Taylor & Francis
Taylor & Francis Group

MYOCARDIAL PERFUSION IMAGING

Determinants of myocardial response in CMR perfusion imaging using Gd-BOPTA (Multihance®)

ROLF GEBKER,[1,*] I. PAETSCH,[1] M. NEUSS,[1] B. SCHNACKENBURG,[2] A. BORNSTEDT,[1] C. JAHNKE,[1] O. GOMAA,[1] E. FLECK,[1] and E. NAGEL[1]

[1]*Deutsches Herzzentrum, Berlin, Germany*
[2]*Philips Medical Systems, Hamburg, Germany*
[3]*Medizinische Klinik, University of Freiburg, Germany*

Purpose. Different centers and vendors use different sequences and contrast agent application schemes for MR myocardial perfusion imaging. The purpose of this study was to evaluate the role of different sequences, dosages, and injection speeds of contrast media for semiquantitative MR-perfusion assessment. *Methods.* In a pilot study with 58 consecutive patients three of the most commonly used sequences for MR myocardial perfusion imaging (T1-GrE, GrE-EPI or SSFP) were compared to each other in terms of peak myocardial enhancement and image quality. For the main part of the study dynamic first pass MR perfusion imaging (Philips Intera CV, Best, the Netherlands) was performed in 24 patients using the most favorable sequence from the pilot study (SSFP) after peripheral i.v. administration of Gd-BOPTA during adenosine stress. Two doses (0.05 mmol/kg bw and 0.025 mmol/kg bw) and four different injection speeds (8, 4, 3, 2 ml/s) were used. Signal intensity time curves were determined in the LV and myocardial segments supplied by normal coronary arteries and correlation between LV and myocardial upslope as well as peak enhancement were noted. *Results.* The SSFP-sequence showed a higher peak enhancement when using 0.05 mmol/kg bw of Gd-BOPTA and a superior image quality for both dosage regimen compared with the other sequences and was consequently applied for the main study. A significant correlation was found between the upslopes in the LV and the myocardium (r square = 0.85, p < 0.001). However, LV and myocardial upslopes were largely independent of the dosage. Myocardial upslope was significantly slower at an injection rate of 2 ml/s compared to 3 and 4 ml/s. Higher Gd-doses led to significantly higher enhancement (p < 0.001). *Conclusion.* In healthy myocardial segments, the myocardial upslope is mainly determined from the LV upslope. Both myocardial enhancement and upslope are largely independent from the injection rate of a contrast agent bolus as long as the injection speed is not below 3 ml/s. Myocardial enhancement, however, is dose dependent. Thus, a simple correction for LV upslope allows to normalize a wide variety of input parameters. Differences of myocardial upslope or peak signal intensity after correction should be mainly dependent on blood flow.

Key Words: Cardiovascular magnetic resonance; Perfusion; Myocardium; Contrast media/administration and dosage

1. Introduction

Since its introduction in the early 1990s, myocardial first-pass magnetic resonance perfusion imaging has been developed extensively (1) for the detection of coronary artery disease (2, 3) and measurement of absolute myocardial blood flow (4). The most important choices for imaging during the first pass of an injected contrast agent relate to the pulse sequence protocol (5) and the type and dosage of the contrast agent (6, 7) that is being used. There is general agreement among most investigators that fast T1-weighted imaging during a rapid bolus injection of a low dose of a T1-shortening extracellular contrast agent (CA) currently produces the best results in MR perfusion imaging whereas the role of intravascular CAs still needs clarification (8). While the use of low doses of extracellular contrast agents is recommended for quantifying absolute myocardial blood flow and volume (9) or semiquantification, higher doses are predominantly used for visual assessment. Further technical issues regarding first-pass imaging are the mode of injection of the contrast agent and the application of postprocessing algorithms. A systematic evaluation of the contrast agent application scheme (dose/injection speed) has not been reported yet. The objective of this study was to evaluate the role of different sequences, dosages, and injection rates of contrast media for semiquantitative MR-perfusion assessment using myocardial enhancement and myocardial and left ventricular upslope.
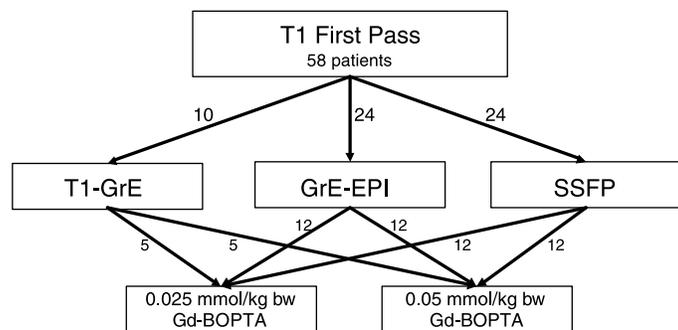
Figure 1. Design of the pilot study showing that three different sequences combined with two different CA dosages were applied. The respective number of patients examined with each scheme is shown as well.

