Microvascular Dysfunction in Chronic Total Coronary Occlusions

Gerald S. Werner, MD; Markus Ferrari, MD; Barbara M. Richartz, MD; Oliver Gastmann, MD; Hans R. Figulla, MD

Background—Microvascular dysfunction is defined as reduced coronary flow reserve in the absence of an epicardial stenosis. This study determined its prevalence and relation to regional myocardial function in chronic total coronary occlusions (TCO).

Methods and Results—After recanalization and stenting of a TCO (duration, >4 weeks) in 42 patients, coronary flow velocity reserve (CFVR) was measured by intracoronary Doppler. In a subset of 27 patients, intracoronary pressure was recorded to obtain the fractional flow reserve (FFR). In 21 patients, the CFVR was reassessed after 24 hours. CFVR was <2.0 in 55% of all patients. In the subgroup with simultaneous pressure recordings, 52% of patients showed a CFVR <2.0 and a FFR $\geq 0.75$, indicating microvascular dysfunction. Both reduced CFVR and reduced FFR occurred in only 2 patients (7.7%). CFVR and FFR were not correlated ($r = 0.03$). A low CFVR was associated with a higher baseline average peak velocity (35.6 ± 16.6 versus 22.4 ± 11.5 cm/s; $P = 0.006$). Doppler parameters did not change within 24 hours. Regional dysfunction had no influence on CFVR. Patients with diabetes and/or hypertension had a lower CFVR than those without this comorbidity (1.86 ± 0.69 versus 2.36 ± 0.45; $P < 0.05$).

Conclusions—Microvascular dysfunction was observed in 55% of TCOs, independent of the impairment of regional myocardial function. Dysfunction was observed more often in patients with diabetes and hypertension. Neither CFVR or FFR alone is appropriate for assessing angioplasty results in patients with a TCO; CFVR should be combined with FFR to differentiate microvascular dysfunction from residual coronary stenosis or diffuse disease. (Circulation. 2001; 104:1129-1134.)

Key Words: coronary disease • occlusion • blood flow • microcirculation

The coronary flow reserve assesses the physiological relevance of a coronary lesion.1,2 With miniaturized Doppler sensors, coronary flow velocity reserve (CFVR) can be recorded in humans.3,4 This method depends on intact vasodilation of the peripheral microvasculature, which is impaired in arterial hypertension, diabetes mellitus, and myocardial infarction (MI).5–7 These conditions are common in patients with coronary artery disease, and using alternative methods of assessment such as the relative CFVR8,9 or fractional flow reserve (FFR), which employs intracoronary pressure recordings, has been suggested.5–11

In patients with acute coronary occlusions, the CFVR can be impaired after recanalization,1,2 but it is unknown whether this impairment also applies to chronic total coronary occlusions (TCOs). In TCOs, the extent of collateral-dependent preserved, irreversibly damaged, or hibernating myocardium may influence CFVR after recanalization, and data obtained with PET imaging suggest the presence of microvascular dysfunction.13

The hypothesis of this study was that microvascular dysfunction would be frequent in patients with TCOs and that it would be related to the extent of regional dysfunction. We also wanted to investigate if short-term changes in CFVR occur after recanalization.

Methods

Patients

Forty-two consecutive patients with a successful recanalization of a TCO were studied. Inclusion criteria were (1) duration of occlusion of >4 weeks, (2) TIMI 0 coronary flow, (3) evidence of ischemia by a noninvasive test related to the occluded vessel or (4) viable myocardium in an akinetic segment assessed by PET using fluoro-deoxyglucose, and (5) written, informed consent. All diagnostic angiograms showed collateral flow grade 2 (partial epicardial filling of the occluded artery) or 3 (complete epicardial filling). The duration of the occlusion ranged from 1 to 152 months (median, 4 months).

All patients were studied using Doppler measurement of CFVR. The first 21 patients underwent a repeat angiography with CVFR measurement within 24 hours after PTCA. After the first 15 patients, the protocol was modified, and in the following 27 patients, both FFR and CFVR were measured.
Angioplasty Procedure
The recanalization was performed through the femoral approach using 7F guiding catheters. The interventional strategy was to use stents in all patients to cover the lesion site with a balloon/artery ratio of at least 1.1.14 In 45% of lesions, multiple stents were implanted.

