Impaired Coronary Flow Reserve as a Marker of Microvascular Dysfunction to Predict Long-Term Cardiovascular Outcomes, Acute Coronary Syndrome and the Development of Heart Failure

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**Background:** In the absence of obstructive coronary narrowing, impaired coronary flow reserve (CFR) represents coronary microvascular dysfunction. Transthoracic Doppler echocardiography (TTDE) allows non-invasive measurement of CFR in the left anterior descending (LAD) artery. This study aimed to assess the prognostic value of TTDE-derived CFR (as a marker of microvascular function) in predicting long-term cardiovascular events, acute coronary syndrome (ACS) events, and the development of heart failure (HF).

**Methods and Results:** This study consisted of 272 patients with coronary artery disease not involving obstructive narrowing (≥50%) in the LAD. Patients underwent TTDE examination for CFR measurement in the LAD. During the follow-up period of 4.0±1.9 years, 32 patients (12%) had cardiovascular events. Cox proportional hazard analysis identified lower CFR as an independent risk factor of cardiovascular events (P<0.001), ACS events (P=0.008), and HF development (P=0.003). A CFR less than 2.4 was the best cut-off value for predicting all events (area under the curve=0.82). CFR excellently predicted the development of HF (area under the curve=0.95), but not ACS events (area under the curve=0.67).

**Conclusions:** This TTDE study demonstrated that CFR was a significant and independent determinant of long-term cardiovascular events, ACS events and HF in patients with coronary artery disease. A CFR greater than 2.0 was not suitable to predict a favorable long-term outcome, even in the absence of obstructive coronary narrowing. (Circ J 2012; 76: 1958–1964)

**Key Words:** Acute coronary syndrome; Coronary flow reserve; Heart failure

Coronary flow reserve (CFR) is dependent on the combined effects of epicardial coronary stenosis and microvascular dysfunction. Therefore, impaired CFR reflects the presence of microvascular dysfunction in the absence of obstructive coronary artery narrowing. Advances in transthoracic Doppler echocardiography (TTDE) allow non-invasive, physiological assessment of CFR in the left anterior descending (LAD) artery. Previous TTDE investigations have reported that a CFR of less than 2.0 is associated with cardiac death and acute coronary syndrome (ACS) events in patients with coronary artery disease (CAD). However, it is unclear whether a CFR greater than 2.0 is a sign of favorable long-term cardiovascular outcome. Furthermore, the association between reduced CFR and the development of heart failure (HF) has not been investigated, although microvascular impairment causes left ventricular (LV) systolic and diastolic dysfunctions. This study therefore aimed to investigate the prognostic value of CFR to predict future cardiovascular outcome, ACS events and the development of HF in patients with suspected or known CAD.
Methods
Study Population
This study consisted of 272 consecutive patients (181 men, mean age 68±12 years) who underwent a coronary angiography and TTDE examination. The indication for CFR measurement was suspected CAD in 170 (63%) subjects, and risk stratification of known CAD in 102 (37%) subjects. The exclusion criteria included a history of myocardial infarction, coronary revascularization in the LAD, more than moderate valvular disease, cardiomyopathy, and chronic kidney disease. Patients with obstructive narrowing (≥50%) in the LAD as confirmed by coronary angiography were also excluded. All patients were followed for more than 1 year through structured interviews by physicians.

The presence or absence of the following risk factors was evaluated in each patient based on their medical records: hypertension (blood pressure more than or equal to 140/90 mmHg on repeated measurements, or taking antihypertensive medications), hypercholesterolemia (serum total cholesterol level ≥200 mg/dl, or treatment with statins), diabetes (fasting plasma glucose level >126 mg/dl, treatment with hypoglycemic drugs