2. Methods

2.1. *Study design*

In a pilot study, we sought to determine the most suitable pulse sequence from a pool of three of today′s most commonly used sequences for MR perfusion measurements: T1 weighted turbo gradient echo (T1-GrE), T1 weighted turbo gradient echo EPI (GrE-EPI) and Steady State Free Precession (SSFP) in combination with two contrast agent (CA) doses (Fig. 1). The main study was then carried out with the most favorable sequence. In this sequence (SSFP), the effects of two different doses of an extracellular CA and four different injection rates were compared (Fig. 2).

2.2. *Study population*

Both for the pilot and main study patients with suspected or known coronary artery disease referred for adenosine stress perfusion imaging were examined after written informed consent was obtained. Fifty-eight consecutive patients for the pilot study (45 male, 13 female; age: 62 ± 9) and 24

Figure 2. Design of the main study. The SSFP-sequence was applied on a total of 24 patients using two different CA dosages and four different injection rates. The respective number of patients examined with each scheme is shown next to each arrow.

consecutive patients for the main study (15 male, 9 female; age: 63 ± 9) were examined. Twelve patients were assigned to each of the two dose groups for SSFP and GrE-EPI and five patients to each of the two dose groups for T1-GrE. This smaller group size was possible since the study group had gained broad experience with T1-GrE over the past years (10) and preliminary results showed a superior performance of both GrE-EPI and SSFP. Patients were excluded from the study if they had contraindications for an MR examination, were hemodynamically unstable, had reasons for inadequate image quality such as frequent ventricular or supraventricular arrhythmias, or had contraindications to adenosine. The patients refrained from any caffeine or antianginous medication intake at least 12 hours prior to the examination. Each patient received two 18 gauge i.v. cannula in an antecubital vein of the right and left arm for adenosine and for contrast agent injection.

2.3. *Magnetic resonance imaging*

All patients were examined in the supine position with a whole body 1.5 Tesla MR system (Philips Intera CV, Best, the Netherlands) and a five-element cardiac phased-array coil for signal reception. Three different sequences with identical spatial resolution ($2.7 \times 2.7 \times 8$ mm) were used: T1-GrE (TR/TE/α: 2.7 ms/1.7 ms/15°), GrE-EPI (TR/TE/α: 9.3 ms/ 3.3 ms/30°), steady state free precession (SSFP) (TR/TE/α: 2.8 ms/1.4 ms/50°). T1-GrE, GrE-EPI, and SSFP allowed 3 slices per heart beat up to a heart rate of 90, 105, and 85 minutes, respectively. In all three sequences, a saturation prepared prepulse of 90° was applied for each slice in order to obtain T1 weighting. A similar prepulse delay was used for all three sequences. The SENSE technique was applied for the SSFP and T1-GrE sequences, which inherently includes a correction for the coil profile.

Adenosine was administered at a dose of 140 µg/min/kg for at least 4 minutes before starting MR perfusion imaging. The images were acquired during breath holding for 10 heartbeats before and 50 heartbeats during the first pass of a bolus of either 0.025 mmol/kg bw or 0.05 mmol/kg bw of gadobenate dimeglumine (Gd-BOPTA, Multihance,® Byk Gulden, relaxivities of Gd-BOPTA in aqueous solution are $r_1 = 4.39$ and $r_2 = 5.56$ mM^{-1}s^{-1} at 20 MHz), followed by a flush of 20ml NaCl both for the pilot and main study. While the concentration of the CA was kept constant the injected volume was doubled when the dose was increased from 0.025 to 0.05 mmol/kg bw. An automated injector pump (Spectris, Medrad Inc., Indiana, PA, USA) was used. Before conducting the study, the actual injection rate was measured using a beaker. This was necessary since manufacturers of venflons limit the maximum amount of fluid that can be passed through an 18 gauge venflon to 80 ml/min using a regular intravenous drip. However, using an automated injector pump the amount that can be injected through such a needle could accurately be increased up to 8 ml/s.

After 15 minutes to allow for the clearance of the first bolus, the perfusion scan was repeated at rest. While the
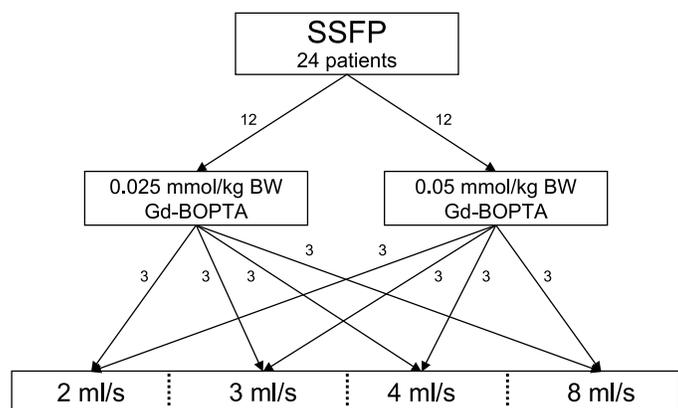
a

