Dynamic 3-Dimensional Stress Cardiac Magnetic Resonance Perfusion Imaging

Detection of Coronary Artery Disease and Volumetry of Myocardial Hypoenhancement Before and After Coronary Stenting

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Objectives

The aim of this study was to establish a new, dynamic 3-dimensional cardiac magnetic resonance (3D-CMR) perfusion scan technique exploiting data correlation in k-space and time with sensitivity-encoding and to determine its value for the detection of coronary artery disease (CAD) and volumetry of myocardial hypoenhancement (VOLUME<sub>hypo</sub>) before and after percutaneous coronary stenting.

Background

Dynamic 3D-CMR perfusion imaging might improve detection of myocardial perfusion deficits and could facilitate direct volumetry of myocardial hypoenhancement.

Methods

In 146 patients with known or suspected CAD, a 3.0-T CMR examination was performed including cine imaging, 3D-CMR perfusion under adenosine stress and at rest followed by delayed enhancement imaging. Quantitative invasive coronary angiography defined significant CAD (>50% luminal narrowing). Forty-eight patients underwent an identical repeat CMR examination after percutaneous stenting of at least 1 coronary lesion. The 3D-CMR perfusion scans were visually classified as pathologic if ≥1 segment showed an inducible perfusion deficit in the absence of delayed enhancement. The VOLUME<sub>hypo</sub> was measured by segmentation of the area of inducible hypoenhancement and normalized to left-ventricular myocardial volume (%VOLUME<sub>hypo</sub>).

Results

The 3D-CMR perfusion resulted in a sensitivity, specificity, and diagnostic accuracy of 91.7%, 74.3%, and 82.9%, respectively. Before and after coronary stenting, %VOLUME<sub>hypo</sub> averaged to 14.2 ± 9.5% and 3.2 ± 5.2%, respectively, with a relative VOLUME<sub>hypo</sub> reduction of 79.4 ± 25.4%. Intrareader and inter-reader reproducibility of VOLUME<sub>hypo</sub> measurements was high (Lin’s concordance correlation coefficient, 0.96 and 0.96, respectively).

Conclusions

The 3D-CMR stress perfusion provided high image quality and high diagnostic accuracy for the detection of significant CAD. The VOLUME<sub>hypo</sub> measurements were highly reproducible and allowed for the assessment of the treatment effect achievable by percutaneous coronary stenting. (J Am Coll Cardiol 2011;57:437–44)

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Cardiac magnetic resonance (CMR) imaging offers the potential to comprehensively assess myocardial function on the basis of combined cine, stress perfusion, and scar imaging. Stress scintigraphic techniques have been extensively employed to establish the diagnosis of and to predict outcome across the entire spectrum of patients with suspected or known coronary artery disease (CAD). For estimation of ischemic burden a semiquantitative segmental scoring system for perfusion at stress and rest is usually applied incorporating the extent and severity of reversible defects. However, radiation-free determination of myocardial ischemic burden of the entire heart with a high in-plane spatial resolution with volumetric measurements on the basis of disk summation methods is desirable.

Prior knowledge-driven imaging represents a new CMR technique to achieve faster dynamic imaging by means of reduced data acquisition on the basis of exploiting correlations in k-space and time (k-t) (1,2). Such accelerated CMR imaging strategies provide the opportunity of full coverage of the heart while preserving adequate temporal and spatial resolution. Consequently, k-t accelerated 2-dimensional...
(2D) multislice CMR perfusion imaging has recently been introduced as a highly attractive diagnostic tool, providing information on the presence and transmurality of myocardial regional hypoperfusion with high in-plane spatial resolution (typically $1.4 \times 1.4 \text{mm}^2$) (3,4). Potentially, dynamic 3-dimensional cardiac magnetic resonance (3D-CMR) perfusion imaging with full left ventricular (LV) coverage might further improve detection of myocardial perfusion deficits and has been proposed in a feasibility study (5). In addition, dynamic 3D-CMR perfusion imaging with preserved high in-plane resolution could facilitate direct volumetric measurements of myocardial hypoenhancement without extrapolating the distribution of hypoperfused regions.

