Frame Count Reserve

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Background—The Doppler wire–derived (relative) coronary flow velocity reserve (CVR) that is used to evaluate functional significance of a coronary stenosis is a well-established method.1 In absence of coronary stenosis, CVR can also be used to evaluate microvascular function.2,3 By comparing CVR of a coronary artery with stenosis to CVR of a normal reference vessel, relative coronary flow velocity reserve (rCVR) is calculated. This corrects for influence of microvascular dysfunction.4,5 CVR >2.0 and rCVR >0.65 are considered appropriate cutoff values to defer angioplasty (percutaneous coronary intervention [PCI]).6,7 Because of the need of an intracoronary Doppler wire and dedicated equipment, only an experienced cardiologist in an interventional catheterization laboratory can perform these measurements. In daily practice, nevertheless, intermediate coronary stenoses of uncertain significance are often encountered during diagnostic angiography. Therefore, an angiographic method to estimate (relative) coronary flow reserve would be very useful.

Although TFC is an index of basal flow velocity, during pharmacologically induced hyperemia, it becomes an index of hyperemic flow velocity. By dividing both counts, an estimate of coronary flow velocity reserve is made. This study was done to compare this (relative) frame count reserve [(r)FCR] with (r)CVR. In addition, with the length of the coronary arteries measured with an intracoronary guidewire,14 frame count velocity (FCV) was calculated and compared with APV determined with the Doppler wire.

Methods

Patients

In 38 selected patients referred for diagnostic coronary angiography or PCI for stable angina, FCR and CVR were calculated for both left anterior descending (LAD) and left circumflex coronary artery (LCx). At least 1 of these 2 vessels was normal (visually no stenosis >50%), and all vessels had TIMI 3 flow. In the case of PCI, measurements were repeated thereafter. No patient had left main stenosis >30%, history of obstructive pulmonary disease, or myocardial infarction in the territory of the left coronary artery, and all patients had sinus rhythm. The Medical Ethics Committee of the

To assess functional significance of a coronary stenosis, intracoronary Doppler wire–derived coronary flow velocity reserve (CVR) is a well-established method.1 In absence of coronary stenosis, CVR can also be used to evaluate microvascular function.2,3 By comparing CVR of a coronary artery with stenosis to CVR of a normal reference vessel, relative coronary flow velocity reserve (rCVR) is calculated. This corrects for influence of microvascular dysfunction.4,5 CVR >2.0 and rCVR >0.65 are considered appropriate cutoff values to defer angioplasty (percutaneous coronary intervention [PCI]).6,7 Because of the need of an intracoronary Doppler wire and dedicated equipment, only an experienced cardiologist in an interventional catheterization laboratory can perform these measurements. In daily practice, nevertheless, intermediate coronary stenoses of uncertain significance are often encountered during diagnostic angiography. Therefore, an angiographic method to estimate (relative) coronary flow reserve would be very useful.

Some investigators have found good correlation between CVR and (digital subtraction) angiographic estimation of myocardial perfusion,4,6-11 but these 2 methods are essentially different. The TIMI frame count (TFC) is an inverted index of coronary flow velocity that correlates with Doppler wire–derived average peak velocity (APV),12 and it can be used online if angiography is recorded digitally. However, only 1 study investigated the use of TFC as an estimation of coronary flow velocity reserve.13

CVR and (digital subtraction) angiographic estimation of coronary flow reserve would be very useful. Therefore, an angiographic method to estimate (relative) coronary flow reserve would be very useful.
hospital of the Free University Amsterdam, the Netherlands, approved the protocol. All patients gave written informed consent.

**Procedure**

One operator (M.S.), using 7F guiding catheters without side holes (Guidant) and ionic contrast agent (Hexabrix, Guerbet), performed all procedures. At the beginning of the procedure, an intravenous bolus of heparin (5000 IU) was given. In all but 1 case of PCI, a stent (Guidant) and ionic contrast agent (Hexabrix, Guerbet), performed by manual injection through the contrast-filled guiding catheter, synchronized to an acoustic heart beat signal. It was performed at least 10 minutes after last balloon inflation and 2 minutes after last contrast injection to prevent reactive hyperemia attributable to ischemia or contrast agent.