* p < 0.01 vs. all other groups
** p < 0.01 vs. GrE-EPI and T1-GrE at 0.025 mmol/kg bw

b

 * p < 0.05 vs. all other groups except for GrE-EPI at 0.05 mmol/kg bw
** p < 0.05 vs. T1-GrE at 0.05 and 0.025 mmol/kg bw
 † p < 0.05 vs. T1-GrE at 0.025 mmol/kg bw
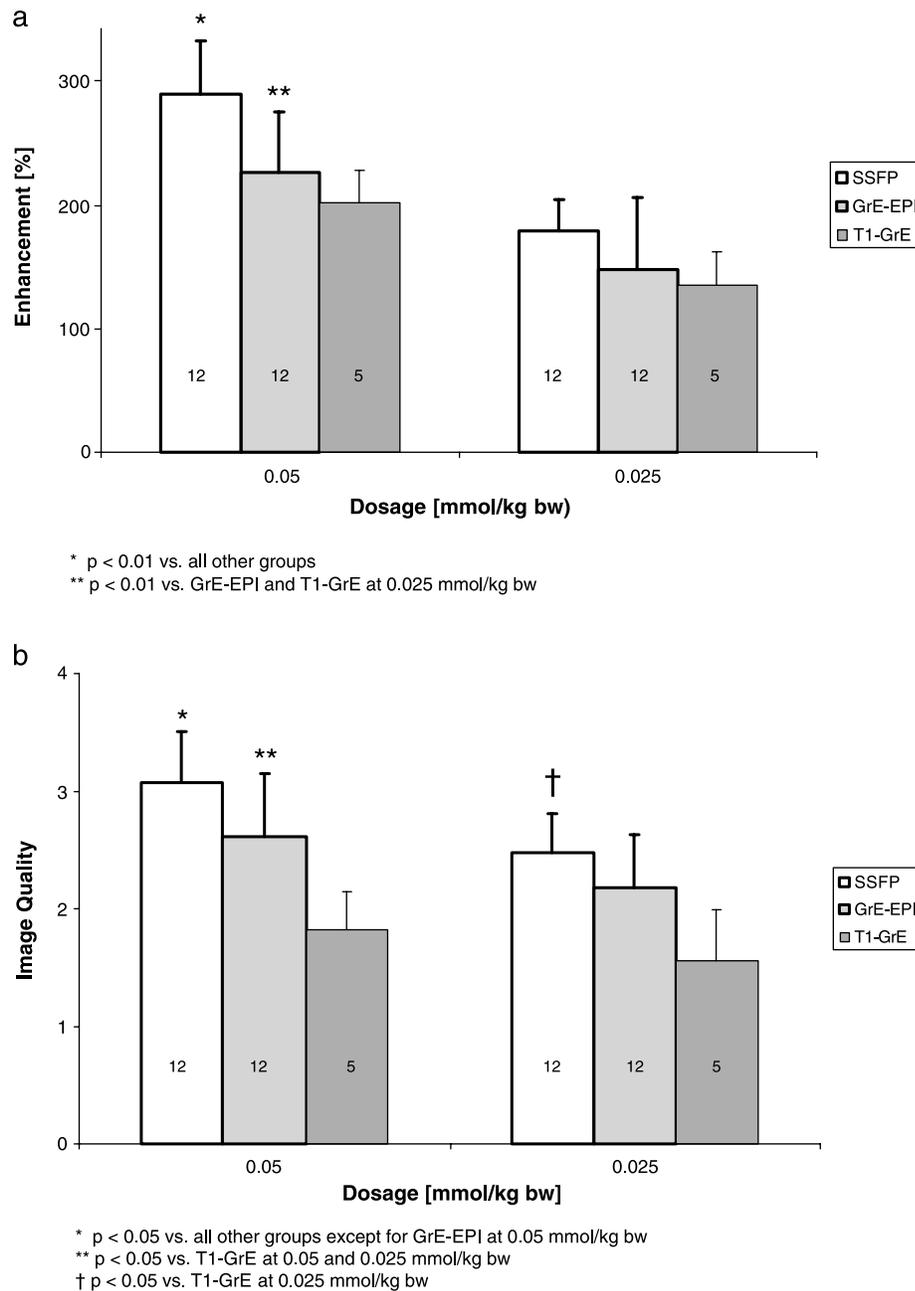
Figure 3. a. Results of the pilot study showing that SSFP performs significantly better than the other two sequences in terms of myocardial enhancement when a CA dosage of 0.05 mmol/kg bw is used. It also shows that myocardial enhancement is dose dependent for all three sequences. b. Shows the results of the pilot study demonstrating that SSFP combined with a CA dosage of 0.05 mmol/kg bw has a superior image quality compare to all other sequences except for GrE-EPI at 0.05 mmol/kg bw where only a trend for an improved image quality could be seen.

injection rate for the contrast agent was kept constant at 4 ml/s for the pilot study, four different injection rates (2, 3, 4 and 8 ml/s) were used during the main part of the study.

