MR perfusion in the detection of myocardial ischemia

Daniël Lubbers

MR perfusion in the detection of myocardial ischemia

Stellingen behorend bij het proefschrift

MR perfusion in the detection of myocardial ischemia

1. MR perfusie imaging is thans de beste techniek voor de detectie van myocardischemie.

2. Een normaal adenosine "stress-only" perfusie MR onderzoek rechtvaardigt een conservatieve behandeling en het niet verrichten van een invasief onderzoek in een patiëntengroep met angina pectoris en geen myocardinfarct in de voorgeschiedenis. *(dit proefschrift)*

3. Een systematische analyse van "stress-only" adenosine perfusie MR beelden is een vereiste, waardoor het onderzoek vrijwel ervaringsonafhankelijk wordt. *(dit proefschrift)*

4. In de bepaling van globale linkerventrikel functionele parameters kan men in de post-processing volstaan met de analyse van iedere tweede korte as cine serie in een normaal gevormd hart. *(dit proefschrift)*

5. Perfusie imaging op piekdosis dobutamine gedurende een dobutamine stress CMR onderzoek verhoogt de specificiteit van dobutamine stress CMR wandbewegingsanalyse. *(dit proefschrift)*

6. Bij hoge hartslagen is een parallelle imaging techniek, zoals TSENSE geïndiceerd om met een consistente CNR en SNR voldoende spatiële coverage te behouden. *(dit proefschrift)*

7. De bepalende factor in het samenstellen van een MR "stress" protocol is de bekendheid met een eerder doorgemaakt myocardinfarct.

8. Het advies in de ACC/AHA guideline update voor exercise testing om een stresstest in laag risico patiënten te kiezen op basis van zijn eenvoud, lagere kosten en meer algemene bekendheid in plaats van louter diagnostische accuraatheid is omgekeerd denken.

9. In ons huidige tijdperk van snelle technologische ontwikkelingen geeft de trage implementatie van nieuwe, betere technieken helaas onze menselijke beperkingen weer.

10. Bij de verdergaande verbeteringen van de temporele resolutie, z-as coverage en reconstructie algoritmen krijgt CT ook een rol bij perfusie imaging van het myocard.

11. Ten gevolge van het beperkte vermogen tot informatieverwerking van het centrale zenuwstelsel maakt het organisme een keuze tussen de aanwezige zintuiglijke informatie. *(Valerie Muzet, 1998)*

12. Ten gevolge van beperkingen in het PACS maakt het systeem een keuze ten aanzien van de gepresenteerde gegevens.

13. De term standaardprotocol kan heel goed worden vervangen door een "ah-gelukkig-ik-hoef-niet-na-te-denken" protocol.

14. Het voornaamste credo van de Gestalttheorie ("het geheel is meer dan de som der delen") zou nog beter zijn als de minnen uit de sommatie werden gehaald.

15. Vrijwel de gehele radiologie bestaat uit grijstinten, er dus ook NIETS mis met grijs.

Daniël Lubbers
9 december 2009

Daniël D. Lubbers
MR perfusion in the detection of myocardial ischemia
PhD thesis University of Groningen, with a summary in dutch

ISBN: 978-90-367-4042-5

Cover design: Gonda de Jonge & Daniël Lubbers
Skyline Groningen op de cover door Onix©

Layout: Jaap Groen & Daniël Lubbers
Printed by: Gildeprint BV, Enschede

The publication of this thesis was financially supported by :
The University of Groningen, Medis medical imaging systems bv, Oldelft Benelux B.V., Astrazeneca, Bracco Imaging Europe BV, GE Healthcare, Siemens, Medrad, Vital Images, Medtronics, Guerbet and Koos & Betty van Huis.

cmb.

rijksuniversiteit groningen

MR perfusion in the detection of myocardial ischemia

Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 9 december 2009
om 13.15 uur