Measurement of Intracoronary Doppler Velocity
After completion of the angioplasty with a residual stenosis <20%, a 0.014-inch Doppler guidewire (FloWire, EndoSonics Corporation) was advanced downstream of the stented segment. In cases involving the left anterior descending and circumflex arteries, the wire was positioned distal to large diagonal or obtuse marginal branches; in cases involving the right coronary artery, the wire was positioned ~2 cm proximal to the crux cordis, with a distance to the side branches of at least 5 mm. The average peak velocity (APV) was recorded.

When the Doppler signal showed a stable baseline, 20 µg of intracoronary adenosine was injected rapidly, and the maximum hyperemic APV was recorded. CFVR was calculated as the ratio of hyperemic to baseline APV. The contour detection algorithm of the Doppler console was used (FloMap, EndoSonics Corporation). If this algorithm failed, the measurements were traced on printouts and analyzed manually using SigmapScan Pro (Version 5.0, SPSS Inc). Three cardiac cycles were averaged at baseline and during maximum hyperemia. The comparison of automated and manual measurements in 15 arbitrary patients showed a difference <3%. The adenosine injection was repeated 3 times, and the average was used for further calculations.

During repeat angiography on the following day in 21 patients, the Doppler wire was advanced to an identical position, and the CFVR was determined as described above.

Measurement of Intracoronary Pressure
Twenty-seven patients were studied using additional intracoronary pressure recordings. A 0.014-inch wire mounted with a piezoelectric pressure sensor (PressureWire, RADI Medical) was advanced to the same position as the sensor of the Doppler guidewire. The wire was connected to a console that provided an analog output to the recording system of the catheterization laboratory. The aortic pressure, which was obtained from a transducer connected to the 7F guiding catheter, and the intracoronary distal pressure were recorded at a speed of 10 mm/s.

Particular care was taken to avoid artifacts by the guiding catheter, the pressure transducer position, and the selective intracoronary injection of adenosine.15 A nadir of the hemodynamic response to adenosine was observed within 15 s, and the minimum mean aortic and distal pressures after adenosine were determined. Because none of the patients had congestive heart failure, the central venous pressure was not determined, and FFR was calculated as the distal/aortic pressure.11 FFR was measured 3 times, and the average was used for further computation. A pullback of the pressure wire was not done because an intracoronary bolus was given instead of a continuous intravenous adenosine infusion.

Definition of Microvascular Dysfunction
The “normal” value of CFVR is a matter of dispute, but a cut off value of 2.0 is used in many studies.3 Patients with a TCO and a CFVR<2.0 were considered to show microvascular dysfunction in the absence of a residual epicardial lesion, and they were compared with those with a CFVR≥2.0.

Analysis of Left Ventriculography
Biplane left ventricular angiograms were obtained at the time of the diagnostic procedure before the PTCA and analyzed (Left Ventricular Analysis 1.1, Pie Medical Imaging). The regional wall motion was assessed by a consensus of 2 experienced investigators who were blinded to the Doppler data. It was graded as either normal/moderately hypokinetic or severely hypokinetic/akineti. Examples are shown in Figure 1.

Statistical Analysis
Data are given as the mean±SD. Changes between 2 consecutive measurements were evaluated by a paired t test. A Student’s paired t test or a χ2 test (when appropriate) were used to analyze differences between groups. The correlation coefficient between CFVR and FFR was calculated using a linear regression model. P<0.05 was considered significant. All calculations were done with SPSS for Windows (Version 10, SPSS Inc).

Results
Coronary Flow Immediately and 24 Hours After Recanalization
Doppler flow in the recanalized coronary artery after stent implantation was recorded 44±16 minutes after the first guidewire passage. The baseline APV was 29.6±15.8 cm/s, and the CFVR was 2.01±0.66. CFVR was <2.0 in 55% of all patients. Twenty-one patients were reexamined 19.3±3.8 hours after the recanalization. There were some individual changes in baseline and hyperemic APV and in CFVR, but mean values remained unchanged (Figure 2).

CFVR and FFR After Recanalization
The comparison of CFVR and FFR in the 27 patients is plotted in Figure 3. FFR was 0.85±0.08 after the recanalization. There was no correlation between CFVR and FFR. A CFVR<2.0 was observed in 16 of 27 patients (59%), but in 14 patients (52%), the FFR was ≥0.75. Two patients (7.7%) had both a CFVR<2.0 and a FFR<0.75. No patient showed a FFR<0.75 with a CFVR≥2. Both patients with a FFR<0.75 had diffuse atherosclerosis proximal to the occlusion. To limit the number of stents used, the proximal disease was not treated.