2.4. *Image analysis*

The signal intensity (SI) time curves of the images were analysed with commercially available software (Mass,® Medis, Leiden, the Netherlands). The endocardial and epicardial borders were drawn manually on each dynamic image. Only the equatorial short axis slice was used for analysis. The myocardium was divided into six equiangular segments and numbered clockwise starting with the anterior insertion of the right ventricle. Only segments that were supplied by intact coronary arteries as determined by coronary catheterisation or a negative dobutamine stress
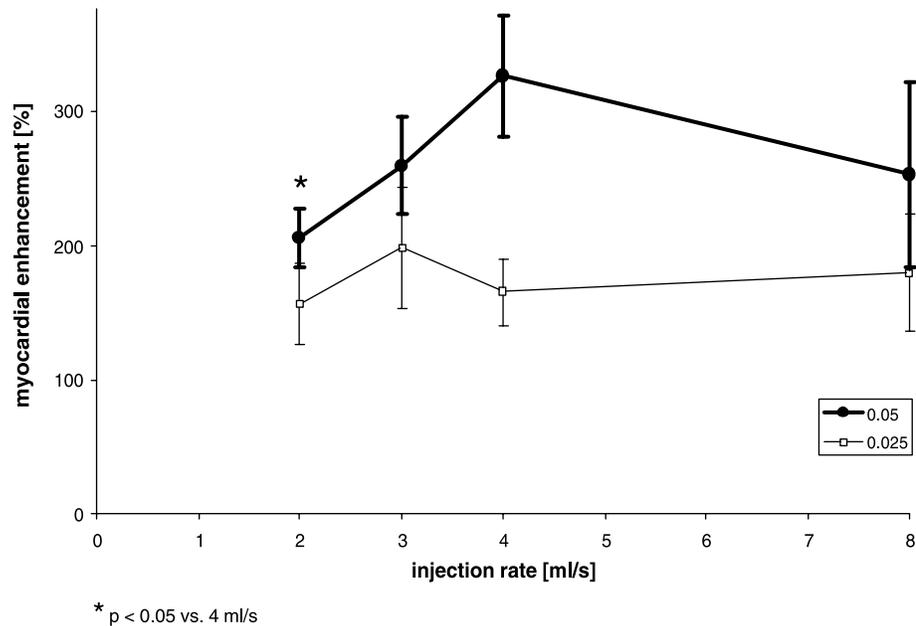
Figure 4. The influence of different injection rates on myocardial enhancement is depicted here for both dosage regimen. The application of a slow injection rate of 2 ml/s led to a significantly lower myocardial enhancement when compared to an injection rate of 4 ml/s at a dosage of 0.05 mml/kg bw. Using a lower CA dosage resulted in a lower myocardial enhancement.

magnetic resonance test were analysed and averaged. The percentage increase of myocardial enhancement during the first pass of the contrast agent was determined. Furthermore, the maximal upslope of each myocardial segment and of the left ventricular blood pool were calculated by a linear fit from the SI profiles using four points for the upslope calculation.

A visual score for image quality (4 = excellent, 3 = slight restriction [mild artifacts, mild blurring, mild signal inhomogeneities], 2 = profound restriction [severe artifacts, severe blurring, severe signal inhomogeneities], 1 = non-diagnostic [artifacts make diagnosis impossible]) was applied by three blinded observers.