**Protocol and Calculations**

After positioning the Doppler wire in a normal segment of LAD or LCx, as proximal as possible but >2 cm distal to the culprit lesion if present, basal average peak velocity (APV) was recorded together with blood pressure and heart rate. Angiography was performed for basal TFC of both vessels. Hyperemia was induced by adenosine, 140 μg/kg per min intravenously for at least 3 minutes. Hyperemic APV was recorded, and contrast injection for hyperemic TFC was given. The Doppler wire was then repositioned in the ipsilateral vessel with recording of hyperemic APV, after which adenosine was stopped. More than 3 minutes later, basal APV of this vessel was recorded.

CVR was determined by dividing hyperemic by basal APV. With the digitally numbered frames, TFC was calculated as described before. FCR was calculated by dividing basal by hyperemic TFC.

Relative CVR and rFCR were determined by the ratio of the reserve of LCx and LAD.

The frames between the last QRS complex and the first frame of the TFC were counted. By dividing this number by 25 (frames/s), an estimate was made of the beginning of the contrast injection in relation to the phase of the cardiac cycle.

Length of both coronary arteries was measured by using the Doppler or regular guidewire, as described by Gibson et al. The distal end of the guidewire was placed 1 to 3 mm in the distal landmark, marked outside the proximal end of the guiding catheter, then pulled back until 1 to 3 mm was still visible outside the distal end of the guiding catheter and marked again. The measured distance between the 2 marks was used to estimate the length of the coronary artery from the tip of the guiding catheter to the landmark used for the TFC. By multiplying this length by 25/TFC, FCV was calculated.

The diameter of the proximal segment of the coronary artery and the percentage stenosis of the target lesion if present was calculated by quantitative coronary angiography as the mean of 2 orthogonal measurements using the contrast-filled catheter as reference diameter. Coronary volume flow was estimated by the following equation:

\[
\text{flow (mL/min)} = \text{FCV (cm/s)} \times 60 \times \pi \times \text{diameter}^2
\]

A coronary vascular resistance index (mm Hg per mL/min) was calculated by dividing mean arterial blood pressure by coronary flow, assuming right atrium pressure was zero.

**Statistical Analysis**

For statistical analysis, Student’s unpaired t-test and linear regression analysis (SPSS 9.0) were used. All continuous variables are expressed as mean±1 SD with their range. P<0.05 was considered statistically significant.

**Results**

In 9 patients, both LAD and LCx were normal; in 11 patients, there was visually no significant (<50%) stenosis in LAD and LCx; and in 13 patients, either the proximal LAD (8

**TABLE 1. Baseline and Procedure Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Basal</th>
<th>Hyperemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>38</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.9±8.3 (34.2 to 73.3)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>68.4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>47.4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>65.8</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>31.6</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>β-Blocker use, %</td>
<td>71.1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LAD (n=35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>3.2±0.6 (2.2 to 4.8)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Length, cm</td>
<td>14.3±1.6 (9.5 to 18.0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Stenosis, % (n=7)</td>
<td>70.9±11.2 (59.0 to 90.7)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LCx (n=35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>3.3±0.6* (2.3 to 4.1)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Length, cm</td>
<td>11.4±1.6‡ (7.2 to 15.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Stenosis, % (n=5)</td>
<td>68.2±19.3* (41.4 to 86.6)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>...</td>
<td>100.7±10.8 (76 to 125)</td>
<td>93.4±10.4‡ (71 to 115)</td>
</tr>
<tr>
<td>Heart rate, per min</td>
<td>...</td>
<td>67.4±9.0 (42 to 87)</td>
<td>76.3±9.9‡ (60 to 101)</td>
</tr>
<tr>
<td>QRS to first frame, s</td>
<td>...</td>
<td>0.38±0.09 (0.16 to 0.6)</td>
<td>0.36±0.08* (0.08 to 0.52)</td>
</tr>
</tbody>
</table>

*P=not significant for LCx vs LAD and hyperemic vs basal.
†P<0.001 for LCx vs LAD.
‡P<0.005 for hyperemic vs basal.
patients) or proximal LCx (5 patients) had significant stenosis for which angioplasty was thought appropriate. In 5 patients with intermediate (50% to 70%) lesions, PCI was deferred because of CVR >2.0 and rCVR >0.65. In 2 patients, the study protocol was terminated early, 1 because of advanced atrioventricular block during adenosine infusion and 1 because of damping of the pressure signal of the guiding catheter during hyperemia. Final analysis consisted of 96 flow velocity reserve measurements performed in 38 patients.

