How We Perform Myocardial Perfusion With Cardiovascular Magnetic Resonance

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ABSTRACT

Cardiovascular magnetic resonance first-pass perfusion imaging has developed considerably over the past decade. Several studies have shown that this technique is accurate for the detection of myocardial ischemia. In this article we outline the procedure of myocardial perfusion imaging with cardiovascular magnetic resonance as it is performed at our centers, describe the sequences that are currently used in more detail, review our process of image interpretation, and highlight potential pitfalls that we have encountered in our experience with performing this technique in over 2000 patients.

INTRODUCTION

The rationale for myocardial perfusion assessment is based on a fundamental concept, i.e., a decrease in myocardial perfusion representing the first event in the progression of myocardial ischemia, which is known as the ischemic cascade (1). Over the past three decades, single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have dominated myocardial perfusion imaging in clinical practice on the basis of an extensive amount of research. These techniques do, however, have several important limitations, which include the occurrence of attenuation artifacts using SPECT (2) and the application of radioactive tracers which prohibits close follow-up examinations. At the same time PET, which is considered to be the standard of reference for myocardial perfusion imaging, is limited by its reduced availability. Furthermore, the low spatial resolution of nuclear techniques prohibits the assessment of subendocardial ischemia. Cardiovascular magnetic resonance (CMR) first-pass perfusion imaging has developed considerably over the past years, showing promising results in single center studies (3–5) and first multicenter trials (6, 7). An in-plane resolution of 2–3 mm allows separate visualization of the endo- and epicardial layers of the left ventricle. Recently, it could be shown that CMR perfusion imaging can identify regional reductions in myocardial blood flow over a wider range than SPECT imaging (8). Furthermore, a direct comparison of CMR perfusion imaging versus SPECT for the detection of CAD demonstrated superiority of the CMR approach (9). Superiority of CMR perfusion imaging versus SPECT is also demonstrated in the multicenter, multivendor CMR Impact program (Magnetic Resonance Imaging for Perfusion Assessment in Coronary artery disease Trial) (10). High performance of CMR perfusion imaging, however, mandates profound knowledge of the CMR hardware and software potential, the characteristics of paramagnetic contrast agents (CA) and the underlying pathophysiology of myocardial perfusion. Additionally, it is necessary to consider the differences, advantages, and limitations of CMR perfusion measurements with respect to other clinically available methods. This article is intended to provide the reader with instructions for the application and performance of perfusion measurements with cardiac magnetic resonance imaging.

PATHOPHYSIOLOGY

Myocardial perfusion is controlled by the interplay of the driving pressure gradient and the resistance of the coronary vascular bed. Within certain limits, changes in this pressure will be counteracted by changes in resistance to keep coronary flow constant (in case of constant myocardial oxygen consumption). This behavior is generally known as coronary autoregulation. By means of autoregulation, the coronary bed maintains myocardial...
perfusion within a narrow range in spite of wide fluctuations in coronary perfusion pressure. In canine experiments progressive dilatation of resistance vessels is able to maintain coronary blood flow in the presence of an obstruction or stenosis for up to 90% coronary artery diameter narrowing at rest (11). During exercise or pharmacological stress, however, autoregulation becomes fully exhausted in stenosis-dependent myocardium leading to ischemia. Thus, the initial abnormality that occurs at the onset of the ischemic cascade is an imbalance between blood flow and oxygen demand in stenosis-dependent myocardium, whereas blood flow matches oxygen demand in normally perfused myocardium. Coronary angiography is considered the reference standard for evaluating the presence and the severity of coronary stenoses in clinical practice. Although the anatomical extent of the disease is best demonstrated by coronary angiography, perfusion imaging can provide the hemodynamic significance of epicardial stenoses. As a prerequisite the applied perfusion technique has to identify 2-fold regional differences in vasodilated flow because hyperemic flow in regions supplied by 70% diameter stenoses is reduced by about 50% (12). In dogs, first-pass contrast-based MR perfusion imaging using a steady-state free-precession (SSFP) technique with inversion recovery preparation was shown to fulfill this important diagnostic requirement (13). At the same time, angiographic evidence of stenosis severity has been reported to show poor correlation with clinical or physiologic parameters such as coronary flow reserve and reactive hyperemia (14). Hence, discrepancies between coronary anatomy and perfusion imaging do not necessarily indicate a failure in the assessment of either; instead, they may indicate the complexity of the relationship between anatomical and physiological conditions.