2.5. Statistics

All variables are expressed as mean ± SD. Comparisons between the three sequence groups for the pilot study were made by means of a One-Way ANOVA test while comparisons
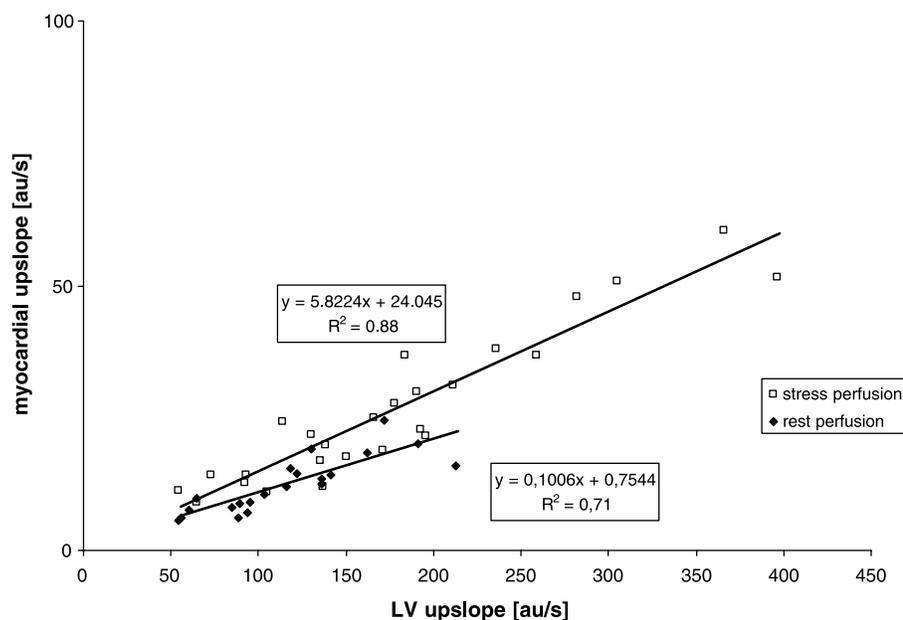
Figure 5. Illustrates the correlation between the LV bloodpool and myocardial upslopes both for rest and during adenosine stress for all CA dosages and injection rates.
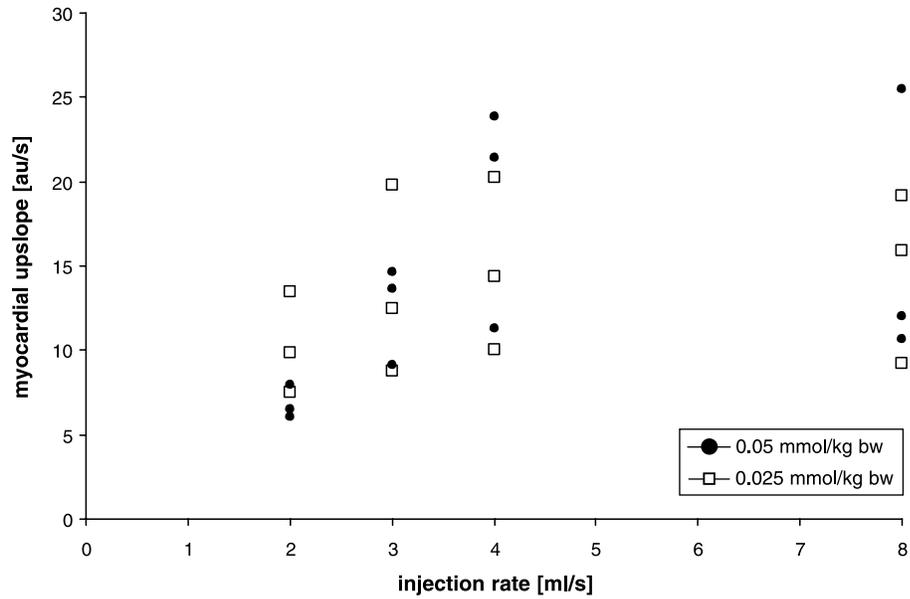
Figure 6. Displays the results for myocardial upslope vs. injection rate for the two dosage groups under resting conditions. Using the slowest injection rate of 2 ml/s led to significantly slower upslopes compared to 3 and 4 ml/s. The graph demonstrates the inter-individual dispersion of the data when an injection rate of 3 ml/s or faster is chosen. It also shows that doubling the injection rate from 4 to 8 ml/s does not have an effect on the myocardial upslope.

between two groups for the main part of the study were made by means of unpaired *t*-test. A 2-tailed probability value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. *Pilot study*

Determination of myocardial enhancement yielded significantly better results for SSFP at 0.05 mmol/kg bw versus all other sequences and dosage regimen (Fig. 3a). Using GrE-EPI at a dosage of 0.05 mmol/kg bw resulted in a significantly higher myocardial enhancement compared to GrE-EPI and T1-TFE at 0.025 mmol/kg bw. At a CA-dose of 0.025 mmol/kg, only a trend for higher myocardial enhancement with SSFP, but no significant differences between SSFP and GrE-EPI, could be detected. Both SSFP and GrE-EPI showed significantly better image quality at a CA-dosage of 0.05 mmol/kg bw in comparison to T1-GrE at 0.025 mmol/kg bw (Figs. 3b and 7). There were no significant differences between SSFP and GrE-EPI when comparing them at the level of CA dosage. Since overall results for SSFP for both enhancement and image quality were either significantly or
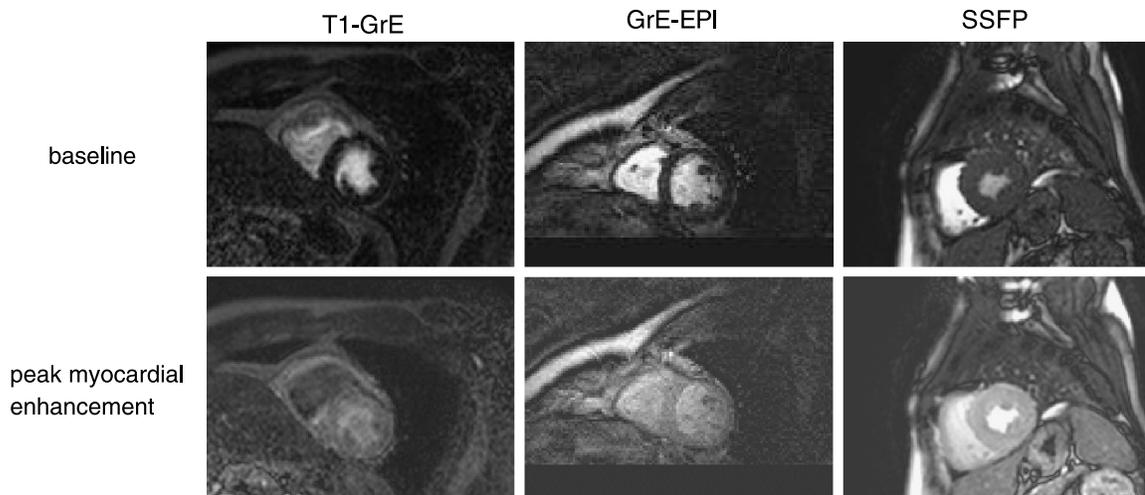
Figure 7. Shows the differences in signal intensity of the three sequences at baseline and during peak myocardial enhancement (0.05 mmol/ kg bw). SSFP is associated with a superior myocardial enhancement and image quality.

