Noninvasive Determination of Coronary Blood Flow Velocity With Cardiovascular Magnetic Resonance in Patients After Stent Deployment

Eike Nagel, MD; Thomas Thouet; Christoph Klein, MD; Simon Schalla, MD; Axel Bornstedt, PhD; Bernhard Schnackenburg, PhD; Jürgen Hug, MD; Ernst Wellnhofer, MD; Eckart Fleck, MD

**Background**—In patients with coronary artery stents, no direct noninvasive coronary artery imaging is possible with magnetic resonance (MR). A well-established method for the assessment of the functional significance of a coronary lesion is the measurement of coronary flow reserve by invasive intracoronary Doppler. The purpose of the study was to determine coronary flow velocity reserve (CFVR) with MR after stent deployment.

**Methods and Results**—Thirty-eight patients after successful PTCA and stent deployment were included. CFVR was measured perpendicular to the artery distal to the stent using phase-contrast velocity quantification at rest and during adenosine-stimulated hyperemia with a 1.5T MR tomograph (ACS NT, Philips). Measurements were repeated after 3 months and compared with invasive coronary angiography. In 18 patients, additional invasive Doppler flow measurements were obtained. CFVR could be determined in 29 of 38 (76%) of the patients. After 3 months, significant differences were obtained between coronary arteries with and without restenosis. Using a threshold of 1.2, a sensitivity of 83% with a specificity of 94% was achieved for ≥75% stenoses. CFVR with CMR was similar to Doppler results (r=0.87), with a mean relative difference of 7.5%.

**Conclusions**—In patients with preserved coronary microcirculating vasoreactivity that are suitable for MR coronary angiography and flow assessments, CMR measures of coronary blood flow velocities reserve may be used to detect in-stent restenosis. (*Circulation*. 2003;107:1738-1743.)

Key Words: magnetic resonance imaging ■ coronary disease ■ angiography ■ restenosis

Even though stents do not prohibit cardiovascular magnetic resonance (MR) examinations at 1.5 Tesla,1 no direct visualization of the coronary arteries is possible after stent placement because of artifacts induced by the metallic stents.2 In these patients, an assessment of the stents may be possible with the direct determination of coronary artery blood flow velocities using MR flow measurements. Such measurements would not only serve to determine whether an in-stent restenosis has occurred but also to assess its hemodynamic relevance.

The aims of the present study were to evaluate the feasibility of MR phase-contrast flow measurements for the noninvasive assessment of intracoronary blood flow velocity reserve after stent deployment, to determine its accuracy for the detection of restenosis, and to compare the results to invasive Doppler flow measurements.

**Methods**

**Patients**

After approval of the study from the institutional review committee, 38 patients (29 males and 9 females, age 63±10 years) with clinically indicated stent deployment in the left anterior descending coronary artery (LAD) or the right coronary artery (RCA) were prospectively included in the study after obtaining informed consent. Patients with diabetes, cardiac arrhythmias, left ventricular hypertrophy, and previous myocardial infarction or wall motion abnormalities at rest were excluded from the study to guarantee a homogeneous patient population. Patients were ineligible for enrollment if they had a contraindication for adenosine (heart block or reactive respiratory disease) or MR (pacemaker, intracranial metal, claustrophobia, or obesity >150 kg) or were medically unstable.

**Coronary Angiography**

All patients underwent biplane left-sided cardiac catheterization and selective coronary angiography in Judkin’s technique before and after stent deployment as well as after 3 months, as routinely done in our institution. Coronary stenoses were filmed in the center of the field from multiple projections, avoiding as much as possible overlap of side branches and foreshortening of relevant coronary stenoses. Quantitative assessment was performed using quantitative coronary angiography (QANSAD QCA System; ARRI Munich) by an experienced observer blinded to the results of the MR examination. Coronary arteries were graded as having a 50% to 74% cross-sectional area reduction or a ≥75% cross-sectional area reduction with respect to prestenotic segment area.

**Coronary Angiography**

All patients underwent biplane left-sided cardiac catheterization and selective coronary angiography in Judkin’s technique before and after stent deployment as well as after 3 months, as routinely done in our institution. Coronary stenoses were filmed in the center of the field from multiple projections, avoiding as much as possible overlap of side branches and foreshortening of relevant coronary stenoses. Quantitative assessment was performed using quantitative coronary angiography (QANSAD QCA System; ARRI Munich) by an experienced observer blinded to the results of the MR examination. Coronary arteries were graded as having a 50% to 74% cross-sectional area reduction or a ≥75% cross-sectional area reduction with respect to prestenotic segment area.