Patients With and Without Microvascular Dysfunction
FFR was similar in both groups. A CFVR<2.0 was associated with a higher baseline APV, whereas the hyperemic APV tended to be lower (Table 1). Patients with microvascular dysfunction more often had a history of hypertension; they also had a tendency toward more frequent diabetes and extensive coronary artery disease.

Influence of Diabetes and Hypertension
Twenty-nine patients (67%) with TCO had hypertension, diabetes, or both. The baseline APV was not significantly different among subgroups, but there was a trend toward a lower hyperemic APV and a lower CFVR in patients with diabetes and hypertension (Table 2). The baseline and hyperemic APV showed wide overlap in these groups, but the CFVR was significantly lower in patients with diabetes and/or hypertension compared with patients without a comorbidity (1.86±0.69 versus 2.36±0.45; P<0.05; Figure 4).

Influence of Regional Dysfunction
The area distal to the TCO was akinetic or severely hypokinetic in 24 patients (57%). This was related to a prior MI in 96% of these 24 patients. Only 33% of patients without regional dysfunction had a prior MI. Regional dysfunction was associated with a reduced left ventricular ejection fraction and a higher left ventricular end-diastolic pressure, but
there was no difference in baseline APV, hyperemic APV, or in CFVR (Table 3). The history of MI and the duration of the occlusion (>3 months or ≤3 months) had no influence on APV or CFVR.

Discussion

On the basis of a CFVR <2.0 and a FFR ≥0.75, half of the patients with TCO had evidence of microvascular dysfunction and/or diffuse atherosclerosis, which would impede the assessment of the angioplasty result by Doppler or pressure recordings.

Detection of Microvascular Dysfunction

A CFVR ≥2.0 predicts a negative stress test for myocardial ischemia,3,16 and it can be applied in clinical decision-making to defer angioplasty in patients with intermediate coronary lesions.17,18 A CFVR <2.0 was observed in only 12% of normal subjects, indicating dysregulation of the peripheral resistive arterioles (ie, microvascular dysfunction).19 To discriminate between epicardial and myocardial flow impairment, relative CFVR can be calculated; however, this measurement requires a normal reference vessel without stenosis.8,9 This approach is limited in patients with a TCO,

Figure 1. Top left, left ventriculography; bottom left, coronary angiogram before and after PTCA. Right, CFVR measurement. A, Data from a 59-year-old man with a circumflex occlusion that had been present for 6 months. He had severe global dysfunction and lateral akinesia (left anterior oblique view) and a CFVR of 2.4. B, Data from a 54-year-old woman with a right coronary occlusion that had been present for 1 year. She had normal regional function (right anterior oblique view) and a CFVR of 1.5.

Figure 2. Changes of baseline APV (left), hyperemic APV (middle), and CFVR (right) in TCO after recanalization (day 0) and 24 hours (day 1).

Figure 3. Simultaneous CFVR and FFR measurements in 27 patients after successful recanalization of TCO. The lines indicate the cut off values for CFVR (2.0) and FFR (0.75) in patients with hypertension and/or diabetes (●, n=19) and in those without a comorbidity (○; n=8).
TABLE 1. Patients With and Without Microvascular Dysfunction After PTCA of TCO