Characteristics
Baseline and procedure characteristics are listed in Table 1. In 4 patients, the length of LAD (3 patients) or LCx (3 patients) was not measured, mainly because of severe tortuosities. Most patients used β-blockers. The LAD was significant longer by a factor of 1.3 compared with the LCx (mean, 14.3 ± 1.6 cm versus 11.4 ± 1.8 cm, P <0.001), whereas there were no differences in diameter of proximal segments (mean 3.2 ± 0.6 mm versus 3.3 ± 0.6 mm) and percentage stenosis of the target lesion. During hyperemia, there was significant decrease in blood pressure (mean 100.7 ± 10.8 to 93.4 ± 10.4 mm Hg, P <0.005) and significant increase in heart rate (mean 67.4 ± 9.0 to 76.3 ± 9.9/min, P <0.005). The mean time interval between last QRS complex and first frame included in the TFC was 370 ± 9 ms. The mean difference between basal and hyperemic injection in relation to the cardiac cycle was 0.07 ± 0.06 seconds.

Measurements
The results of 48 paired (both LAD and LCx) measurements are displayed in Table 2, consisting of 38 patients with repeated protocol after PCI in 10 cases. The values of FCV, volume flow, and resistance index were derived from 44 paired measurements. In 3 vessels, CVR was not measured because the Doppler wire was not repositioned in the nontarget vessel after PCI. TFC of LAD was significantly higher than TFC of LCx (basal 32.5 ± 15.1 versus 23.6 ± 9.1 and hyperemic 12.1 ± 6.6 versus 8.7 ± 3.2, both P <0.02), but there were no significant differences in mean basal and hyperemic flow velocity, flow velocity reserve, volume flow, and resistance index between the vessels. Mean FCR and rFCR did not differ significantly from mean CVR and rCVR.

The results of 30 paired (both LAD and LCx) measurements concerning only coronary arteries without visually significant (<50%) stenosis are listed in Table 3, consisting of 20 patients without significant stenosis at baseline and 10 paired measurements after PCI. Again, TFC of LAD was significant higher than TFC of LCx (basal 35.1 ± 17.0 versus 25.1 ± 9.5 and hyperemic 10.3 ± 3.6 versus 8.3 ± 2.7, both P <0.02), without significant differences in mean basal and hyperemic flow velocity, flow velocity reserve, volume flow, and resistance index between the 2 vessels. As in the total group, mean FCR and rFCR did not differ significantly from mean CVR and rCVR.

Discussion
In this study, the FCR, an angiographic method using TIMI frame count to estimate coronary blood flow velocity reserve, was compared with Doppler wire–derived CVR. The results demonstrate strong correlation between (r)FCR and (r)CVR.
There were no significant differences between mean (r)FCR and mean (r)CVR.

In contrast to normal basal flow velocity, when the coronary artery is usually filled with contrast in >1 complete cycle of the heart (including systole with relative low flow velocity), high coronary flow velocity during hyperemia can cause contrast filling within 1 diastole (with relative high flow velocity). This will result in an augmented FCR compared with CVR in which peak flow velocity is averaged during diastole as well as systole. This can explain the fact that the correlation of FCR and CVR is not so good in the range of high (>3.0) flow velocity reserve compared with low (<3.0) flow velocity reserve, as shown in Figure 1. Low heart rate with relatively more influence from diastole can contribute to this effect, but in this study population, heart rate during hyperemia was higher compared with basal heart rate. In addition, the influence of the moment of contrast injection in relation to the cardiac cycle is more important in case of low TFC (high flow velocity or relative short vessels) compared with high TFC. Because CVR of 2.0 is used as cutoff value, the weaker correlation of values >3.0 has few clinical implications.

The correlation of rFCR and rCVR is stronger also in high values, as is shown in Figure 2, because differences in methods of flow velocity assessment are partially normalized, just like influence of microvascular resistance.

