.32-fold increase in hazard for long-term cardiac mortality. The impairment in reference vessel CFVR was found to originate from a significantly higher baseline APV in the presence of a significantly lower baseline microvascular resistance. In contrast, hyperemic microvascular resistance and hyperemic APV did not differ between abnormal and normal reference vessel CFVR groups. Furthermore, similar alterations in baseline flow velocity and microvascular resistance were also present in the target vessel.

Reference Coronary Flow Velocity and Microvascular Function

In the absence of a significant coronary stenosis, the vasodilator response of the coronary circulation is determined by the resistance vessels of the coronary microcirculation.[3] In response to a potent vasodilatory stimulus, such as adenosine, this CFVR in a reference vessel may increase >4-fold in healthy young volunteers.[10,13] In adult patients with chest pain syndromes and risk factors for CAD, reference vessel CFVR is expected to increase >2.7-fold.[10,13,14] As CFVR is determined as the ratio of hyperemic to basal coronary blood flow velocity, impairment of reference vessel CFVR may follow from either a decrease in hyperemic or an increase in basal coronary blood flow. While the former may be ascribed to impaired vasodilatory function of the coronary microvasculature and is usually associated with a high hyperemic microvascular resistance, the latter may be ascribed to disturbed coronary autoregulation and is usually associated with low microvascular resistance under baseline conditions.[15] The discrimination between these 2 entities, which can only be made by selective evaluation of the relative contributions of baseline and hyperemic components of CFVR, may provide essential insights into the pathophysiological origin of the impaired vasodilator reserve.

Interpretation of Impaired Reference Vessel CFVR in the Present Study

An increased baseline flow velocity in the presence of decreased baseline microvascular resistance has previously been described in patients with stable CAD after angioplasty and coronary stenting, contributing to the impaired flow velocity reserve frequently found in this setting.[15–17] This increase in baseline flow velocity was repeatedly ascribed to disturbed coronary autoregulation.[15,17] Under physiological circumstances, coronary autoregulation regulates vasodilation and vasoconstriction of the coronary resistance vessels to maintain stable coronary blood flow to the distal myocardium within a physiological range of perfusion pressures.[18] In response to a loss of perfusion pressure to the distal myocardium as a result of progressive epicardial coronary narrowing, autoregulation facilitates compensatory vasodilation of the coronary resistance vessels to maintain stable resting coronary blood flow to the distal myocardium. This mechanism is capable of maintaining resting blood flow until the epicardial artery becomes narrowed by >85% of the lumen diameter, after which basal flow starts to decrease.[19] In the setting of stable CAD, prolonged compensatory vasodilation of the coronary resistance vessels because of chronic deprivation of perfusion pressure in the presence of progressive epicardial artery narrowing may impair the autoregulatory mechanism of the coronary microvasculature. An abrupt restoration of perfusion pressure by percutaneous intervention may then fail to induce appropriate adaptation of the microvasculature, resulting in an increased flow velocity at rest.[15,17] However, after percutaneous coronary intervention, this change in baseline flow velocity in response to coronary intervention was found to be transient, normalizing toward reference values at ≈6-month follow-up.[15,17]

In contrast to the previous investigations after percutaneous intervention, we assessed CFVR in vessels without flow-limiting coronary stenoses. Furthermore, we performed the intracoronary measurements at the start of the procedure before revascularization of the target lesions. The combination of an increased baseline flow velocity in the presence of decreased microvascular resistance in the present study, therefore, implies pre-existent disturbance of the coronary autoregulatory mechanism in adequately perfused myocardium. Furthermore, the same alterations were present in the target vessel, indicating that disturbance of the autoregulatory mechanism is present throughout the myocardium and implicating a systemic origin of such microvascular dysfunction. Apparently, in patients with impaired reference vessel CFVR, coronary autoregulation fails to adapt distal vascular tone appropriately to regulate coronary flow, resulting in an increase in baseline flow velocity and impairing the achievable CFVR, which apparently puts these patients at high risk for future events. In contrast, the microvascular response to a potent vasodilator remains intact and, therefore, does not provide an explanation for the adverse outcome observed in these patients.

The combination of findings in the present study allocates the cause of the impaired flow reserve to the coronary autoregulatory mechanism. Preclinical studies suggest a role of hypertension-associated left ventricular hypertrophy,[20–22] diabetes mellitus,[23,24] and acute renal failure,[25] although the latter condition was an exclusion criterion in the present study. Disturbance of coronary autoregulation may arise from a wide variety of pathophysiological mechanisms,[1,3,26,27] and larger cohorts of patients with disturbed coronary autoregulation are necessary to elucidate the origin of such dysfunction in patients with stable CAD.