<table>
<thead>
<tr>
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<th>CFVR &lt;2.0</th>
<th>CFVR ≥2.0</th>
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<td>n</td>
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<td>Age, y</td>
<td>66.2±9.8</td>
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<td>Disease arteries, 1/2/3</td>
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<td>8/8/3</td>
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<tr>
<td>Duration of occlusion, &lt;3 mo</td>
<td>10/13</td>
<td>10/9</td>
<td>0.56</td>
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<td>Previous MI, %</td>
<td>74</td>
<td>63</td>
<td>0.46</td>
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<td>Angina pectoris, CCS class 1/2/3/4</td>
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<td>1/11/7/0</td>
<td>0.26</td>
</tr>
<tr>
<td>Heart failure, NYHA class 0/1/2/3/4</td>
<td>0/6/13/4/0</td>
<td>1/9/4/5/0</td>
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<tr>
<td>Ejection fraction, %</td>
<td>50.7±19.3</td>
<td>50.7±18.6</td>
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<td>Regional function, normal/akinetiC</td>
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<td>11/8</td>
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<td>LVEDP, mm Hg</td>
<td>10.0±4.2</td>
<td>11.3±7.1</td>
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<td>Mean aortic pressure, mm Hg</td>
<td>97±16</td>
<td>94±13</td>
<td>0.62</td>
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<td>Stent diameter, mm</td>
<td>3.2±0.5</td>
<td>3.1±0.4</td>
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<td>Multiple stents, %</td>
<td>39</td>
<td>53</td>
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<td>History of smoking, %</td>
<td>52</td>
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<td>Hypercholesterolemia, %</td>
<td>78</td>
<td>74</td>
<td>0.79</td>
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<tr>
<td>Diabetes, %</td>
<td>52</td>
<td>26</td>
<td>0.09</td>
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<tr>
<td>Hypertension, %</td>
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<td>42</td>
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<td>CFVR</td>
<td>1.53±0.24</td>
<td>2.60±0.53</td>
<td>&lt;0.001</td>
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<td>Baseline APV, cm/s</td>
<td>35.6±16.6</td>
<td>22.4±11.5</td>
<td>0.006</td>
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<td>Hyperemic APV, cm/s</td>
<td>53.5±23.9</td>
<td>58.2±31.5</td>
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<tr>
<td>FFR</td>
<td>0.82±0.08</td>
<td>0.87±0.07</td>
<td>0.10</td>
</tr>
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Values are mean±SD unless otherwise indicated.
CCS indicates Canadian Cardiovascular Society classification of angina; LVEDP, left ventricular end-diastolic pressure; and NYHA, New York Heart Association classification of heart failure.

who often have multivessel disease and no reference artery, and by the fact that microvascular function is not uniformly impaired in patients with coronary artery disease and MI.

Instead of the relative CFVR, we measured FFR because it does not require a reference artery.14,15 In patients with normal ventricular function, a FFR <0.75 predicts positive stress test results.11,21,22 The concept of FFR requires maximum peripheral vasodilation by pharmacological agents, which is impeded in patients with microvascular dysfunction or diffuse atherosclerosis. Diffuse disease along the length of a coronary artery may impair flow reserve and cause a longitudinal perfusion gradient.23 Under these conditions, the severity of epicardial lesions may be underestimated because the theoretical maximum pressure gradient during maximum flow cannot be achieved.10 From a clinical standpoint, as stated by Pijls et al, FFR would still represent the relative contribution of a residual epicardial lesion to total myocardial perfusion. The combination of a Doppler and pressure recording along the length of an epicardial coronary artery can assess the contribution of epicardial resistance, diffuse atherosclerosis, and microvascular dysfunction or some combination of these for myocardial flow impairment.

Microvascular Dysfunction in TCO

The prevalence of microvascular dysfunction in TCO was considerably higher than that reported in nonocclusive lesions, in which 20% of patients had a CFVR <2.0 after PTCA.5,6 Even with stents and intracoronary ultrasound-guided PTCA, CFVR remained impaired in 10% to 15% of patients, indicating microvascular dysfunction.9,24,25 These patients with microvascular dysfunction typically had an elevated baseline APV and increased microvascular resistance.26 Like in nonocclusive lesions, the impaired CFVR in patients with a TCO was associated with a high baseline APV. Baseline APV could also be influenced by diffuse atherosclerosis with lumen narrowing and involvement of the peripheral microvasculature.27 In fact, we observed a trend toward more multivessel disease in patients with a reduced CFVR, but no significant difference in the number of stents and vessel diameters.

Aside from differences in the extent of atherosclerosis, comorbidities such as diabetes and hypertension can contribute to microvascular dysfunction.7,26 In patients with a TCO, both conditions had a considerable influence on CFVR, because the majority of patients with a CFVR <2.0 (despite a FFR >0.75) had diabetes and/or hypertension (Figure 3). In contrast to a former study using PET in a small, selected group of patients with a non–infarct-related TCO,28 we did not observe a positive correlation between coronary flow

TABLE 2. CFVR in Diabetic and Hypertensive Patients

<table>
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<th>No Diabetes</th>
<th>Diabetes</th>
<th>P</th>
<th>No Hypertension</th>
<th>Hypertension</th>
<th>P</th>
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</thead>
<tbody>
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<td>17</td>
<td>...</td>
<td>17</td>
<td>25</td>
<td>...</td>
</tr>
<tr>
<td>Baseline APV, cm/s</td>
<td>29.8±16.7</td>
<td>29.3±14.9</td>
<td>0.93</td>
<td>26.9±15.5</td>
<td>31.5±16.1</td>
<td>0.37</td>
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<tr>
<td>Hyperemic APV, cm/s</td>
<td>60.9±31.9</td>
<td>47.8±16.9</td>
<td>0.09</td>
<td>58.7±32.4</td>
<td>53.5±23.8</td>
<td>0.55</td>
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<tr>
<td>CFVR</td>
<td>2.16±0.63</td>
<td>1.79±0.66</td>
<td>0.08</td>
<td>2.24±0.46</td>
<td>1.86±0.74</td>
<td>0.07</td>
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</table>