### PULSE SEQUENCES

Different centers and vendors use different sequences and contrast agent application schemes for CMR myocardial perfusion imaging. Although there is no standardized technical approach, most centers rely on a T1-weighted sequence to create images that enhance with the passage of gadolinium contrast agents into the coronary bed, resulting in a brightening of the myocardium compared with precontrast images. T1-weighting can be obtained by inversion recovery or saturation recovery, either non-slice selective or slice-selective (= notched pulse saturation). The main issue in the design of CMR perfusion sequences is the trade-off between spatial and temporal resolution, acquisition time, and signal-to-noise ratio. A sufficient temporal and spatial resolution, which is required to image several cardiac slices every or at least every other heartbeat and to achieve an in-plane resolution of 2–3 mm to separately visualize the endo- and epicardial layers, can be obtained with a fast data readout by means of gradient echo (GrE), echo planar imaging (EPI) or SSFP techniques. Recommendations for CMR perfusion equipment with 1.5 Tesla scanners can be found in Table 1.

In a direct comparison of 3 standard sequences (T1-GrE, GrE-EPI, balanced SSFP), we could show that the balanced SSFP-technique is associated with higher peak enhancement when using 0.05 mmol/kg bw of Gd-BOPTA and superior image quality compared with the other sequences (15) (Figs. 1–3). Other groups provided evidence that SSFP results in a higher signal-to-noise ratio, superior spatial resolution and also improved image quality when compared with spoiled T1-GrE in first-pass myocardial perfusion MRI (16, 17). Consequently, balanced SSFP has become the standard MR perfusion sequence at the German Heart Institute Berlin. A detailed description of the methodology, which was developed for a clinical whole body 1.5 Tesla MR system (Philips Intra, Best, The Netherlands) and a 5 element cardiac phased-array coil for signal reception, can be downloaded at the website (http://www.cmr-academy.com/cookbooks.html). Based on the multicenter results (6, 7), the notched-prepared hybrid echo-planar pulse sequence used on a GE scanner is the standard approach at the Cardiology Division of the University Hospital in Zurich.

### STRESS AGENTS

To induce differences between normal and ischemic myocardium, pharmacological vasodilation is applied in the patients
using adenosine or dipyridamole (18). These pharmacological agents proved to be safe and well-tolerated. Adenosine, an endogenous nucleotide, is a potent vasodilator of most vascular beds, except for hepatic and renal arterioles. It exerts its pharmacological effect through the activation of purine A1 and A2 cell-surface adenosine receptors. The essence of the pharmacological mechanism lies in the inhibition of the slow inward Ca \textsuperscript{2+} current, thereby reducing calcium uptake, and in the activation of adenylate cyclase through A2 receptors in smooth muscle cells. Dipyridamole is the prodrug of adenosine and is activated by metabolism in the liver. Thus, vasodilatory capacity depends on the individual metabolic rate, and a longer half-life potentially translates into prolonged side effects after administration. We prefer adenosine as the stress agent of choice for myocardial perfusion imaging at both institutions since its half life is extremely short, allowing a high degree of controllability (furthermore, dipyridamole has been withdrawn from the market in Switzerland recently).

Both the microcirculation supplied by normal and stenotic coronary arteries is dilated to their maximum using these drugs (with a mildly stronger effect of adenosine [19]). Since autoregulation already causes compensatory maximal dilation at rest in stenosis-dependent myocardium, these vessels cannot be dilated any further. Thus, pharmacologic vasodilation induces an increase of blood flow in myocardial areas supplied by normal coronary arteries whereas no (or only minimal) change is found in areas supplied by stenotic coronary arteries. Maximal coronary vasodilation can be achieved safely with intracoronary adenosine administration, and an intravenous infusion at a rate of 140 μg/kg/minute will induce nearly maximal coronary hyperemia comparable to an intracoronary infusion (20).