Previous Studies on the Prognostic Value of Coronary Flow Velocity Abnormalities

Two other studies reported on the prognostic value of intracoronary-derived CFVR in a reference vessel for long-term clinical outcome. Pepine et al[2] showed a similar prognostic value of CFVR in a normal reference coronary artery in women with suspected myocardial ischemia. At 5.4 years of follow-up, a reference vessel CFVR<2.32 was associated with a major adverse cardiac event rate (defined as the composite of death, myocardial infarction, stroke, and hospital stay for heart failure) of 27.0% compared with 12.2% when CFVR≥2.32 (P<0.01). Overall mortality was low at 6% (11 of 189 patients), but the mortality difference between low and high reference vessel CFVR values was not reported. The authors concluded that an impaired microvascular vasodilatory response to a potent vasodilator is associated with increased risk for major adverse cardiac event, even in the absence of significant obstructive CAD.

In addition, Britten et al[5] evaluated the prognostic value of the coronary flow reserve index, an index analogous to CFVR, in a normal coronary artery in patients undergoing either diagnostic cardiac catheterization for symptoms of angina or single-vessel percutaneous coronary intervention. They found a low major adverse cardiac event rate (defined as the composite of death, myocardial infarction, stroke, unstable angina, and revascularization of a de novo coronary artery lesion) of 11% (13 of 120 patients) during 6.5 years of follow-up. Notably, cardiac mortality amounted to only 1.7% (2 of 120 patients) at long-term follow-up. Coronary flow reserve index in a normal coronary artery was found to be independently associated with cardiovascular events at long-term follow-up. The authors concluded that the coronary flow reserve index, as an integrative measure of the maximal vasodilator capacity of the microcirculation as well as epicardial resistance because of subclinical atherosclerosis, is an independent predictor of long-term adverse outcome.

Differences Between Study Results: Outcome Measures and Impaired CFVR Interpretation

In part, our conclusions are consistent with these previous reports, because we found a similar important prognostic value of microvascular function determined by CFVR in reference vessels for long-term clinical outcome in patients with stable CAD. However, the present study is the first to indicate a significant association between reference vessel vasodilator reserve and long-term fatal events. In the previous evaluations of the prognostic value of reference vessel CFVR for long-term adverse events, nonfatal adverse events were included in the composite end points, such as stroke and revascularization of de novo coronary artery lesions, of which a direct relationship with pre-existent coronary microvascular functional alterations documented during the index procedure may be questionable.

The most important difference between our findings and the conclusions from Pepine et al[2] and Britten et al[5] is the origin of the impaired reference vessel CFVR. Both reports conclude that microvascular reactivity to a potent vasodilator was impaired in patients with an abnormal reference vessel CFVR. However, the relative influence of baseline and hyperemic flow velocity and microvascular resistance was not reported to support this conclusion, even though such discrimination seems important because an impaired vasodilator response to a potent vasodilator is most likely because of different pathophysiology than disturbed autoregulation under basal conditions. Therefore, identification of the exact origin of reference vessel CFVR impairment may alter the potential target for risk stratification or evaluation of preventive therapeutic strategies.[2]

According to the combination of observations in the present study, we postulate that impaired reference vessel CFVR does not originate from an impaired hyperemic vasodilator response of the coronary microvasculature as reported previously, but from pre-existent disturbed coronary autoregulation under baseline conditions that is present throughout the myocardium. The disturbed autoregulation results in an increased baseline flow velocity, and thereby in depletion of the vasodilator reserve throughout the myocardium. Further elucidation of factors underlying this disturbed autoregulation in patients with stable CAD may identify appropriate targets for risk stratification or evaluation of preventive treatment strategies.

Limitations

There are some limitations to this study that deserve mention. First, the present study represents a relatively small study population. Consequently, although all-cause mortality, as well as cardiac mortality, is strikingly different between patients with normal or abnormal reference vessel CFVR, these results should be considered hypothesis generating.

Second, measurement of intracoronary blood flow velocity is considered technically challenging, and accurate evaluation of CFVR is dependent on the experience of the cardiologist. However, in this study, all coronary flow velocity measurements were performed by operators with ample experience in intracoronary flow velocity measurements.

Finally, no intracoronary pressure measurements were performed in the reference coronary artery. Thereby, although reference vessels with significant epicardial narrowing were not selected for coronary flow velocity measurements, a potential role of subclinical atherosclerosis of the conduit artery in the absence of focal narrowing in the impairment of reference vessel CFVR cannot be excluded. However, (subclinical) narrowing of the reference vessel in patients with abnormal reference vessel CFVR would have resulted in a decreased hyperemic flow velocity.[4,28] Furthermore, in the absence of disturbed autoregulation, the normal physiological compensatory vasodilation by means of autoregulation in response to a decreased perfusion pressure induced by coronary narrowing is not associated with an increase in basal flow velocity.[18,19] Therefore, these findings locate the cause for an impaired reference CFVR to the coronary microvasculature, and the combination of finding implies disturbed autoregulation as the key impediment to CFVR.

Conclusions

An impaired reference vessel CFVR is associated with an increased hazard for fatal events at long-term follow-up in patients with stable CAD. Impairment of reference vessel CFVR results from disturbed coronary autoregulation, leading to an increased coronary flow velocity under baseline conditions. Further studies are warranted to elucidate the origin of dysfunction of the coronary autoregulatory mechanism, as well as its role in the unfavorable outcome of patients with stable CAD.

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Disclosures

None.

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