Values are mean±SD.
reserve and regional function. In our unselected study population, we observed patients with regional dysfunction and a CFVR $\geq 2.0$. However, we also had patients with normal ventricular function and a CFVR $< 2.0$ (Figure 1). In the former patients, the CFVR could be influenced by vasodilation of the collateral donor vessels, but the vasodilation may also identify patients with a preserved microvasculature and the potential for myocardial recovery. No improvement of CFVR occurred within 24 hours but, especially in patients with normal ventricular function, CFVR may improve within months, as reported in nonocclusive lesions.

Lesions in TCOs will contain organized thrombus, and distal embolization may cause a CFVR $< 2.0$. This was observed in acute MI, which lead to both a low baseline and a FFR $< 0.75$. Diffuse arterial narrowing, microvascular dysfunction, and a FFR $< 0.75$ may explain why a FFR $< 0.90$ was achieved in only 26% of TCOs, approximately half of the patients had a CFVR $\geq 2.0$ and a FFR $< 0.75$ due to microvascular dysfunction or diffuse disease.

In recent studies, CFVR $\geq 2.5$ or FFR $< 0.90$ were associated with a low adverse event rate after PTCA. These data were obtained in patients with nonocclusive lesions, predominantly single-vessel disease, and normal ventricular function; they are not applicable to patients with TCO, multivessel disease, and ventricular dysfunction. Diffuse atherosclerosis in TCO may cause an increased epicardial resistance and explain why a FFR $< 0.90$ was achieved in only 26% of patients. The need for more extensive stenting raises doubts about whether a FFR $< 0.90$ could be reached in a larger proportion of TCOs.

### Limitations of the Study

Adenosine was administered intracoronary. When care is taken to ensure selective intracoronary injection and a correct guiding catheter position, the hyperemic effect of intracoronary adenosine on coronary perfusion is comparable to that of intravenous adenosine. A pullback during continuous intravenous adenosine infusion would allow the assessment of serial epicardial lesions and diffuse atherosclerosis, which may add to the effect of microvascular dysfunction. With the short-acting intracoronary bolus, we could not perform such a pullback. The pressure and Doppler wires had been positioned distal to the occlusive lesion, and the FFR at this position should represent the sum of the epicardial resistance upstream. Although there was no angiographic evidence of lesions further downstream, possible residual epicardial resistance might have been missed. Nonetheless, the cut off values in our study seem relevant for TCO, because all patients with a CFVR $\geq 2.0$ were those who also had a FFR $< 0.75$ (Figure 3); although after angioplasty for the TCO, approximately half of the patients had a CFVR $< 2.0$ and a FFR $< 0.75$ due to microvascular dysfunction or diffuse disease.

### Clinical Implications

Microvascular dysfunction is frequent in TCOs and is not related to regional myocardial function. Microvascular dysfunction impedes the assessment of the PTCA result (which is done by intracoronary Doppler and pressure recordings) in TCOs, which is of relevance in these often extensively diseased segments. The reduced CFVR in $> 50\%$ of lesions was not explained by a residual epicardial lesion, as shown by a FFR $< 0.75$. Diffuse arterial narrowing, microvascular dysfunction, and the additional influence of diabetes and hypertension accounted for the reduced CFVR. Both Doppler and pressure recordings, the latter information enhanced by a pullback along the entire length of the coronary artery, are required to assess the relative contribution of residual stenosis, diffuse arterial narrowing, and microvascular dysfunction to impaired myocardial flow in patients with angiographically successful PTCA of TCO. Future studies should focus on the

<table>
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<th>TABLE 3. Patients With and Without Regional Dysfunction</th>
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<tr>
<td>n</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Disease arteries, 1/2/3</td>
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<tr>
<td>Duration of occlusion, ≤/&gt;3 mo</td>
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<td>Previous MI, %</td>
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<td>FFR</td>
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clinical relevance of physiological measures of coronary flow reserve in patients with microvascular dysfunction.

References


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