**Side effects**

The vasodilatory effect of adenosine may result in a mild-to-moderate reduction in systolic, diastolic and mean arterial blood pressure (< 10 mmHg) with a reflex increase in heart rate. Some patients complain about chest pain, which is rather nonspecific and does not reliably indicate the presence of CAD. Since adenosine exerts a direct depressant effect on the SA and AV nodes transient first-, second- and third-degree AV block and sinus bradycardia have been reported in 2.8%, 4.1% and 0.8% of patients, which usually resolve spontaneously without alteration in the adenosine infusion (21). Also, adenosine can cause significant hypotension. Patients with intact baroreceptor reflex are able to maintain blood pressure in response to adenosine by increasing cardiac output and heart rate. Because adenosine is a respiratory stimulant primarily through activation of carotid body chemoreceptors, intravenous administration showed increases in minute ventilation, reduction in arterial PCO\textsubscript{2} and respiratory alkalosis. Approximately 14% of patients complain of dyspnea and an urge to breathe deeply during adenosine infusion. These side effects are transient and usually do not require medical intervention.

**Safety**

During stress examinations monitoring of the patient within the magnet is mandatory and requires the same precautions and emergency equipment as any other stress examination. Apart from specific contraindications for CMR such as retro-orbital metal, cerebral clips or pacemakers, the contraindications related to the application of adenosine are listed in Table 2. Prior to performing stress examinations, we record a twelve lead ECG to make sure that no signs of resting ischemia, AV-Block > I or arrhythmia are present. Although adverse events are rare, preparation and practice for rapid removal of the patient from the magnet needs to be borne in mind. In addition, the adenosine infusion should be discontinued in patients developing persistent or symptomatic AV block (type II or complete heart block), severe hypotension (systolic blood pressure < 90 mmHg) and bronchospasm. Fortunately, these adverse effects are transient and
were no sustained episodes of A V block. third-degree in 72) and resolved spontaneously in most patients. episode of pulmonary edema. Transient A V node block occurred. myocardial infarction, 7 episodes of severe bronchospasm and 1 were reported in 81.1% of patients. There were no deaths, 1 received aminophylline. Minor and well-tolerated side effects. 13%, infusion was terminated early in 7%, and 0.8% of patients. completed in 80% of patients, dose reduction was required in 9,256 consecutive patients (21). The infusion protocol was. at 140 mcg/kg/min was evaluated during radionuclide imaging. acquiring stress imaging data. Safety of an adenosine infusion. pharmacological stress with adenosine presents a safe method of. echocardiography, SPECT and CMR, which shows that phar- macological stress in different diagnostic modalities of cardiac imaging. So far, there is evidence accumulated in. over 10,500 patients studied with thallium radionuclide imaging, echocardiography, SPECT and CMR, which shows that pharmacological stress with adenosine presents a safe method of acquiring stress imaging data. Safety of an adenosine infusion. at 140 mcg/kg/min was evaluated during radionuclide imaging of 9,256 consecutive patients (21). The infusion protocol was. completed in 80% of patients, dose reduction was required in 13%, infusion was terminated early in 7%, and 0.8% of patients. received aminophylline. Minor and well-tolerated side effects. were reported in 81.1% of patients. There were no deaths, 1 myocardial infarction, 7 episodes of severe bronchospasm and 1 episode of pulmonary edema. Transient AV node block occurred. in 706 patients (first-degree in 256, second-degree in 378 and third-degree in 72) and resolved spontaneously in most patients (n = 508) without alteration in the adenosine infusion. There were no sustained episodes of AV block.