| Table 1. Clinical Characteristics of Patients With and Without Cardiovascular Events |
|-----------------------------------------------|------------------|------------------|------------------|------------------|
| Age, years                                     | 68±12            | 75±12            | 67±12            | 0.001            |
| Male gender, n (%)                             | 181 (67)         | 19 (59)          | 162 (68)         | 0.4              |
| Hypertension, n (%)                            | 193 (71)         | 22 (69)          | 171 (71)         | 0.8              |
| Diabetes, n (%)                                | 82 (30)          | 9 (28)           | 73 (30)          | 0.8              |
| Hypercholesterolemia, n (%)                    | 133 (49)         | 12 (38)          | 121 (50)         | 0.2              |
| Smoking, n (%)                                 | 106 (39)         | 12 (38)          | 94 (39)          | 0.9              |
| Obesity, n (%)                                 | 12 (4)           | 2 (6)            | 10 (4)           | 0.6              |
| Obstructive coronary narrowing                  |                  |                  |                  |                  |
| Right coronary artery, n (%)                  | 45 (17)          | 6 (19)           | 39 (16)          | 0.7              |
| Left circumflex coronary artery, n (%)         | 55 (20)          | 7 (22)           | 48 (20)          | 0.8              |
| Medications                                    |                  |                  |                  |                  |
| ACEI or ARB, n (%)                             | 121 (44)         | 18 (56)          | 103 (43)         | 0.2              |
| Calcium channel blocker, n (%)                 | 88 (32)          | 13 (41)          | 75 (31)          | 0.8              |
| Statin, n (%)                                  | 95 (35)          | 7 (22)           | 88 (37)          | 0.1              |
| CRP, mg/L                                      | 1.6±1.5          | 2.8±1.7          | 1.4±1.4          | <0.001           |
| Echocardiographic parameters                   |                  |                  |                  |                  |
| LV ejection fraction, %                        | 59±10            | 54±12            | 59±9             | 0.001            |
| LV mass index, g/m²                            | 107±31           | 124±36           | 104±29           | 0.001            |
| Left atrium diameter, mm                       | 39±6             | 40±5             | 38±6             | 0.3              |
| E/e’ ratio                                     | 11.8±4.8         | 14.2±7.0         | 11.3±4.3         | 0.004            |
| Deceleration time, ms                          | 221±64           | 212±57           | 222±65           | 0.5              |
| CFR                                            | 2.9±0.8          | 2.1±0.7          | 3.0±0.8          | <0.001           |

Values are mean±SD or n (percentage).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRP, C-reactive protein; LV, left ventricular; E/e’, peak velocity/early diastolic mitral annular velocity; CFR, coronary flow reserve.

Table 2. Multivariate Analysis for Predictors of All Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>1.49 (1.15–1.95)</td>
<td>0.003</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>1.00 (0.96–1.05)</td>
<td>0.9</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>1.01 (0.99–1.02)</td>
<td>0.1</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>1.02 (0.93–1.11)</td>
<td>0.7</td>
</tr>
<tr>
<td>CFR</td>
<td>0.18 (0.07–0.42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes, and medications including ACEI, ARB, calcium channel blocker, and statin.
OR, odds ratio; CI, confidential interval. Other abbreviations as in Table 1.
or insulin, or a combination of the 2), and smoking. Obesity was defined as a body mass index \( > 30 \text{ kg/m}^2 \). Blood samples were taken at TTDE examination for the measurement of serum C-reactive protein (CRP). The study was approved by the ethics committee of the Osaka Ekisaikai Hospital and Higashisumiyoshi Morimoto Hospital.

**TTDE Examination**

An echocardiographic examination was performed with the Vivid 7 (General Electric, Milwaukee, WI, USA) or the Sequoia 512 (Siemens Medical Solution Inc, Mountain View, CA, USA) echocardiography device. A modified foreshortened 2-chamber view was applied to explore the flow in the distal portion of the LAD. The angle between color flow and the Doppler beam was corrected if it was >20%. Coronary blood flow velocity was estimated at baseline and after intravenous infusion of adenosine triphosphate at a rate of 0.14 mg · kg\(^{-1}\) · min\(^{-1}\) for 2 min to produce hyperemia. The mean diastolic flow velocity was measured by tracing the contour of the spectral Doppler signal. The CFR was calculated as the ratio of hyperemic to basal flow velocities. Each parameter of the CFR measurements was expressed as the average value of 3 cycles.

The LV ejection fraction was obtained by using the Simpson’s methods from apical 4- and 2-chamber views. The LV mass was calculated based on the area-length formula. Pulsed-wave Doppler examination of mitral inflow was performed to measure peak velocity (E) and deceleration time of the early diastolic flow. Early diastolic mitral annular velocity (e’) was also measured from tissue Doppler imaging in the septal wall. The ratio of E to e’ was then calculated (E/e’).

**Coronary Angiography**

A coronary angiography was performed in all patients by a using standard technique. Coronary stenosis was evaluated using multiple projections by 1 investigator blinded to the results of TTDE. Quantitative analysis of the % diameter stenosis was then performed. Obstructive coronary stenosis was considered when the diameter stenosis on the quantitative coronary angiography was ≥50%.

