Novel insights into the complexity of ischaemic heart disease derived from combined coronary pressure and flow velocity measurements

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Part C

Prognostic implications of and therapeutic strategies directed towards the microcirculation
Chapter 11

Impaired coronary autoregulation is associated with long-term fatal events in patients with stable coronary artery disease


ABSTRACT

Background
Abnormalities in the coronary microcirculation are increasingly recognized as an elementary component of coronary artery disease (CAD), 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 CAD.

Methods and results
We included patients with stable CAD who underwent intracoronary physiological evaluation of at least one 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 (KM) estimates of twelve-year all-cause mortality were 16.7% when refCFVR>2.7, and 39.6% when refCFVR≤2.7 (p<0.001), whereas KM-estimates for cardiac mortality were 7.7% 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 to 4.44; P=0.020), and a 3.32-fold increase in cardiac mortality hazard (hazard ratio 3.32; 95% confidence interval 1.27 to 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 etiology.

Conclusion
In patients with stable CAD, impaired refCFVR, resulting from increased baseline flow velocity indicating disturbed coronary autoregulation, is associated with a significant increase in mortality at long-term follow-up.
INTRODUCTION

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, and may arise from a wide array of pathogenetic mechanisms. Such alterations may contribute to adverse outcome in patients with stable coronary artery disease, and may, potentially, offer a target for risk stratification and evaluation of preventive treatment strategies.

In the absence of significant epicardial disease, the vasodilator response of the coronary circulation, as measured by the coronary flow velocity reserve (CFVR), is determined by the functional status of the resistance vessels of the coronary microcirculation, and can therefore be considered a direct marker of microvascular function. Defined as the ratio of hyperemic to basal average peak flow velocity, impairment of reference vessel CFVR may originate from either an increased basal flow velocity or an impaired hyperemic flow velocity. Although there has been interest in the prognostic value of the vasodilatory function of the coronary microcirculation, 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 coronary artery disease, 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 coronary artery disease whose diagnostic angiography showed at least one intermediate coronary artery lesion at visual assessment. These patients were enrolled in a series of study protocols, and patient and procedural characteristics were entered into a dedicated database. We excluded patients with ostial lesions, two or more stenoses in the same coronary artery, severe renal function impairment (sMDRD calculated glomerular filtration rate less than 30mL/min/1.73m²), significant left main coronary artery stenosis, atrial fibrillation, recent myocardial infarction (<6 weeks prior to 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 (QCA) analysis. QCA 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).

Prior to PCI, intracoronary pressure was measured with a 0.014” pressure-sensor equipped guide wire (Volcano Corp., San Diego, USA). Coronary blood flow velocity was subsequently measured with a 0.014” Doppler-crystal equipped guide wire (Volcano Corp., San Diego, USA). Hyperemia was induced by an intracoronary bolus of adenosine (20-40 µg). Fractional flow reserve (FFR) was defined as the ratio of mean distal coronary pressure to mean aortic pressure in the target vessel(s) during maximal hyperemia. CFVR was defined as the ratio of hyperemic to baseline average peak blood flow velocity (APV) distal to the target lesion(s). CFVR was additionally assessed in an angiographically normal reference coronary artery, defined as a coronary artery with less than 30% irregularities on visual assessment, if present. A reference vessel CFVR>2.7 was considered normal. From the recorded intracoronary hemodynamic data both the hyperemic stenosis resistance index (HSR), defined as the ratio between the pressure gradient across the stenosis and distal APV during maximal hyperemia, as well as the microvascular resistance index (MR), defined as mean distal coronary pressure divided by distal APV, were calculated. In the absence of significant epicardial disease, MR in the reference vessel was calculated as the mean aortic pressure divided distal APV. In the presence of two-vessel coronary artery disease, the most severe coronary lesion by HSR was depicted the target lesion, and was used for subsequent target vessel analyses.