### CONTRAST AGENTS AND INJECTION SCHEME

During the first pass of commercially available extracellular agents, myocardial signal intensity depends not only on perfusion, but also on tissue blood volume, the size of the extravascular compartment, and the degree of capillary permeability (22). Animal studies have shown that the myocardial upslope during the first pass correlates well with blood flow as determined with microspheres (23). In order to achieve a linear relationship between CA concentration and signal intensity in blood, it is mandatory to use low concentrations of CAs, while higher concentrations are advantageous to generate sufficient signal change during first pass in myocardium. Dosage regimen have varied between 0.025 and 0.15 mmol/kg of extracellular CAs in different studies. A systematic evaluation of the contrast agent application scheme (dose/injection speed) was performed by our group (15). We could show that both myocardial enhancement and upslope are largely independent from the injection rate of the CA-bolus as long as the injection speed is not below 3 mL/s. For clinical purposes a bolus with a dosage of 0.05 mmol/kg bw of an extracellular CA (e.g., gadopentetate dimeglumine [Gd-DTPA], Magnevist, Schering, Berlin, Germany, or gadobenate dimeglumine [Gd-BOPTA], Multihance, Bracco-Byk Gulden, Konstanz, Germany) at an injection speed of 4 mL/s is used at the German Heart Institute Berlin, while a dose of 0.1 mmol/kg bw (of Gd-DTPA or Gd-DTPA-BMA, Gadodiamide injection, Omniscan, GE Healthcare, Chalfont St. Giles, United Kingdom) at 5 mL/s is used at the Zurich University Hospital. The bolus is followed by a 20 mL saline flush using the same injection rate to facilitate a compact bolus passage. We recommend the use of an automatic infusion system (e.g., Spectris, Medrad Inc., Indiana, Pennsylvania, USA) for exact and reproducible dosage and timing. We advise use of 218 gauge venflons for separate administration of the stress agent and CA. If one intravenous line is used, a bolus injection will cause an abrupt increase in the infusion rate of the adenosine running through the same line, which can lead to significant AV nodal block. Summarizing, there is general agreement among most investigators that fast T1-weighted imaging during a rapid bolus injection of a T1-shortening extracellular CA currently produces the best results in CMR perfusion imaging whereas the optimum CA dose depends on the pulse sequence used. For extracellular conventional CA, approximately 50% of the CA is leaking into the interstitial space during first pass. For intravascular CA, this is not the case in healthy tissue, but leakage is present in ischemic tissue, potentially complicating model calculations for perfusion in ischemic and non-ischemic tissue. Also, proton exchange rate across capillary membranes has to be taken into account for intravascular CA. The role of intravascular CAs still needs clarification (24).

### IMAGING PROCEDURE

The overall procedure consists of cine wall motion imaging of the heart at rest, perfusion imaging under vasodilator stress, and finally delayed enhancement imaging, as described elsewhere (25) (Fig. 4). Whether a stress only (3, 6, 7) or a stress-rest perfu- sion protocol (5, 26) performs better is still open for debate. De- pending on the clinical question and consequently the protocol used, the examination time may vary between 40–75 minutes. The myocardial perfusion scan is typically completed within 15–25 seconds, i.e., long enough to capture the first pass of the CA, and the scan is generally performed during a prolonged breathhold.
It is of special importance to explain not only the course of the examination to the patient but also the breathhold procedure. Generally the breathhold should be performed during end expiration to ensure reproducible slice geometry. At the German Heart Institute Berlin, the perfusion scan consists of two breathhold periods. The first is a short one, lasting about 6 to 10 seconds during baseline acquisition of myocardial signal intensity. Then the patient is asked to inhale and exhale once more and to hold his breath as long as possible. Right before starting this breathhold command, the contrast bolus is administered. The patient should stop breathing at least for 15 to 20 seconds resulting in a fixed slice geometry during the first-pass of the contrast agent; if the patient cannot hold his breath throughout the whole scan, he or she should inhale and exhale once voluntarily and hold the breath again (Fig. 5). At the University Hospital Zurich, perfusion imaging is typically performed during end-inspiration, since breath-holding appears somewhat easier in this position. However, ECG-triggering might be more demanding in end-inspiration. Since breath-holding is feasible in end-inspiration for 20–30 seconds in most patients, only one breath-hold is required for first pass imaging in end-inspiration starting simultaneously with the begin of scanning and CA injection.