**Endpoint**

The primary endpoint of the analysis was major cardiovascular events (the composite of cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization, and HF). Myocardial infarction and unstable angina were considered as ACS events. Myocardial infarction was diagnosed based on the presence of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram. Unstable angina pectoris was defined based on the criteria of the ACC/AHA guidelines. Angiographic restenosis incidentally found by a routine follow-up coronary angiography without clinical symptoms was excluded from cardiovascular events. HF was defined by the simultaneous presence of at least 2 major criteria or 1 major criteria and 2 minor criteria as reported by the Framingham Heart Study. HF was divide into systolic HF and diastolic HF. Diastolic HF was defined according to the European guidelines, namely as signs or symptoms of HF (exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or crepitations), normal or near-normal LV systolic function (ejection fraction >45%), and abnormal age-adjusted diastolic filling parameters.

**Statistical Analysis**

Categorical variables are presented as frequencies and con-
continuous variables as mean±SD. Variables were compared with the chi-square statistic for categorical variables and by an unpaired t-test for continuous variables. A Cox proportional hazard analysis was performed to identify the predictor(s) of cardiovascular events, ACS events, and the development of HF. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into the analysis. The sensitivity and specificity of various cut-off points for prediction of the cardiovascular events were determined using the receiver operating characteristic (ROC) curves. Cumulative event rates were estimated by the Kaplan-Meier survival curves, and the log-rank test was used to examine the impact of CFR on the survival. Differences were considered significant at P<0.05.

Results

Impact of CFR on All Cardiovascular Events

During a mean follow-up of 4.0±1.9 years, ranging from 1 year to 8 years, cardiovascular events occurred in 32 (11.8%) patients, including ACS in 17 patients (myocardial infarction in 8 patients and unstable angina in 9 patients) and HF in 15 patients (systolic HF in 5 patients and diastolic HF in 10 patients). Table 1 summarizes the clinical characteristics of patients with and without cardiovascular events. Patients with cardiovascular events were more likely to be older (P=0.001), had a higher level of serum CRP (P<0.001), a lower LV ejection fraction (P=0.001), an increased LV mass index (P=0.001), a higher E/e’ ratio (P=0.004) and a decreased CFR (P<0.001) than those without cardiovascular events (Figure 1). A Cox proportional hazard analysis identified CRP (P=0.003) and CFR (P<0.001) as independent risk factors for future cardiovascular events (Table 2).

The results of a ROC curve analysis for the prediction of all cardiovascular events are shown in Figure 2. The best cut-off value was 2.4 (area under the curve=0.82), providing a sensitivity of 75% and specificity of 76%. Kaplan-Meier analysis showed significantly worse event-free survival in patients with a CFR less than 2.4 compared with those with a CFR equal or greater than 2.4 (P<0.001; Figure 2). In 32 patients with cardiovascular events, CFR was greater than 2.0 in 15 (47%) patients. In contrast, only 3 (9%) patients with cardiovascular events had a CFR greater than 3.0.

ACS and HF

Of the 17 ACS events, the culprit lesion was in the LAD in 8 (47%) patients, and in other vessels in 9 (53%) patients. A Cox proportional hazard analysis after adjustment of age, sex, hypertension, diabetes, hypercholesterolemia, and medications including angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, and statin showed that CFR was the independent risk factor for future ACS events (P=0.008; Table 3). Figure 3 shows the results of ROC curve analysis to predict ACS events. A CFR less than 2.8 was the best cut-off value, resulting in a sensitivity of 82% and specificity of 53%. Patients with a CFR <2.8 were at higher risk for ACS events than those with a CFR ≥2.8 (Figure 3). However, the diagnostic accuracy of CFR to predict ACS events was relatively low, with an area under the curve of 0.67.

A Cox proportional hazard analysis after adjustment of age, sex, hypertension, diabetes, hypercholesterolemia, and medications including angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, and statin...
identified LV mass index (P=0.008) and CFR (P=0.003) as significant determinants of future development of HF (Table 4). A ROC curve analysis showed that a CFR of less than 2.1 was the best cut-off value to predict future HF, providing excellent sensitivity of 93% and specificity of 88% (area under the curve=0.95). An increased rate of HF was observed in patients with a CFR less than 2.1 compared to those with a CFR greater than 2.1 (P<0.001; Figure 4).

Discussion

Previous Studies of TTDE-Derived CFR on Prognosis

Recent developments in TTDE technology have allowed the visualization of coronary blood flow and assessment of CFR in the LAD. This technique has been validated by an intracoronary Doppler flow wire technique advanced into the coronary vessels. Based on its non-invasive, relative inexpensive, and physiological nature, TTDE-derived CFR measurement opens intriguing applications not only to diagnose obstructive coronary artery narrowing, but also to assess microvascular function after modification of various coronary risk factors.