Thus, the objective of this study was to determine the value of dynamic 3D-CMR perfusion imaging for the detection of CAD and volumetry of myocardial hypo-enhancement before and after percutaneous coronary stenting.

**Methods**

**Study population.** The study was approved by the Charité Institutional Review Board. From July 2009 through November 2009, 146 consecutive patients referred to clinically indicated invasive coronary angiography (i.e., evaluation of chest pain syndromes or dyspnea, formally positive exercise electrocardiography, cardiac risk stratification before non-cardiac surgery) underwent a stress CMR perfusion examination. All patients gave written informed consent before CMR imaging and were instructed to refrain from caffeine-containing beverages or food, smoking, and antianginal medication for at least 24 h before the study. Patients were eligible if they had suspected or known CAD (with or without prior percutaneous revascularization) but were not considered for study inclusion if they had typical contraindications for CMR imaging or administration of adenosine. Cardiovascular risk factors and clinical status were recorded at the time of CMR stress testing.

In a subgroup of 48 patients, a repeat stress CMR perfusion examination was performed within 24 h after percutaneous stenting of at least 1 significantly obstructive coronary lesion in an epicardial vessel of $\geq 2 \text{ mm luminal diameter.}$

**CMR study.** The CMR imaging was performed with the patient in the supine position with a 3.0-T MR scanner (Philips Achieva, Best, the Netherlands) equipped with a Qsar Dual gradient system (40 mT/m; 200 mT/m/ms) and with Philips software release 2.6.3. A 6-element cardiac synergy coil was used for signal reception, and cardiac synchronization was performed with a vector-electrocardiogram.

For the assessment of LV function and wall motion at rest, cine imaging was employed with balanced turbo field echo sequences with retrospective gating (repetition time [TR]/echo time [TE]/flip angle: 3.3 ms/1.6 ms/40°; 50 phases/cardiac cycle; spatial resolution: $1.5 \times 1.5 \times 8.0 \text{ mm}^3$) during short repetitive breathholding. Cine scans were acquired in 3 short-axis (apical, mid-, and basal short-axis views) and 3 long-axis geometries (4-, 2-, and 3-chamber views) according to standard definitions.

Subsequently, adenosine infusion (140 $\mu\text{g/kg/min}$) was started, and after at least 3 min of adenosine infusion 3D-CMR stress first-pass perfusion imaging (intravenous bolus application of 0.1 mmol/kg of gadopentetate dimeglumine [Magnevist, Schering, Berlin, Germany]; injection rate 4.0 ml/s followed by 20 ml saline flush) was performed in short-axis geometry with full LV coverage. After termination of adenosine infusion and a 10- to 15-min waiting period for equilibration of the contrast agent within the myocardium, the identical 3D-CMR perfusion scan was repeated at rest. After another 10-min waiting period delayed enhancement (DE) imaging was done in the identical short-axis geometry used for full coverage of the LV during 3D-CMR perfusion imaging with a 3D inversion prepared spoiled gradient-echo sequence (TR/TE/flip angle: 3.6 ms/1.8 ms/15°, voxel size 1.6 $\times$ 1.6 $\times$ 10.0 mm$^3$).

The inversion recovery prepulse delay was determined from a Look-Locker sequence and adjusted accordingly (range, 190 to 240 ms).

**3D-CMR perfusion imaging technique.** The 3D-CMR perfusion imaging protocol consisted of a saturation-recovery gradient-echo pulse sequence (TR/TE/flip angle 1.8 ms/0.7 ms/15°, saturation prepulse delay 150 ms, partial Fourier acquisition, field of view $350 \times 350$ mm, measured voxel size $2.3 \times 2.3 \times 10.0$ mm$^3$ reconstructed to $2.3 \times 2.3 \times 5.0$ mm$^3$, number of slices 16). For saturation, a tailored composite prepulse was implemented to compensate for field inhomogeneity effects in the heart at 3.0-T (6). The acceleration technique k-t with sensitivity-encoding was employed to speed up data acquisition by a net factor of 6.3, thereby permitting data collection during a 200-ms window/cardiac cycle. For image reconstruction, information from so-called training data collected together with the actual data in each cardiac cycle were used to unfold the undersampled 3D perfusion datasets. Image reconstruction was performed with a previously described algorithm (2).