Patients underwent PCI 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. Additionally, the cause of death was verified by evaluating hospital records, or contacting the general practitioner. Death was considered cardiac unless an unequivocal non-cardiac cause was documented.
Statistical analysis

Cumulative event rates were estimated using the Kaplan-Meier method, and were compared with the log-rank test. Twelve-year cumulative 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 two sets of Cox proportional hazards models. An 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 (± standard deviation), median with first and third quartiles (Q1-Q3), or frequency (percentage), where appropriate. Comparison between groups was performed using Student’s t-test or Fisher exact test where appropriate. A two-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 of 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 (CCS) class 3, 21% CCS class 2, and 6% CCS class 1). Two-vessel coronary artery disease was present in 69% of patients (123 out of 178). In 36% of patients (64 out of 178), the coronary lesion of interest was treated during the index procedure. All baseline clinical and procedural characteristics are presented 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 suffered from hyperlipidemia. All other clinical characteristics were balanced between the two groups. Lesion characteristics and epicardial lesion severity assessed either angiographically, or by FFR or HSR, were similar between groups. Accordingly, PCI 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.
### Table 1 | Clinical and procedural characteristics of study population, and stratified according to patients with a normal or abnormal reference vessel CFVR (n=178)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Reference CFVR</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal &gt;2.7</td>
<td>Abnormal ≤2.7</td>
</tr>
<tr>
<td>Number of patients</td>
<td>178</td>
<td>101</td>
<td>77</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>59±13</td>
<td>57±9</td>
<td>61±16</td>
</tr>
<tr>
<td>Male Sex</td>
<td>128 (72)</td>
<td>77 (76)</td>
<td>51 (66)</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 (39)</td>
<td>38 (37)</td>
<td>32 (42)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>102 (57)</td>
<td>67 (66)</td>
<td>35 (45)</td>
</tr>
<tr>
<td>Family History of CAD</td>
<td>86 (48)</td>
<td>50 (50)</td>
<td>36 (47)</td>
</tr>
<tr>
<td>Smoking</td>
<td>61 (34)</td>
<td>36 (36)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>27 (15)</td>
<td>14 (14)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>65 (37)</td>
<td>36 (36)</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention</td>
<td>25 (14)</td>
<td>14 (14)</td>
<td>11 (14)</td>
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<tr>
<td><strong>Medication at hospital admission</strong></td>
<td></td>
<td></td>
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<tr>
<td>B-Blocker</td>
<td>141 (79)</td>
<td>80 (79)</td>
<td>61 (79)</td>
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<tr>
<td>Calcium Antagonist</td>
<td>112 (63)</td>
<td>65 (64)</td>
<td>47 (61)</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>34 (19)</td>
<td>20 (20)</td>
<td>14 (18)</td>
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<td>Nitrates</td>
<td>120 (67)</td>
<td>66 (65)</td>
<td>54 (70)</td>
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<td>Lipid Lowering Drugs</td>
<td>102 (57)</td>
<td>62 (61)</td>
<td>40 (52)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>159 (89)</td>
<td>92 (91)</td>
<td>67 (87)</td>
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<td><strong>Ventricular Function</strong></td>
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<td>Abnormal Left Ventricular Function (EF &lt;50%)</td>
<td>14 (8)</td>
<td>5 (5)</td>
<td>9 (12)</td>
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<td>Left Ventricular Hypertrophy</td>
<td>9 (5)</td>
<td>4 (4)</td>
<td>5 (6)</td>
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<td><strong>Hemodynamics during measurements</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>68±11</td>
<td>67±11</td>
<td>69±10</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>98±13</td>
<td>96±11</td>
<td>101±14</td>
</tr>
<tr>
<td>Hyperemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>68±11</td>
<td>67±11</td>
<td>70±10</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>94±13</td>
<td>93±11</td>
<td>97±14</td>
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<td><strong>Functional parameters prior to PCI/deferral</strong></td>
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<tr>
<td>Two-vessel coronary artery disease</td>
<td>123 (69)</td>
<td>69 (68)</td>
<td>54 (70)</td>
</tr>
<tr>
<td>Diameter stenosis most severe lesion (%)</td>
<td>57±10</td>
<td>57±10</td>
<td>57±11</td>
</tr>
<tr>
<td>Reversible ischemia on MPS</td>
<td>61 (34)</td>
<td>37 (37)</td>
<td>24 (31)</td>
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<tr>
<td>CFVR</td>
<td>2.2±0.8</td>
<td>2.4±0.8</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Baseline APV target vessel (cm/s)</td>
<td>17±8</td>
<td>15±6</td>
<td>20±10</td>
</tr>
<tr>
<td>Hyperemic APV target vessel (cm/s)</td>
<td>36±17</td>
<td>35±16</td>
<td>38±19</td>
</tr>
<tr>
<td>FFR</td>
<td>0.73±0.17</td>
<td>0.73±0.17</td>
<td>0.73±0.18</td>
</tr>
</tbody>
</table>
Impaired coronary autoregulation in stable CAD

Chapter 11

Coronary flow velocity parameters

Reference vessel APV during baseline conditions was significantly higher, and microvascular resistance during 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 was similar between both groups (Table 1).