**ANALYSIS OF CMR PERFUSION STUDIES**

This article does not claim to provide an in-depth discussion of all analysis methods. A detailed discussion of analysis of perfusion data is available elsewhere (27). Since many different analysis procedures were reported, some common definitions for analysis characteristics are proposed in Figure 6. Visual reading depends on reader experience and thus, can yield highly accurate results, but is limited by inter-reader variability, unless reading criteria are easily applicable and clearly defined. Unlike visual analysis, quantitative approaches yield numbers, which can be correlated with perfusion (e.g., upslope data), so-called perfusion-linked parameters, or which directly represent tissue perfusion (in absolute units in mL/min/g). Such quantitative data can be extracted from the images manually (time-consuming), semi-automatically (with less observer-interaction with the data), or automatically (no interaction with data, but high quality data needed).

**Visual analysis**

Generally, a qualitative analysis can be performed in clinical practice by visual comparison of the contrast enhancement in different myocardial regions. The perfusion technique with MRI itself is simply that of an impulse response technique: after the intravenous bolus administration of the CA, normal myocardium will show a homogeneous increase in signal intensity, followed by contrast washout. Conversely, areas supplied by a coronary artery with a high-grade stenosis will show delayed signal intensity increase (Fig. 7 and Supplemental movies). However, several aspects need to be taken into account. Despite significant improvements of imaging methods, data quality is still heterogeneous (7). Besides breathing-related motion artifacts and those resulting from ECG mistriggering, dark subendocardial artifacts may occur in normal subjects depending on the pulse sequence employed and the CA dose and type used. These artifacts are most likely related to susceptibility between blood pool and subendocardium. Since CA concentration in the blood pool rapidly declines during first pass, these artifacts, if caused by susceptibility, diminish during the first few dynamics after CA arrival in the left ventricular cavity. Perfusion defects, on the other hand, usually persist beyond the point of peak myocardial enhancement, which render this important differentiation possible (Fig. 8 and Movie 2). Recently, Klem et al. published a study using a pre-defined visual interpretation algorithm that combines data from stress/rest perfusion and delayed enhancement imaging and could show that rest-perfusion is an important component, because in combination with delayed enhancement imaging, it can help distinguish true defects from artifact on the stress-perfusion images (28). However, at this point, we would like to emphasize that the efficacy of this analysis algorithm is
dependent on the presence of artifacts and thus, it is not expected to be useful in data sets of adequate quality.

**Quantification**

Most quantitative analysis methods rely on time intensity curves measured from regions of interest in the myocardium. While the use of higher doses of extracellular contrast agents is recommended for a visual assessment, lower doses (0.025–0.05 mmol/kg bw) are preferred to measure absolute or relative changes in myocardial blood flow and volume (29).

Various perfusion-linked parameters for the distinction of ischemic and nonischemic myocardial segments, such as maximal signal intensity, contrast appearance time, time to maximal signal intensity and the steepness of the signal intensity curve’s upslope determined by a linear fit have been evaluated. A measure of the perfusion reserve index can be calculated from the myocardial upslopes during stress and rest and shows the most significant difference between ischemic and nonischemic myocardial segments (26). The parameters are relatively easy to extract from the curves and are associated with a high reproducibility and low inter- and intra-observer variability (4). Recently, this approach yielded a sensitivity of 88%, specificity of 90% and accuracy of 89% for the diagnosis of significant CAD(5).

The application of this method involves the following steps: the endo- and epicardial contours are traced and corrected manually for changes of diaphragmatic position due to breathing or diaphragmatic drift. Care needs to be taken to place the contours on the myocardium and to exclude the left ventricular cavity and the pericardium. In case transmural data are analyzed, the epicardial coronary arteries should also be excluded from the contours. The myocardium is then typically divided into 6-8 equiangular segments per slice and numbered clockwise beginning with the anterior septal insertion of the right ventricle. An additional region of interest is placed within the cavity of the left ventricle excluding the myocardial segments and the papillary muscles. Images acquired after premature ventricular beats or with insufficient cardiac triggering need to be excluded from the analysis to guarantee steady-state conditions. Signal intensity is determined for all dynamics and segments. To correct for inhomogeneous coil sensitivity, the signal change during first pass (= upslope) is divided by the pre-contrast signal intensity of the corresponding segment. For possible differences in the input function the upslopes of the myocardial segments are corrected for by dividing these upslopes by the upslope of the left ventricular signal intensity curve. Perfusion reserve index can be calculated by dividing the results at maximum adenosine infusion by the...
results at rest. This analysis is based on the calculation of differences in upslope between normally perfused and hypoperfused regions, but underestimates high perfusion values (3, 30).