Previous reports showed the prognostic value of reduced CFR in patients with non-obstructive CAD. Cortigiani et al reported that impaired CFR, defined as a CFR less than 2.0, was associated with cardiac death and ACS events in 1,130 CAD patients with negative dipyridamole stress echocardiography during a 16 month follow up. They confirmed similar observations by using a cut-off value of 2.0 in near normal and intermediate LAD stenosis. However, they used a cut-off value of 2.0, which was generally used to detect obstructive coronary artery narrowing, and this might not be sufficient to assess microvascular dysfunction for the prediction of cardiovascular outcomes. As a matter of fact, we found that 47% of patients with cardiovascular events had a CFR greater than 2.0. A CFR less than 2.4 was the best cut-off value of CFR for the prediction of cardiovascular events, and only 9% of patients with cardiovascular events had a CFR greater than 3.0. Therefore, as a marker for microcirculation dysfunction, a CFR greater than 2.0 might not be appropriate to predict a favorable long-term outcome.

Impact of CFR on ACS and HF Events

Impaired endothelial function is strongly associated with the onset and development of atherosclerosis and ACS events. Coronary microcirculation, in part, reflects endothelial function in coronary arteries. However, we demonstrated that CFR was a suitable predictor of ACS events, although its accuracy was relatively low. This could be explained by the fact that the culprit plaque often comprises a large amount of necrotic core with only mild to moderate stenosis overlying thin fibrous cap, which might not be detectable on CFR. Furthermore, all patients with CAD had optimized therapy during the follow-up period for reduction of atherosclerotic risk factors, which improves endothelial function.

The degree of modification of endothelial function varies in each patient due to underestimated risk factors or genetic predisposition.

In contrast, the lower CFR value provided excellent sensitivity and specificity to predict the development of systolic and diastolic HF. Coronary microvascular abnormalities might reduce the functional capability of the myocardium in the long term. Previous studies reported that regional LV dysfunction correlated with impaired CFR, and that the coronary microvascular abnormalities occurred even in the early stage of the disease when LV contractility was preserved. Others reported that improvement in CFR was noted earlier than recovery of LV systolic dysfunction. Similarly, a close relationship between coronary microcirculation and diastolic function has also been reported, supporting the notion that coronary microvascular damage plays a mechanistic role in diastolic dysfunction. In fact, insulin resistance, LV hypertrophy, disor-
Study Limitations

Our study has several limitations. First, this included a relatively low number of patients (n=272), although the incidence of cardiovascular events of 29 per 1,000 population per year in the present study was similar to that reported in previous studies in patients with CAD (range: 17–65 per 1,000 population per year).4,5,35 Further large-scale multicenter studies are necessary to confirm our findings. In this regard, there were no significant differences in certain clinical features between patients with and without events, which have been otherwise reported as risk factors for cardiovascular events in previous large studies.36,37

Second, medications, such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, and statin, were not determinants for cardiovascular outcome, ACS events and the development of HF in this echocardiographic study. Considering the acute effects of these medications and smoking on endothelial function and CFR,17,24,25,38 the time interval from latest smoking and/or taking medications to CFR measurement should be assessed in future investigations.

Third, despite a CFR greater than 3.0, 3 patients suffered cardiovascular events. The cardiovascular event was acute myocardial infarction in all 3 patients, which occurred 1.1 years, 2.7 years and 4.6 years after CFR examination, respectively. A CFR value might change during the follow-up period, resulting from optimized therapy for the improvement of atherosclerotic risk factors. Serial CFR measurements during follow up might help to explain this finding, and strengthen the use of this non-invasive method in clinical practice.

Forth, this study included patients with CAD who underwent angiography. Therefore, the application of our results into other study populations might be limited. Also, patients with obstructive narrowing in the LAD were excluded from the study based on the influence of such stenosis on CFR measurement. The additive or synergistic effect of reduced CFR and microvascular dysfunction under obstructive epicardial coronary narrowing on the outcome was not clear.

Finally, the TTDE method allows for the measurement of coronary flow velocity without estimation of coronary artery diameter. However, a close relationship between absolute coronary flow and flow velocity has been reported.39 Furthermore, a CFR derived from changes in coronary flow velocity only has been already used in previous invasive studies.40,41

Conclusion

Our TTDE study demonstrated that impaired microcirculation, expressed by reduced CFR, was associated with a long-term cardiovascular outcome, ACS events and the development of HF. A CFR greater than 2.0 was not appropriate for the prediction of favorable long-term outcome, even in the absence of obstructive coronary narrowing. Nevertheless, CFR was useful for the prediction of the development of HF, but its value in predicting ACS event might be limited.

References

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