baseline

peak myocardial
enhancement
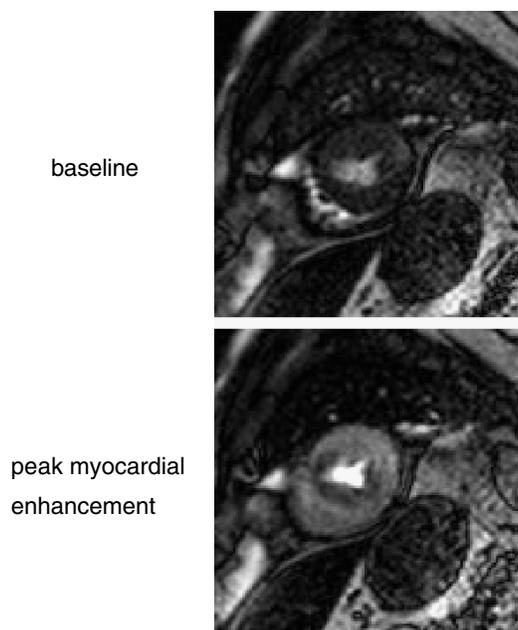
Figure 8. Exemplary displays a patient with a high grade proximal LAD stenosis leading to a perfusion defect of the septum, inferior and anterior wall using the SSFP sequence.

tendentially superior to the other two sequences this sequence was used for the main study (Figs. 7 and 8).

3.2. *Main study*

Higher Gd-doses led to a significantly higher myocardial enhancement ($p < 0.001$). The lowest injection rate of 2 ml/s was associated with a significantly lower myocardial enhancement when compared with 4 ml/s at a CA-dosage of 0.05 mmol/kg bw ($p < 0.05$) (Fig. 4). No differences of myocardial enhancement with respect to injection rates were found at 0.025 mmol/kg bw. A significant correlation was found between the upslopes in the LV and the myocardium for both rest and stress (r square = 0.71 and 0.88, respectively, $p < 0.001$) (Fig. 5). No significant differences of myocardial upslope versus injection rate were measured between the two dosage groups (Fig. 6). The myocardial SI-curves displayed a significantly slower upslope under both rest and stress conditions when the CA was injected at a rate of 2 ml/s compared to 3 and 4 ml/s (Fig. 6). The amount of inter-individual dispersion increases with faster injection speeds. It also shows that doubling the injection rate from 4 to 8 ml/s does not have an effect on further increasing the myocardial upslope.

4. **Discussion**

Our study sought to assess the influence of variable parameters applied for perfusion imaging on myocardial enhancement and upslope of the contrast agent wash in. It was found that myocardial enhancement highly depends on sequence and CA dose but to a lesser extent on injection speed if 3 ml/s or more is used. Speed of CA wash in (upslope) depends on injection rate but not on dosage. Since injection rate has a similar effect on LV- and myocardial upslope, this effect can be accounted for by correcting the myocardial upslope with the LV upslope.

4.1. *Comparison of sequences—pilot study*

For the pilot study, we could show that using the SSFP-sequence results in a significantly higher myocardial signal enhancement compared to the GrE-EPI- and T1-GrE-sequence when using a CA-dosage of 0.05 mmol/kg bw. Both SSFP and GrE-EPI displayed a higher myocardial signal response under both dosage regimen compared to T1-GrE. These results support the findings by Hunold et al who reported that SSFP compares favourably with T1-GrE in terms of signal and contrast to noise ratio and peak signal intensity (11). The results of the pilot study did not allow us to determine a single best sequence in terms of image quality. One of the major limitations of SSFP sequences is their disposition to susceptibility artifacts along the endocardium during the first pass of the CA. However, we decided to apply the SSFP-sequence for the main study since a clear trend for better image quality could be seen (Figs. 3b and 7).