After the unfolding procedure the training data were substituted back into the reconstruction matrix for improved data consistency (4).

**Image quality.** Overall image quality of stress and rest 3D-CMR perfusion scans was graded on a scale between 1 and 4 (1 = nondiagnostic, 2 = poor, 3 = good, 4 = excellent). In addition, the occurrence of image artifacts was noted and classified as breathing- or k-t reconstruction-related (i.e., image flickering), and the presence of suben-
occardial dark rim artifacts was noted. To compare image quality with conventionally employed 2D rest and stress
CMR perfusion scans at 3.0-T, 150 consecutive cases from our routine database were evaluated accordingly (7).

**Visual assessment of dynamic 3D-CMR stress and rest perfusion scans.** The 3D-CMR perfusion examinations were analyzed visually with the observer (Dr. Manka) being fully blinded to clinical and angiographic patient data. All short-axis slices with clearly identifiable LV cavity enhancement during contrast agent first-pass and with >75% circumferential LV myocardium were considered (i.e., depending on the size of the heart the most apical slice was excluded from the analysis if no blood pool signal/ endocardial border was present or the most basal slice if the mitral valve annulus was visualized predominantly). These short-axis views were then divided in 6 equally distributed segments and evaluated visually for the presence of inducible perfusion deficits with the following criteria being rigorously applied: on adenosine 3D-CMR stress perfusion scans, a regional hypoenhancement in any segment with ≥25% transmurality persisting for ≥3 consecutive dynamics not being visible on the rest perfusion scan and in the absence of DE was considered to be pathologic (= inducible perfusion deficit).

For comparison with a 2D CMR perfusion approach, the standardized 3-slice model with equally distributed short-axis slices covering 16 segments was applied to all 3D-CMR perfusion datasets (slice 4, 8, and 12), and diagnostic values resulting from evaluation of these 3 slices only were calculated on a per patient basis.

**Volumetry of myocardial hypoenhancement.** In the patient group with CMR stress perfusion examinations before and after coronary stenting a volumetric analysis of stress inducible perfusion deficits was carried out. Volumetry of 3D-CMR perfusion datasets was performed with GTVolume (version 1.3.9, GyroTools, Zurich, Switzerland) with the software containing a specifically designed module for myocardial segmentation and calculation of total myocardial hypoenhancement (VOLUMEhypo) according to the disk summation method.

For measurements of VOLUMEhypo the single dynamic slice images of the stress perfusion scan showing the maximum extent of regional hypoenhancement during peak signal enhancement of remote myocardium were chosen, and the observer manually outlined LV endocardial and epicardial borders in all slices. Subsequently, segmentation of LV myocardium was done on a pixel-by-pixel basis by adjusting the signal-intensity threshold >2 SDs below the signal of remote myocardium, and the area of hypoenhancement was measured. Total LV myocardial volume and total VOLUMEhypo (both in ml) were calculated with the disk summation method, and total VOLUMEhypo was normalized to LV myocardial volume (%VOLUMEhypo). In case subendocardial or transmural scarring was present in corresponding DE images (n = 11), the amount of scar was quantified by manual segmentation with the signal intensity threshold set to >2 SD above the mean signal intensity of a remote myocardial region and subtracted from VOLUMEhypo to identify the amount of inducible ischemia in the border zone of chronic myocardial infarction only.