Received November 13, 2002; revision received January 16, 2003; accepted January 16, 2003.

From the Department of Internal Medicine/Cardiology, German Heart Institute, Berlin, and Philips Medical Systems (B.S.), Hamburg, Germany.

Dr Nagel received grant support from Philips Medical Systems, Best, the Netherlands, and Dr Schnackenburg is an employee of Philips Medical Systems, Hamburg, Germany.

Correspondence to Eike Nagel, MD, Internal Medicine/Cardiology, German Heart Institute, Augustenburger Platz 1, D-13353 Berlin, Germany. E-mail eike.nagel@dhzb.de

© 2003 American Heart Association, Inc.

*Circulation* is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000060542.79482.81
In vitro measurements of stent artifacts yielded a maximal artifact size exceeding stent size by 10 mm (5 mm each side). In vitro measurements in our institution showed that flow measurements should not be influenced if their distance to the stent doubles the distance of the visible artifact. Thus, measurements were performed perpendicular to the vessel, 5 mm distal to the stent artifact (Figure 1) at rest and during an adenosine-induced hyperemia, applying the identical stress protocol as for the invasive procedure. This position should be very close to the position of the invasive Doppler measurements, because it is well defined by the stent position.

Magnetic Resonance Flow Measurements

**Image Acquisition**

Patients were examined with a 1.5-Tesla whole-body MR tomograph (ACS NT, Philips) using a dedicated phased-array cardiac surface coil (5 elements) 24 hours and 3 months after stent deployment. After a rapid survey, transversal slices were acquired in breath hold technique during expiration to localize the coronary arteries. In these images, the position of the stent could be easily determined because of the artifacts induced by the stents. Double-angulated slices, which included a long segment of the vessel, were acquired (Figure 1). In vitro measurements of stent artifacts yielded a maximal artifact size exceeding stent size by 10 mm (5 mm each side). In vitro measurements in our institution showed that flow measurements should not be influenced if their distance to the stent doubles the distance of the visible artifact. Thus, measurements were performed perpendicular to the vessel, 5 mm distal to the stent artifact (Figure 1) at rest and during an adenosine-induced hyperemia, applying the identical stress protocol as for the invasive procedure. This position should be very close to the position of the invasive Doppler measurements, because it is well defined by the stent position.

**Table 1: Patient Characteristics**

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>n</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>33</td>
<td>87</td>
</tr>
<tr>
<td>Hypercholesterinemia</td>
<td>32</td>
<td>84</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>32 (LVH: exclusion criterion)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>0 (exclusion criterion)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>0</td>
<td>0 (exclusion criterion)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>18</td>
<td>47</td>
</tr>
</tbody>
</table>

**Medication**

- Aspirin: 33 (87%)
- Statins: 33 (87%)
- β-Blocker: 28 (74%)
- Nitrates: 27 (71%)
- ACE inhibitor: 18 (47%)
- Calcium antagonists: 6 (16%)

A segmented k-space phase-contrast turbo gradient echo technique with symmetric bipolar gradient pulses⁶ with a spatial resolution of 1×0.9×4 mm and a temporal resolution of 45 ms (TE/TR/flip: 6.9 ms/11.5 ms/40°; 4 k-lines per phase per heartbeat) was used. To improve signal to noise ratio, 2 acquisitions were performed and the resulting signal was averaged. Breathing artifacts were reduced by prospective navigator gating with adaptive motion correction (gating window: 5 mm). The imaging sequence was adapted to the actual diaphragmatic position in real time. This correction was performed by shifting the cranio-caudal imaging position by 30% of the actual diaphragmatic offset.⁶

**Image Analysis**

Readers blinded to each technique performed analysis of the MR images and Doppler results. Regions of interest with an area of 2x2 mm² were placed in the center of the vessel on the flow images for each cardiac phase. The region of interest was shifted in each phase to include the 4 voxels with the fastest average flow velocity. The average flow velocity (cm/s) of this region of interest was determined for each phase. To correct for cardiac through plane motion and eddy currents, a region of interest was placed on adjacent myocardium and the velocity of myocardial through plane motion was determined and subtracted from the intracoronary flow values. The highest value was used for the determination of peak flow velocity. CFVR was calculated as the ratio of peak flow velocity during maximal hyperemia to baseline peak flow velocity.