4.2. *Determinants of myocardial enhancement*

Both for the pilot and main part of the study, we could show that myocardial enhancement for healthy myocardial segments is mainly determined by CA-dosage (Figs. 3a and 4). One of the most important characteristics of an MR-perfusion sequence is its ability to differentiate between states of normal and hypoperfusion. As a prerequisite for the delineation of ischemic areas a wide range of signal intensities between the precontrast images and the peak myocardial enhancement should be provided by the sequence. Thus, the strong myocardial signal enhancement of the SSFP-sequence sets the basis for the detection of various degrees in myocardial hypoperfusion (Fig. 8). In order to apply quantitative or semiquantitative techniques, it is important to consider whether linearity exists between the signal at the tissue level and the amount of contrast agent administered (12, 13). Significant differences of myocardial enhancement with respect to the injection rate could only be measured for the higher dosage group between the rates of 2 and 4 ml/s, where the slower injection rate was associated with lower myocardial enhancement. The prolonged administration of a CA bolus associated with very low injection rates leads to dispersion of such an extent that it cannot build up to an enhancement comparable with a more compact bolus at higher injection rates. The strongest myocardial enhancement for the higher dosage group was associated with a faster injection speed of 4 versus 3 ml/s compared to the lower

dosage group (Fig. 4). This phenomenon could be explained by the fact that larger CA boli have a different optimal injection rate in order to build up to a maximum. Based on our results, an injection rate of at least 3 ml/s should be used in order to eliminate a significant effect on the signal response at the myocardial level.

4.3.   *Determinants of myocardial upslope*

The myocardial upslope is strongly influenced by the injection rate of a peripherally administered CA but is independent of the CA-dosage (Fig. 6). The myocardial SI-curves display a significantly slower upslope when the CA-agent was injected at the lowest rate of 2 ml/s compared to 3 and 4 ml/s. Interestingly, no increase was found with even higher rates (8 ml/s). However, the scatter between different patients was more pronounced. Thus, there seems to be an upper limit for improving the compactness of CA arrival in the LV by faster CA injection. According to the result, this limit is reached at an injection speed of approximately 4 ml/s. Most likely the effects of faster injection rates are largely abolished due to dispersion caused by transit through the peripheral and pulmonary vasculature. Whereas the CA did not have an effect on myocardial or LV upslopes, higher doses of CA were associated with a significant increase in peak myocardial enhancement. These findings support the results by Epstein et al. (14) who report that the amplitude of the LV cavity concentration approximately scales with CA dose, while the curve width remains approximately unchanged when the injection rate is increased. As a consequence, future perfusion trials should be performed with injection speeds of 3–4 ml/s since 2 ml/s leads to a slower arrival of the bolus and 8 ml/s causes no further improvement. Other groups which have applied a different imaging modality such as computed tomography, but also an extracellular contrast agent to study myocardial perfusion have pointed out that a significant fraction of the contrast bolus is extracted on the first pass of a bolus through the coronary circulation (15). This needs to be taken into account when deriving absolute values of myocardial perfusion.

We were able to show that the myocardial upslope is mainly determined from the LV upslope (Fig. 5), which is easy to extract. A simple method for correcting myocardial perfusion curves for different hemodynamic conditions can be achieved by dividing the myocardial upslope through the LV upslope which allows for the calculation of a myocardial perfusion reserve index (MPRI) by division of the results at maximal vasodilation through the results at rest. This semiquantitative approach has been successfully applied for the detection of regional ischemia (10) and higher accuracy has been achieved with correction for LV upslopes versus uncorrected data (16). A limitation of this method is that it cannot be derived in mathematical terms as opposed to the quantitative approach with more complex modeling applied by other groups (17, 18) Jerosch-Herold et al. could show that

a quantitative relationship between upslope and myocardial blood flow can be derived from the central volume principle (19). Our study shows that the LV upslope indeed corresponds with the resulting response function over a wide variety of input parameters. The main differences of myocardial upslope after correction largely depend on blood flow.

4.4.   *Study limitations*

For the pilot study, we did not examine the same number of patients with the T1-GrE sequence. Our group has gathered previous experience with T1-GrE sequences (Nagel et al., JCMR, in press). Over the past years, the development of newer sequences like the TGrE-EPI and the SSFP sequence clearly demonstrated their advantages in terms of image quality and myocardial enhancement. In order to keep the number of patients who participate in a research indicated adenosine stress study to a minimum, we decided not to pursue this study arm any further. A clear limitation of the study is that only three predefined sequences were used and no further adaptation of imaging parameters such as TE, TR, flip angle, or prepulse delay was performed. The data represents no final answer to the questions raised. Other results may be achieved with other sequences; however, we tried to avoid further complexity, which would have resulted in a much larger patient population. If we had used a similar study design as shown in Figs. 1 and 2 with 3 different sequences, 2 CA dosages and 4 injection speeds but had used 15 patients per study arm, we would have had to examine a total number of 360 patients, which represents an unattainably high number in a clinical setting.

5.   Conclusion

In healthy myocardial segments, the myocardial upslope is mainly determined by the LV upslope. Both, myocardial enhancement and upslope are largely independent from the injection rate of a CA-bolus as long as the injection speed is not below 3 ml/s. Myocardial enhancement is dose dependent. The study shows that a simple correction for the LV upslope allows to normalize for a wide variety of input parameters. Differences of myocardial upslope or peak signal intensity after correction should be mainly dependent on blood flow. Future studies should concentrate on enhancing theses differences, rather than opimizing injection schemes.