**Determination of intraobserver and interobserver variability.** In all 48 patients undergoing 3D-CMR perfusion imaging before and after coronary stenting VOLUMEhypo measurements were carried out as follows: for determination of intraobserver variability 1 reader (R.M., >4 years experience in reading >300 stress CMR perfusion studies/year) repeated the analysis 4 weeks later, and for determination of interobserver variability a second reader (I.P., >10 years experience in reading >1,000 stress CMR perfusion studies/year) independently performed the evaluation. Both readers were fully blinded to clinical and angiographic patient data.

**Quantitative coronary angiography.** The X-ray coronary angiography was performed by standard techniques with a simultaneous biplane, multidirectional, and isocentric X-ray system. At least 2 orthogonal views of every major coronary vessel and its side branches were acquired. Quantitative coronary angiography (Philips Inturis CardioView, QCA version 3.3, Pie Medical Imaging, Maastricht, the Netherlands) was performed off-line by an independent observer (>12 years experience) who was unaware of the results of CMR imaging. Significant CAD was defined as ≥50% narrowing of the luminal diameter of at least 1 major epicardial artery with ≥2 mm diameter.

**Statistical analysis.** All statistical data analysis was performed with SPSS for Windows version 17.0.0 (SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD; categorical variables are expressed as proportions. The paired Student t test was used to assess statistical significance of continuous variables. Group differences for ordinal variables were tested with the Mann-Whitney U or Wilcoxon’s signed-rank test. All tests were 2-tailed; p < 0.05 was considered significant.

Sensitivity and specificity with corresponding 95% confidence intervals (CIs) were calculated according to standard definitions. Intrareader and inter-reader variability of VOLUMEhypo measurements was investigated with Pearson’s correlation and Lin’s concordance correlation coefficient. The latter was calculated to assess the concordance of continuous data with the following scale to describe the strength of agreement: >0.99 indicates almost perfect agreement; 0.95 to 0.99 indicates substantial agreement; 0.90 to 0.95 indicates moderate agreement; and <0.90 indicates poor agreement. In addition, Bland-Altman analysis was done to compare VOLUMEhypo measurements; the degree of agreement was determined as mean absolute difference (bias) ± 2 SDs of the mean difference. Treatment effect was determined with Cohen’s d effect size calculated as the difference of the means divided by the SD with the following scale: d = 0.2 indicates small; d = 0.5 indicates medium; and d > 0.8 indicates large treatment effect.
Results

Patient characteristics. Table 1 provides the clinical baseline characteristics of the complete patient population. Image quality. The 3D-CMR stress and rest perfusion scans of all 146 patients were of diagnostic image quality (image quality score ≥2) and thus included in the analysis (Table 2). The mean visual score of 2D stress and rest CMR perfusion scans of all 146 patients were of diagnostic image quality (Pearson’s correlation coefficient, 0.96 and 0.96, respectively, both p < 0.001) and substantial concordance (Lin’s correlation coefficient, 0.96 [95% CI: 0.94 to 0.98] and 0.96 [95% CI: 0.93 to 0.98], respectively).

Table 1 Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n</td>
<td>102 (69.9)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Range</td>
<td>20–85</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 3.9</td>
</tr>
<tr>
<td>BMI &gt;25 kg/m²</td>
<td>110 (75.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>122 (83.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (21.9)</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>105 (71.9)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>38 (26.0)</td>
</tr>
<tr>
<td>Known CAD</td>
<td>65 (44.5)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>64 (43.8)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>26 (17.8)</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>44 (30.1)</td>
</tr>
<tr>
<td>Multiple (double/triple)</td>
<td>28 (19.2)</td>
</tr>
</tbody>
</table>

Data are n (%) or mean ± SD.

BMI = body mass index; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

Table 2 Image Quality Scoring of Dynamic 3D-CMR Perfusion

<table>
<thead>
<tr>
<th>Image Quality</th>
<th>4 = excellent</th>
<th>3 = good</th>
<th>2 = poor</th>
<th>1 = nondiagnostic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>83 (56.8%)</td>
<td>58 (39.7%)</td>
<td>5 (3.4%)</td>
<td>0 (0%)</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>Adenosine stress</td>
<td>75 (51.4%)</td>
<td>65 (44.5%)</td>
<td>6 (4.1%)</td>
<td>0 (0%)</td>
<td>3.5 ± 0.6</td>
</tr>
</tbody>
</table>

n = 146 patients. Data are n (%) or mean ± SD.