**Statistical Analysis**

All data are given as mean±1 SD. ANOVA was used to detect differences between groups of different stenosis severity. Significance was tested with a Scheffé procedure. A 2-tailed Student’s t test was used to calculate statistical differences, with P<0.05 being regarded as statistically significant. Comparison between results from Doppler and CMR was performed using the Bland-Altman analysis and a linear regression analysis.

**Results**

Patient characteristics and hemodynamic data are listed in Tables 1 and 2.

**Invasive Procedures**

Stent placement was successfully performed in 25 LAD and 13 RCA vessels ranging from 1.40 to 3.9 mm distal reference.
diameter (mean, 2.50 mm). At 3 months of follow-up, 14 vessels (37%) showed a restenosis of ≥75% cross-sectional area reduction in the invasive coronary angiography. Ten vessels (26%) showed a 50% to 74% cross-sectional area reduction.

### MR Measurements

In 29 of the 38 patients (76%), adequate flow measurements could be obtained distal to the stent. In 4 patients no adequate placement of the imaging plane without a major vessel branch leaving the target vessel could be obtained, in 4 patients image quality did not allow to detect a flow signal, and in 1 patient severe shortness of breath developed during adenosine infusion. Examination time was ≈45 to 60 minutes (3 to 5 minutes for each flow measurement depending on navigator efficiency).

Maximal flow velocity at rest was 66±13 cm/s (LAD) and 37±9 cm/s (RCA). During adenosine stimulation, maximal flow velocity was 121±30 cm/s (LAD) and 70±15 cm/s (RCA), resulting in a mean CFVR of 1.82±0.22 (LAD) and 1.90±0.4 (RCA) (Figure 1).

At follow-up, CFVR of 1.78±0.16 was found in vessels without coronary artery stenosis, 1.46±0.22 in vessels with 50% to 74% cross-sectional area reduction, and 1.10±0.22 in vessels with ≥75% cross-sectional area reduction (P between all groups <0.05).

The diagnostic accuracy of CFVR measurements is shown in Table 3. No overlap was found between vessels without (<50% cross-sectional area reduction) and vessels with ≥75% cross-sectional area reduction; however, vessels with 50% to 74% cross-sectional area reduction showed overlap with both other groups (Figure 2).

### Comparison of MR and Doppler

Flow velocity measurements with the Doppler flow wire resulted in 79±20 cm/s (LAD) and 40±6 cm/s (RCA). After adenosine stimulation, flow velocities were 147±36 cm/s (LAD) and 80±21 cm/s (RCA), resulting in a mean CFVR of 1.88±0.25 (LAD) and 2.0±0.48 (RCA).

Regression analysis for CFVR determined with CMR and Doppler resulted in a slope of 0.74 (r=0.89) at rest and 0.80 (r=0.93) during stress (Bland-Altman analysis in Figure 4). For CFVR, the correlation yielded a slope of 1.04 (r=0.87) (Bland-Altman analysis in Figure 3). The mean relative error of MR CFVR measurements versus Doppler was 7.5±5.0%.

### Discussion

The present study demonstrates that the determination of coronary blood flow velocity and coronary flow velocity reserve with CMR is feasible after stent placement, and the results for CFVR are similar to results from invasive Doppler measurements.

In-stent restenoses are a major problem, and innumerable attempts have been suggested to avoid this drawback. Because all noninvasive tests, such as ECG, SPECT, or EBCT, are relatively insensitive and nonspecific for the detection of restenoses, many of these patients undergo invasive coronary angiography to identify restenosis in recurrent chest pain. In some centers, invasive routine follow-up is performed after stent placement to be able to treat restenosis at an early time point. With CMR, the noninvasive imaging of the proximal and medial coronary arteries becomes more and more feasible; however, the artifacts after stent placement prohibit CMR imaging within the stent. It has been shown to be safe and feasible to measure flow ≈1 cm distal to the stent using phase-contrast techniques, which have been well established and validated for larger vessels. Good accuracy and reproducibility of MR flow measurements have also been shown in small-caliber phantoms or coronary arteries in animals, with close correlations with intravascular and extravascular Doppler techniques despite the complexity of such measurements in small and rapidly moving vessels. Previous investigators have used breath hold techniques to reduce breathing artifacts, which limits the maximal scan duration to 30 seconds or less. Whereas with this approach data can be acquired rapidly and breathing motion artifacts can be well suppressed, a low temporal resolution has to be accepted. Accordingly, in these previous studies the number of heart phases ranged from 1 to 6 and was only increased by calculating interleaved data (view sharing). In 1993, Edelman et al demonstrated for the first time that blood flow velocity can be determined noninvasively in human coronary arteries with MR; however, only a single