References

1. Atkinson DJ, Burstein D, Edelman RR. First-pass cardiac perfusion: evaluation with ultrafast MR imaging. Radiology 1990; 174:757–762.
2. Keijer JT, van Rossum AC, van Eenige MJ, Bax JJ, Visser FC, Teule JJ, Visser CA. Magnetic resonance imaging of regional myocardial perfusion in patients with single-vessel coronary artery disease:

quantitative comparison with (201)Thallium-SPECT and coronary angiography. J Magn Reson Imaging 2000; 11:607–615.

3. Eichenberger AC, Schuiki E, Kochli VD, Amann FW, McKinnon GC, von Schulthess GK. Ischemic heart disease: assessment with gadolinium-enhanced ultrafast MR imaging and dipyridamole stress. J Magn Reson Imaging 1994; 4:425–431.

4. Wilke N, Jerosch-Herold M, Wang Y, Huang Y, Christensen BV, Stillman AE, Ugurbil K, McDonald K, Wilson RF. Myocardial perfusion reserve: assessment with multisection, quantitative, first-pass MR imaging. Radiology 1997; 204:373–384.

5. Reeder SB, Atalar E, Faranesh AZ, McVeigh ER. Multi-echo segmented k-space imaging: an optimized hybrid sequence for ultrafast cardiac imaging. Magn Reson Med 1999; 41:375–385.

6. Canet E, Douek P, Janier M, Bendid K, Amaya J, Millet P, Revel D. Influence of bolus volume and dose of gadolinium chelate for first-pass myocardial perfusion MR imaging studies. J Magn Reson Imaging 1995; 5:411–415.

7. Vallee JP, Lazeyras F, Kasuboski L, Chatelain P, Howarth N, Righetti A, Didier D. Quantification of myocardial perfusion with FAST sequence and Gd bolus in patients with normal cardiac function. J Magn Reson Imaging 1999; 9:197–203.

8. Jerosch-Herold M, Wilke N, Wang Y, Gong GR, Mansoor AM, Huang H, Gurchumelidze S, Stillman AE. Direct comparison of an intravascular and an extracellular contrast agent for quantification of myocardial perfusion. Cardiac MRI Group. Int J Card Imaging 1999; 15:453–464.

9. Wilke N, Kroll K, Merkle H, Wang Y, Ishibashi Y, Xu Y, Zhang J, Jerosch-Herold M, Muhler A, Stillman AE, et al. Regional myocardial blood volume and flow: first-pass MR imaging with polylysine-Gd-DTPA. J Magn Reson Imaging 1995; 5:227–237.

10. Al-Saadi N, Nagel E, Gross M, Bornstedt A, Schnackenburg B, Klein C, Klimek W, Oswald H, Fleck E. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. Circulation 2000; 101:1379–1383.

11. Hunold P, Maderwald S, Eggebrecht H, Vogt FM, Barkhausen J. Steady-state free precession sequences in myocardial first-pass perfusion MR imaging: comparison with TurboFLASH imaging. Eur Radiol 2003; 26:26.

12. Tweedle MF, Wedeking P, Telser J, Sotak CH, Chang CA, Kumar K, Wan X, Eaton SM. Dependence of MR signal intensity on Gd tissue concentration over a broad dose range. Magn Reson Med 1991; 22: 191–194, 195–196.

13. Vallee JP, Sostman HD, MacFall JR, Wheeler T, Hedlund LW, Spritzer CE, Coleman RE. MRI quantitative myocardial perfusion with compartmental analysis: a rest and stress study. Magn Reson Med 1997; 38:981–989.

14. Epstein FH, London JF, Peters DC, Goncalves LM, Agyeman K, Taylor J, Balaban RS, Arai AE. Multislice first-pass cardiac perfusion MRI: validation in a model of myocardial infarction. Magn Reson Med 2002; 47:482–491.

15. Canty JM Jr, Judd RM, Brody AS, Klocke FJ. First-pass entry of nonionic contrast agent into the myocardial extravascular space. Effects on radiographic estimates of transit time and blood volume. Circulation 1991; 84:2071–2078.

16. Nagel E, Klein C, Paetsch I, Hettwer S, Schnackenburg B, Wegscheider K, Fleck E. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. Circulation 2003; 108:432–437.

17. Cullen JH, Horsfield MA, Reek CR, Cherryman GR, Barnett DB, Samani NJ. A myocardial perfusion reserve index in humans using first-pass contrast-enhanced magnetic resonance imaging. J Am Coll Cardiol 1999; 33:1386–1394.

18. Fritz-Hansen T, Rostrup E, Sondergaard L, Ring PB, Amtorp O, Larsson HB. Capillary transfer constant of Gd-DTPA in the myocardium at rest and during vasodilation assessed by MRI. Magn Reson Med 1998; 40:922–929.

19. Jerosch-Herold M, Hu X, Murthy NS, Rickers C, Stillman AE. Magnetic resonance imaging of myocardial contrast enhancement with MS-325 and its relation to myocardial blood flow and the perfusion reserve. J Magn Reson Imaging 2003; 18:544–554.