**Absolute quantification**

For absolute quantification of myocardial perfusion with CMR first-pass perfusion imaging, additional requirements need to be met. The group of Jerosch-Herold has contributed substantially to this field validating their approach in animal experiments by comparison to measurements with labeled microspheres (31, 32). Absolute differences between myocardial regions and between patients can be calculated using the mathematical process of Fermi model-constrained deconvolution (33). In a single center study on heart transplant arteriopathy, this method resulted in a sensitivity and specificity of 100% and 85%, respectively, using a cut-off value for the myocardial perfusion reserve of >2.3 for the exclusion of transplant arteriopathy (34). This method is based on the Fick principle (conservation of mass), where the myocardial tissue curve can be represented as convolution of the tissue impulse response with the arterial input. The initial amplitude of the tissue curve equals tissue blood flow. Recently, a
model-independent approach was proposed avoiding specific assumptions about the shape of the impulse response and applying regularization for robust deconvolution (31). Nevertheless, diagnostic performance of absolute perfusion measurements by first pass MR has not been validated so far in larger clinical studies.

**PITFALLS/ADVANCED ISSUES**

**Coverage**

We are able to cover 16 out of 17 myocardial segments according to the standardized myocardial segmentation of the heart (35) using three short axis views applying the same geometry that is used to plan the short axis views for cine functional imaging. Although this approach does not cover segment 17, studies incorporating the apex adding additional long axis views for myocardial perfusion imaging with CMR could not show ischemia in this region (36). Furthermore, the analysis of only the inner 3 out of 5–8 short axis slices resulted in a significantly improved diagnostic accuracy for the detection of coronary artery disease (5, 7). These findings illustrate that diagnostic quality may differ with the order of slice acquisition and/or slice location. Thus, the question of optimum coverage and segmentation cannot be answered definitely at the present time.

**Stress/rest vs. rest/stress**

There are some advantages of stress/rest imaging in comparison with rest/stress imaging with vasodilator stress. The visual difference between normal and ischemic myocardium is more pronounced during the stress examination. However, using this approach, rest perfusion imaging may not detect an old myocardial infarction, since wash-out of normal myocardium after 15 minutes may be incomplete and the infarcted area might already show late gadolinium enhancement (37, 38). In these cases, late gadolinium enhancement imaging will be able to detect scar tissue and allow a better delineation between ischemic and infarcted tissue. Thus in all patients in whom CMR perfusion imaging is indicated, we recommend performing late gadolinium enhancement imaging as well. Rest perfusion imaging, nevertheless, may be helpful not only for quantitative perfusion reserve calculation but also for visual analysis: Those cases that do show a matching perfusion defect both at stress and rest but do not show any signs of a myocardial scar on late gadolinium enhancement are most likely to represent artifacts on the perfusion scans. Such a strategy can currently help to differentiate reduced signal in areas of hyperperfusion from artifacts (28). However, we would like to point out, that such “algorithms” are no more than a provisional solution, and consequently, efforts to optimize the CMR perfusion pulse sequences and hardware in order to eliminate artifacts of any kind should continue. As mentioned earlier, further studies are warranted to assess the diagnostic performance of stress-only protocols versus stress-rest protocols.

**SUMMARY**

When appropriately performed, CMR myocardial perfusion imaging produces accurate information on the presence of myocardial ischemia. Use of perfusion imaging is under further investigation for larger, unselected patient populations with suspected or known coronary artery disease. As the implementation of this technique continues to expand, myocardial perfusion CMR imaging might become an integral part of the clinical work-up of cardiovascular patients.

**REFERENCES**