### Table 2: Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>CMR</th>
<th>Doppler</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (rest), bpm</td>
<td>72±14</td>
<td>69±12</td>
<td>NS</td>
</tr>
<tr>
<td>HR (stress), bpm</td>
<td>84±15</td>
<td>79±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RRsyst (rest), mm Hg</td>
<td>137±14</td>
<td>134±14</td>
<td>NS</td>
</tr>
<tr>
<td>RRsyst (stress), mm Hg</td>
<td>133±14</td>
<td>132±12</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 3: Diagnostic Value of Coronary Flow Velocity Reserve for the Detection of 50% Cross-Sectional Area Reduction and 75% Cross-Sectional Area Reduction

<table>
<thead>
<tr>
<th>Area Reduction</th>
<th>50%</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>73</td>
<td>89</td>
</tr>
<tr>
<td>Accuracy, %</td>
<td>86</td>
<td>90</td>
</tr>
</tbody>
</table>

A threshold value of 1.5 and 1.25 was used.
A middiastolic value was obtained. In an animal study, Clarke et al\textsuperscript{23} were able to demonstrate that an increase of the temporal resolution from 1 to 6 frames per heartbeat led to a reduction of the limits of agreement between MR and Doppler from 45 to 10 mL/min. However, no additional improvement of temporal resolution was tested at that time to avoid overly long breath holding. Since then, the technique has been additionally optimized and compared with invasive measurements of flow or flow reserve.\textsuperscript{17,19,21,24,25} Hundley et al\textsuperscript{26} have shown a sensitivity and specificity of 100\% and 83\% for the detection of significant coronary artery stenoses of the proximal and middle left anterior descending coronary artery using a breath hold technique with a temporal resolution of 112 to 168 ms. In another study of 17 patients, using the same technique they showed that in patients with recurrent chest pain 6 weeks after a successful percutaneous intervention (8 with stent deployment), the assessment of flow reserve with phase-contrast CMR can be used to identify a 70\% luminal diameter narrowing at the site of the intervention (sensitivity 100\%; specificity 89\%) compared with QCA.\textsuperscript{27} In this study, however, an inhomogeneous patient population was included, eg, a large percentage of patients with myocardial infarction or hypertension. In addition, only patients with proximal and middle left coronary artery disease and 1 patient with right coronary artery disease were included. Especially in the right coronary artery, rapid in-plane motion is to be expected, and a temporal resolution below 25 ms is required to accurately measure coronary artery flow in the RCA with MR methods.\textsuperscript{28} Because the breath hold techniques applied in previous studies resulted in a temporal resolution of <100 ms, the investigators limited themselves to the LAD, except for 1 reported case of flow measurements in the RCA.\textsuperscript{17,19,26,27} With this study we extend MR flow measurements to the RCA, which was possible by using shorter acquisition times per heartbeat. Even though we did not reach the temporal resolution set forth by Hofman et al,\textsuperscript{28} we were able to come very close to this value, thus minimizing motion-induced blurring and inaccuracies. A second advantage of the navigator-gating technique used is the elimination of the need of breath holding for up to 30 seconds. Such breath holds are difficult for many patients, especially with adenosine stimulation, and may influence coronary artery flow due to the Valsalva maneuver.

This study extends previous observations in several aspects. First, we concentrated on a subgroup of patients, which presents a major problem for optimal treatment and follow-up, namely patients after stent deployment. In this group, noninvasive visualization of the coronary arteries with MR or CT imaging is not possible in the stented segments. From a methodological view, MR coronary flow measurements are more difficult in this group, because the exact coronary segment for flow measurements is predefined by the stent, not by the MR examiner. This predefined measurement position, however, allows a more accurate comparison of MR and Doppler flow wire. Second, we included patients with stents in the left or right coronary artery, thus extending the potential application of MR flow measurements. Third, the position of the flow measurement was not predefined by the inclusion criteria but by the clinical decision on where to

Figure 3. Bland-Altman analysis of MR peak flow velocity and intracoronary Doppler flow velocity at rest (A) and stress (B) as well as MR coronary flow velocity reserve and intracoronary Doppler flow velocity reserve (C).
place the stent. Thus, the present study covers the full range of vessel diameters usually stented in clinical practice from 1.4 to 3.9 mm.