**Comparison With Previous Studies**

The findings are in accordance with the study by Manginas et al., the only other study comparing the TIMI frame count method to CVR. In that study, contrast agent was also

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**TABLE 3. Procedural Results, No Stenosis >50%**

<table>
<thead>
<tr>
<th>Artery/Variable</th>
<th>Basal</th>
<th>Hyperemic</th>
<th>Flow Velocity Reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (n=30)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TFC</td>
<td>35.1±17.0 (13 to 78)</td>
<td>10.3±3.6 (5 to 21)</td>
<td>FCR: 3.4±1.3* (1.9 to 7.6)</td>
</tr>
<tr>
<td>FCV, cm/s</td>
<td>12.5±5.3 (4.5 to 26.7)</td>
<td>38.3±10.8 (16.9 to 63.5)</td>
<td></td>
</tr>
<tr>
<td>APV, cm/s</td>
<td>22.3±9.5 (5.7 to 38)</td>
<td>65.7±22.8 (21 to 121)</td>
<td>CVR: 3.2±0.9* (1.9 to 5.3)</td>
</tr>
<tr>
<td>Flow, mL/min</td>
<td>65.7±35.2 (20.1 to 169.3)</td>
<td>209.1±95.4 (70.4 to 395.1)</td>
<td></td>
</tr>
<tr>
<td>Resistance index, mm Hg/min per mL</td>
<td>2.0±1.1 (0.6 to 5.4)</td>
<td>0.6±0.4 (0.2 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>LCx (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFC</td>
<td>25.1±9.5‡ (12 to 60)</td>
<td>8.3±2.7‡ (4 to 14)</td>
<td>FCR: 3.2±1.0* (1.5 to 5.4)</td>
</tr>
<tr>
<td>FCV, cm/s</td>
<td>12.7±3.6‡ (6.2 to 22.1)</td>
<td>37.6±10.3‡ (22.3 to 61.9)</td>
<td></td>
</tr>
<tr>
<td>APV, cm/s</td>
<td>19.1±7.4‡ (8.3 to 35)</td>
<td>54.1±21.2‡ (27 to 102)</td>
<td>CVR: 2.9±0.7* (1.9 to 4.7)</td>
</tr>
<tr>
<td>Flow, mL/min</td>
<td>71.8±34.4† (27.2 to 161.5)</td>
<td>214.3±102.8† (63.2 to 478.2)</td>
<td></td>
</tr>
<tr>
<td>Resistance index, mm Hg/min per mL</td>
<td>1.8±0.9† (0.5 to 3.6)</td>
<td>0.6±0.3† (0.2 to 1.6)</td>
<td></td>
</tr>
<tr>
<td>LAD+LCx (n=60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCV, cm/s</td>
<td>12.6±4.5 (4.6 to 26.7)</td>
<td>38.0±10.5 (16.9 to 63.5)</td>
<td>FCR: 3.3±1.1* (1.5 to 7.6)</td>
</tr>
<tr>
<td>APV, cm/s</td>
<td>20.7±8.6 (5.7 to 38)</td>
<td>59.9±22.6 (21 to 121)</td>
<td>CVR: 3.1±0.8* (1.9 to 5.3)</td>
</tr>
</tbody>
</table>

*P=not significant for rFCR vs rCVR and LCx vs LAD.
†P=not significant for LCx vs LAD.
‡P<0.02 for LCx vs LAD.

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**Figure 1.** Relation between FCR and CVR, n=96 measurements.

**Figure 2.** Relation between rFCR and rCVR, n=45 measurements.
injected manually, but adenosine was given by intracoronary injection. However, because of the short half-life time of adenosine, it is difficult to inject the agent consistently in the maximal hyperemic phase. With intravenous adenosine, a steady state of hyperemia can be obtained, making it possible to inject contrast during maximal hyperemia and easier to synchronize injection to the cardiac cycle, resulting in a more accurate hyperemic TFC. As pointed out by Abaci et al., the phase of the cardiac cycle in which the contrast agent is injected has important influence on TFC. In the present study, there were only small differences in the timing of contrast injections, beginning at or near the end of the T wave, just before diastole.

The FCR using intracoronary adenosine was measured in a trial evaluating eptifibatide, and it correlated highly with digital subtraction angiographic reserve ($r=0.76, P<0.001$). All TFC (but not the ratios) found in the present European study can only be compared with US studies after being multiplied by a factor of 1.2 to convert to a frame rate of 30 per second. To the best of our knowledge, this is the first study to measure relative FCR and compare it with relative CVR.