Discussion

The present study is the first to assess the diagnostic value of dynamic 3D-CMR stress perfusion imaging for the detection of CAD in patients with suspected or known coronary disease and to apply volumetric measurement of myocardial hypoenhancement before and after percutaneous coronary stenting.

The main findings of our study are: 1) dynamic 3D-CMR stress perfusion imaging could be successfully performed in a large, consecutive patient population and resulted in a high percentage of LV myocardium was 14.2 ± 9.5% (range, 1.7% to 37.8%) before stenting and 3.2 ± 5.2% (range, 0% to 28.2%) after stenting (Fig. 5). Relative VOLUME_hypo reduction averaged to 79.4 ± 25.4% with the following distribution of the number of patients grouped according to relative VOLUME_hypo reduction: 100% (n = 18), 99% to 75% (n = 15), 74% to 50% (n = 8), 49% to 25% (n = 5), and <25% (n = 2). Treatment effect was large as estimated by Cohen’s d (1.2 [95% CI: −1.5 to 3.8]). Online Video 4 shows a representative imaging example before and after coronary stenting.

The present study is the first to assess the diagnostic value of dynamic 3D-CMR stress perfusion imaging for the detection of CAD in patients with suspected or known coronary disease and to apply volumetric measurement of myocardial hypoenhancement before and after percutaneous coronary stenting.

The main findings of our study are: 1) dynamic 3D-CMR stress perfusion imaging could be successfully performed in a large, consecutive patient population and resulted in a high percentage of high-quality diagnostic studies; 2) the diagnostic value of 3D-CMR stress perfusion imaging is high and within the range of previously reported studies; 3) dynamic 3D-CMR stress perfusion imaging yielded
a high diagnostic value independent of the number of diseased coronary vessels; 4) volumetry of myocardial hypoenhancement can be carried out with high inter- and intra-reader reproducibility; and 5) relative reduction of total myocardial hypoenhancement at Day 1 after stenting was 79.4 ± 25.4% consistent with a large treatment effect in the current study population.

The impetus for the development and subsequent clinical testing of a dynamic 3D-CMR stress perfusion technique has been primarily 2-fold: to ensure comprehensive coverage of the...
Figure 2 Dynamic 3D-CMR Stress Perfusion Scan in Double-Vessel CAD

Dynamic 3-dimensional cardiac magnetic resonance stress perfusion scan (A) and corresponding X-ray coronary angiogram (B, C) (double-vessel disease of left anterior descending and left circumflex coronary arteries, black arrowheads); the resting perfusion scan was normal. Extensive, strictly inducible perfusion deficits in anterior/anteroseptal and in inferior/inferolateral segments can be appreciated (see also Online Videos 3 and 4).

Figure 3 Intrareader and Inter-Reader Agreement for Volumetry of Myocardial Hypoenhancement