In the present study, we show that an in-stent coronary artery cross-sectional area reduction of $\geq 50\%$ can be detected with an accuracy of $86\%$ and a high positive predictive value of $94\%$. For cross-sectional area reductions of $\geq 75\%$, a diagnostic accuracy of $90\%$ was reached. The slightly reduced sensitivity of $85\%$ for the detection of $50\%$ area reduction may reflect the fact that flow does not measure morphology but function and such luminal area reductions may not have any hemodynamic relevance in some cases.

With CMR, an underestimation of coronary flow velocity was found compared with Doppler. This observation has also been reported from other authors.\(^{19,29,30}\) It can be mainly attributed to the lower temporal resolution (and, thus, the highest flow velocity during the cardiac cycle is missed) and the lower spatial resolution (and, thus, an average flow velocity of a small region of interest, rather than the fastest flow velocity within the vessel, is determined) compared with intravascular Doppler. However, underestimation was systematic and thus can be corrected for. In addition, the calculation of flow velocity reserve rather than the use of absolute values led to similar results for CMR and Doppler.

Mild but significantly higher heart rates were found during the MR stress study in comparison with the Doppler examination. Because exactly the same stress protocol was used for both examinations, this can either be explained by psychological reasons (with the patient more stressed within the MR scanner, leading to a tendency of higher heart rates at rest) or logical reasons (with the patient more stressed within the MR imaging environment). Therefore, these patients were excluded.

A technical limitation applies to the technique used. To achieve high spatial and temporal resolution, long scan times of 3 to 5 minutes for each flow measurement, depending on navigator efficiency, were accepted, which prohibited the assessment of more than one coronary artery during one adenosine stress, because this stress test is limited to a maximum duration of 6 minutes. In addition, planning of image acquisition and image analysis required $>2$ hours, which prohibited the routine clinical use of the technique at the current time.

Conclusions

In conclusion, MR flow measurements allow the noninvasive determination of coronary blood flow velocities after stent deployment similar to Doppler flow measurements. This technique can be used to detect in-stent restenosis with a diagnostic accuracy of $86\%$ for $\geq 50\%$ cross-sectional area reduction and $90\%$ for $\geq 75\%$ cross-sectional area reduction in patients with preserved vasoreactivity.

References

23. Clarke GD, Hundley WG, McColl RW, et al. Velocity-encoded, phase-
difference cine MRI measurements of coronary artery flow: dependence
reserve measurements in humans with breath-held magnetic resonance
flow and flow reserve using magnetic resonance imaging. Cardiology.
1997;88:80–89.
assessment of proximal and middle left anterior descending coronary
stenoses in humans with magnetic resonance imaging. Circulation. 1999;
restenosis with phase-contrast magnetic resonance imaging mea-
28. Hofman MB, Wickline SA, Lorenz CH. Quantification of in-plane motion
of the coronary arteries during the cardiac cycle: implications for acquisi-
tion window duration for MR flow quantification. J Magn Reson
Imaging. 1998;8:568–76.
reserve with fast cine phase contrast magnetic resonance imaging: com-
parison with measurement by Doppler guide wire. J Magn Reson
30. Nagel E, Bornstedt A, Hug J, et al. Noninvasive determination of coro-
nary blood flow velocity with magnetic resonance imaging: comparison
of breath-hold and navigator techniques with intravascular ultrasound.
Noninvasive Determination of Coronary Blood Flow Velocity With Cardiovascular Magnetic Resonance in Patients After Stent Deployment
Eike Nagel, Thomas Thouet, Christoph Klein, Simon Schalla, Axel Bornstedt, Bernhard Schnackenburg, Jürgen Hug, Ernst Wellnhofer and Eckart Fleck

_Circulation_. 2003;107:1738-1743; originally published online March 24, 2003;
doi: 10.1161/01.CIR.0000060542.79482.81

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/13/1738

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/