In addition, target vessel APV during baseline conditions, and baseline microvascular resistance were also significantly different between the normal and abnormal reference vessel 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 1A), whereas twelve-year Kaplan Meier estimates of cumula-
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 1B).

Out of all clinical and procedural characteristics (Table 1), reference vessel CFVR $\leq 2.7$, age above 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 $\leq 2.7$ 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 to 4.44; $p=0.020$). Moreover, 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 1.28 to 8.73; $p=0.014$).
In our study population, we observed that an abnormal reference vessel CFVR of less than or equal to 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 presence of an abnormal reference vessel CFVR. Additionally, 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. Moreover, the same 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.\(^5\) In response to a potent vasodilatory stimulus, such as adenosine, this CFVR in a reference vessel may increase more than 4-fold in healthy young volunteers.\(^10\,13\) In adult patients with chest pain syndromes and risk factors for coronary artery disease, reference vessel CFVR is expected to increase more than 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 a low microvascular resistance during baseline conditions.\(^15\) The discrimination between these two entities, which can only be made by selective evalu-
ation 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 coronary artery disease after angioplasty and coronary stenting, contributing to the impaired flow velocity reserve frequently found in this setting. This increase in baseline flow velocity was repeatedly ascribed to disturbed coronary autoregulation. 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. In response to a loss of perfusion pressure to the distal myocardium due to progressive epicardial coronary narrowing, autoregulation facilitates compensatory vasodilation of the coronary resistance vessels in order 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 more than 85% of the lumen diameter, after which basal flow starts to decrease. In the setting of stable coronary artery disease, prolonged compensatory vasodilation of the coronary resistance vessels due to 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. However, after percutaneous intervention, this change in baseline flow velocity in response to coronary intervention was repeatedly found to be transient, normalizing towards reference values at approximately 6-month follow-up.

In contrast to the previous investigations after percutaneous intervention, we assessed CFVR in vessels without flow-limiting coronary stenoses. Moreover, we performed the intracoronary measurements at the start of the procedure, prior to revascularization of the target lesion(s). The combination of an increased baseline flow velocity in the presence of a decreased microvascular resistance in the present study therefore implies pre-existing disturbance of the coronary autoregulatory mechanism in adequately perfused myocardium. Moreover, 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 etiology of the impaired flow reserve to the coronary autoregulatory mechanism. Preclinical studies suggest a role of hypertension-associated left ventricular hypertrophy, diabetes mellitus, and acute renal failure, 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, and larger cohorts of patients with disturbed coronary autoregulation are necessary to elucidate the origin of such dysfunction in patients with stable coronary artery disease.

**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. 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 (MACE) rate (defined as the composite of death, myocardial infarction (MI), stroke and hospital stay for heart failure) of 27.0% compared to 12.2% when CFVR ≥2.32 (p<0.01). Overall mortality was low at 6% (11 out 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 intracoronary vasodilator is associated with increased risk for MACE, even in the absence of significant obstructive coronary artery disease. Additionally, Britten et al. 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 PCI. They found a low MACE rate (defined as the composite of death, MI, stroke, unstable angina, and revascularization of a de novo coronary artery lesion) of 11% (13 out of 120 patients) during 6.5 years of follow up. Notably, cardiac mortality amounted to only 1.7% (2 out 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 due to 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, as 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 coronary artery disease. 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, non-fatal adverse events were included in the composite endpoints, 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. and Britten et al. 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 were not reported to support this conclusion, even though such discrimination seems important as an impaired vasodilator response to a potent vasodilator is most likely due to different pathophysiology than disturbed autoregulation during 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 during 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 coronary artery disease may identify appropriate targets for risk stratification or evaluation of preventive treatment strategies.

Limitations

There are some limitations to this study that deserve mentioning. First, the present study represents a relatively small study population. Consequently, although all-cause, as well as cardiac mortality are 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 coronary flow velocity reserve 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. Moreover, in the absence of disturbed autoregulation, the normal physiological compensatory vasodilation by means of autoregulation in response to a decreased perfusion pressure induced by a coronary narrowing is not associated with an increase in basal flow velocity. Therefore, these findings locate the etiology for an impaired reference vessel CFVR to the coronary microvasculature, and the combination of findings implies disturbed autoregulation as the key impediment to CFVR.

**CONCLUSION**

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