Bland-Altman plots demonstrating (A) intra- and (B) inter-reader agreement for volumetry of myocardial hypoenhancement (VOLUME$_{hyp}$).
heart with the potential to improve diagnostic accuracy for the detection of ischemic myocardial regions and to allow direct volumetric quantification of LV myocardial hypoenhancement. Our results indicate that full spatial coverage of the heart did not necessarily lead to a significant improvement in diagnostic accuracy on a per patient basis when aiming at the detection of perfusion abnormalities associated with the presence of epicardial coronary stenosis. However, complete visualization of inducible perfusion abnormalities frequently seen in other cardiac disease states (e.g., ventricular hypertrophy, diabetes, cardiomyopathies) might prove beneficial (9). Rather, the main advantage of 3D-CMR stress perfusion imaging lies in its inherent ability to comprehensively quantify myocardial hypoenhancement without underlying geometric assumptions about the distribution of hypoperfused myocardium in the entire heart, and our data corroborated the high interreader and intrareader reproducibility of volumetric quantification in patients with CAD. Accordingly, dynamic 3D-CMR stress perfusion might be considered useful to directly quantify the efficacy of therapeutic approaches targeted at improved myocardial perfusion. In the present study, primary percutaneous stenting was chosen to exemplify that 3D-CMR stress perfusion imaging can be used for direct quantification of the effect size of myocardial perfusion improvement as indicated by the reduction of the volume of myocardial hypoenhancement. The values for percentage of myocardial hypoenhancement with 3D-CMR perfusion were within the range of previously published trials using quantitative single-photon emission computed tomography for determination of myocardial ischemic burden (10). However, additional studies aiming at a direct comparison between 3D-CMR and single-photon emission computed tomography–derived measures of the amount of hypoperfused myocardium are warranted. Perspectively, taking full advantage of the noninvasiveness of CMR imaging, serial 3D-CMR stress perfusion imaging could potentially be employed to measure and compare the efficiency of other medical and interventional measures (e.g., gene therapy) designed to improve regional myocardial blood flow (11). In addition, with myocardial hypoenhancement assessable as a

Figure 4 Segmentation-Based Volumetry of Myocardial Hypoenhancement

(A) Consecutive slices of a dynamic 3-dimensional cardiac magnetic resonance stress perfusion scan. (B) Identical images illustrating volumetry of myocardial hypoenhancement (segmented red areas). Volume of myocardial hypoenhancement was 24% of total myocardium (29.9 of 125.5 ml).

Figure 5 Effect of Coronary Stenting on the Amount of Stress-Inducible Myocardial Hypoenhancement

Diagram illustrating the effect of percutaneous coronary stenting on %VOLUME_hypo as assessed by 3-dimensional cardiac magnetic resonance stress perfusion imaging. Lines track individual patient values before and after coronary stenting. %VOLUME_hypo = VOLUME_hypo was measured by segmentation of the area of inducible hypoenhancement and normalized to left ventricular myocardial volume.
continuous parameter a more distinct prognostication and risk stratification of identifiable patient groups is likely and warrants investigation in future studies.

**Study limitations.** In the present study, volume of myocardial hypoenhancement was considered indicative of reduced myocardial blood flow associated with the angiographically confirmed presence of coronary luminal narrowing. However, invasive coronary angiography has been recognized to be of limited value for the characterization of the functional severity of coronary luminal narrowing at intermediate degrees of stenosis and thus might be considered a poor indicator of hemodynamically relevant (i.e., ischemia-producing) coronary disease. Hence, further validation with fractional flow reserve measurements as the standard of reference is needed. Assessment of interstudy reproducibility of 3D-CMR stress perfusion is of critical importance for serial testing but remains to be determined. Finally, the present study was conducted at a single center with an expert group of physicians carrying out and interpreting the CMR examinations; thus, future large-scale multicenter trials are desirable to ultimately define the value of 3D-CMR perfusion in clinical routine and its usefulness for cardiac risk stratification or determination of the treatment effect of anti-ischemic therapies.

**Conclusions**

Dynamic 3D-CMR stress perfusion imaging at 3.0-T proved to be a robust method with consistently high image quality. In patients with known or suspected CAD dynamic 3D-CMR stress perfusion yielded high diagnostic accuracy for the detection of significant CAD. Volumetry of myocardial hypoenhancement was highly reproducible and allowed for the assessment of the treatment effect achievable by percutaneous coronary stenting. Consequently, dynamic 3D-CMR stress perfusion imaging can be regarded as a powerful, noninvasive diagnostic tool for the detection and serial quantification of myocardial perfusion abnormalities during follow-up of anti-ischemic therapies.

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**APPENDIX**

For supplementary videos, please see the online version of this article.

**REFERENCES**


**Key Words:** 3-dimensional cardiac MR perfusion  adenosine stress  magnetic resonance imaging  volumetry of myocardial hypoenhancement.