**Flow Velocity Measurements**

A comparison between FCV and APV is complex. With the Doppler wire, peak blood flow velocity is measured locally, averaged during 2 cycles of the heart. It has to be converted to a mean velocity, compensating for lower blood flow velocity near the vessel wall. This can be done by multiplying APV by a factor of 0.5 or by using the velocity integral. Because in normal coronary arteries there are no significant differences in proximal and distal flow velocity, additional correction should not be necessary. However, segments in which Doppler measurements are performed are not always completely normal because angiography is often not sensitive enough to show diffuse lumen narrowing causing flow velocity acceleration or a positive remodeled vessel segment with possible influence on flow velocity assessment. In addition, in stenosed arteries, flow velocity can be higher proximal to the lesion compared with distal because of proximal side branches. This will influence FCV but not distal APV. Finally, length of the coronary artery measured with the guidewire and thus FCV can be underestimated because the wire takes the shortest way along the curves of the vessel. As discussed above, FCV can be overestimated when flow velocity is so high that contrast filling of the coronary artery takes place only in diastole. Figure 3 shows the good correlation between FCV and APV ($r=0.75, P<0.001$). In this population the ratio of mean APV and FCV was 0.63.

**Comparison Between LAD and LCx**

Basal and hyperemic TFCs of LAD were significantly higher compared with LCx (basal 32.5±15.1 versus 23.6±9.1 and hyperemic 12.1±6.6 versus 8.7±3.2, both $P<0.02$). The ratio of TFC of LAD and LCx is 1.4, whereas the ratio of length of both vessels is 1.3. This is less than the factor of 1.7 used to adjust TFC of LAD to derive the corrected TFC because the latter was corrected to mean TFC of both LCx and right coronary artery. In the present study, after adjusting TFC to the specific length of the artery, all basal and hyperemic mean blood flow velocity measurements were equal in both vessels. In addition, there were no significant differences in FCR and CVR of LAD compared with LCx. Because the proximal vessel diameter of both vessels was the same, there were also no differences in mean volume flow and resistance index.

**Measurements in Nonsignificant Diseased Vessels**

Table 3 shows the results of measurements in coronary arteries with visually no stenosis >50%. Mean normal basal FCV of LCA is 12.6±4.5 cm/s and hyperemic 38.0±10.5 cm/s, without differences between LAD and LCx. With this method, estimated volume flow of the LCA is basal 137.5±69.6 and 423.4±198.2 mL/min during hyperemia. However, above-mentioned considerations concerning FCV also apply here. In addition, these results cannot be interpreted as completely normal values because some of these patients had possible microvascular dysfunction (hypertension, dyslipidemia), causing lower hyperemic flow velocity with lower flow velocity reserve. Moreover, in 10 patients, measurements were also performed after PCI. Mean basal FCV after angioplasty was borderline significantly higher compared with the total group (15.8±5.2 versus 12.6±4.5 cm/s, $P=0.032$), causing a (not significant) lower FCR (2.7±1.1 versus 3.3±1.1). This is in accordance with previous studies in which high basal flow velocity after angioplasty and stenting sometimes persisted for longer than 10 minutes after the procedure because of persistent low microvascular resistance. Finally, a visual stenosis of <50% can sometimes unexpectedly prove to be functionally significant, and nonsignificant but diffuse epicardial stenosis can cause so much resistance that it impairs flow velocity reserve.

![Figure 3. Relation between FCV and APV, n=174 measurements.](image-url)
Limitations
All procedures were done by a single operator using manual contrast agent injections. Because timing of injection in relation to the phase of the heart cycle is important, it was synchronized to an acoustic heart beat signal. To do this, a basic sense of rhythm is needed. An alternative is the use of an ECG-triggered mechanical injector, but that was not done in this study because diagnostic coronary angiography is usually performed with manual injections. In addition, it has been shown that the impact of the injection rate on the TFC is only minor.

During adenosine infusion, there was a limited but significant drop in blood pressure with an increase in heart rate, as has been described by others. Therefore, hyperemic APV and FCV and thus flow velocity reserve were possibly underestimated.

All measurements were done in LAD and LCx. It is likely but not certain that these results are applicable to the right coronary artery.

The study population consisted of patients who were asymptomatic or had stable angina. Therefore, results may not be applicable to patients with acute coronary syndromes, for example, because flow in normal reference vessels can be impaired.

Conclusion
This study shows that the FCR and rFCR can provide a good estimate of CVR and rCVR. This relative simple, fast, and inexpensive angiographic method can be used during diagnostic catheterization to assess functional significance of a coronary stenosis and, in absence of coronary stenosis, to evaluate microvascular function.

References