door

Daniël Dominicus Lubbers

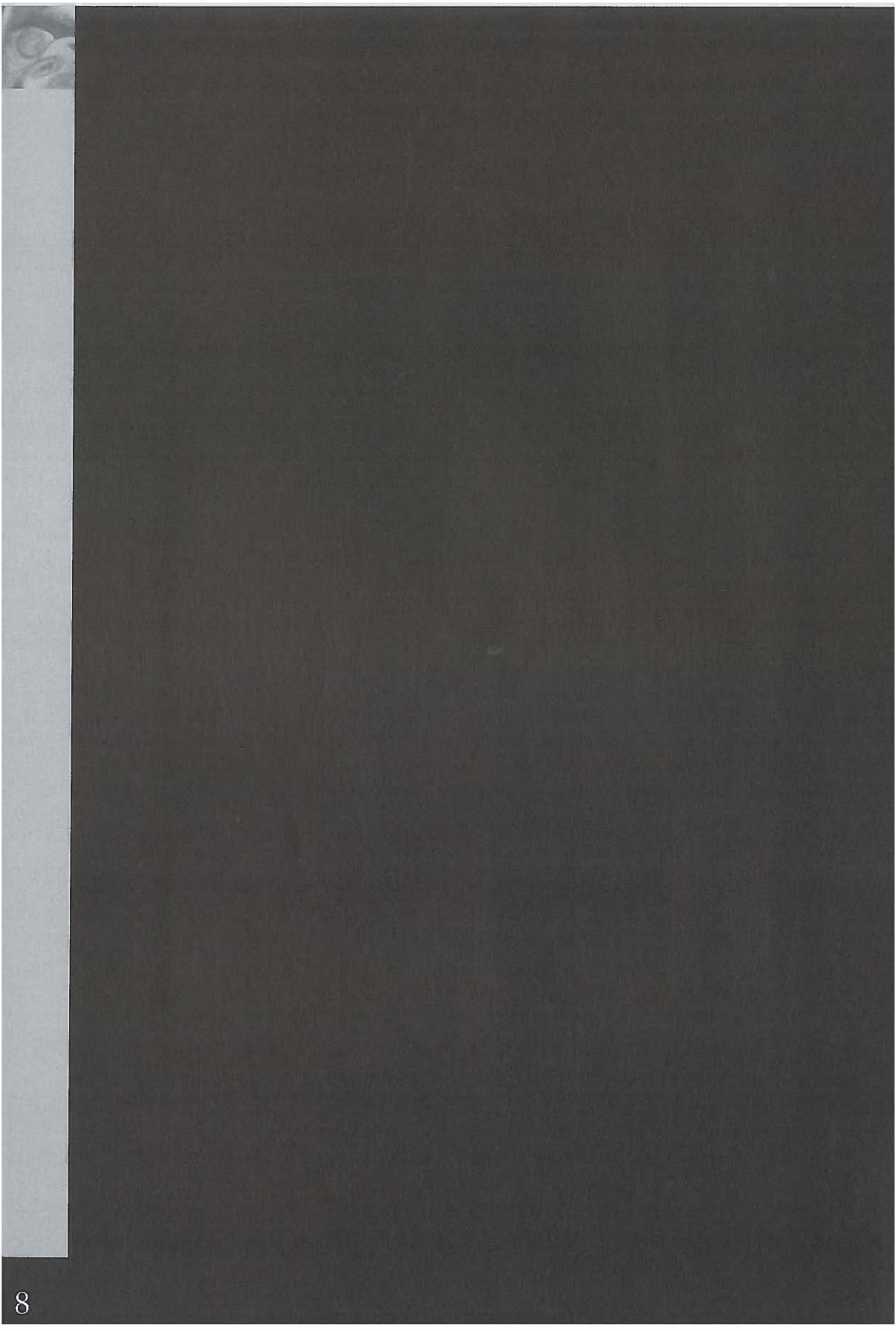
geboren op 24 december 1974
te Groningen

Promotor:	Prof. dr. M. Oudkerk
Copromotor:	Dr. Th.J.A. Kuijpers
Beoordelingscommissie:	Prof. dr. F. Zijlstra
	Prof. dr. W.P.Th.M. Mali
	Prof. dr. R.A. Dierckx

Paranimfen : Gonda J. de Jonge
Anne L.M. Leusveld

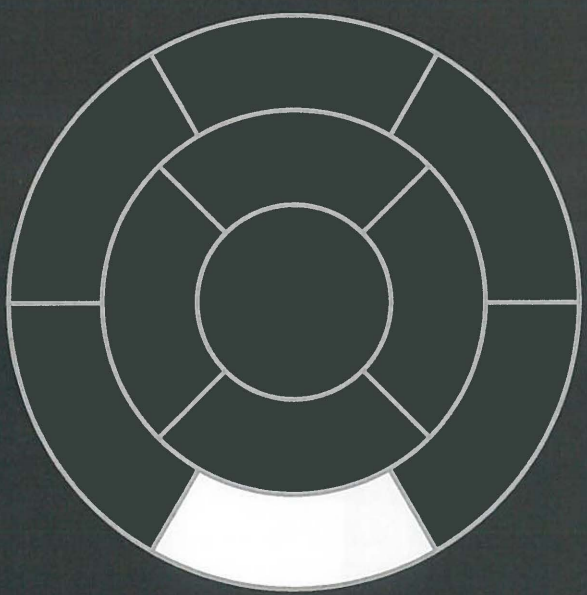
Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged

Contents



chapter 1

General introduction



Based on Imaging Decisions: autumn 2006; vol 10; nr 3

INTRODUCTION

Chest pain accounts for a large number of patients seeking care from a physician. The differential diagnosis however can be broad. The need to diagnose or exclude ischemic heart disease (IHD) is important in this respect. Severity and extent of myocardial ischemia are directly related to prognosis. Besides, revascularization is guided not only by coronary stenosis morphology, but also by its hemodynamic consequences (1). Of course in a large number of cases myocardial ischemia can be made improbable by means of history, physical examination and resting ECG.

This still leaves a large number of patients with stable chest pain for whom the existence of significant coronary artery disease (CAD) or the severity and extent of myocardial ischemia is unclear. Non-invasive methods determine the need for invasive coronary angiography (CAG) and possible revascularization, thereby reducing the pure number of diagnostic CAG's. The assessment of function in this respect has incremental value over morphology alone.

This makes the non-invasive objectification of myocardial ischemia impor-

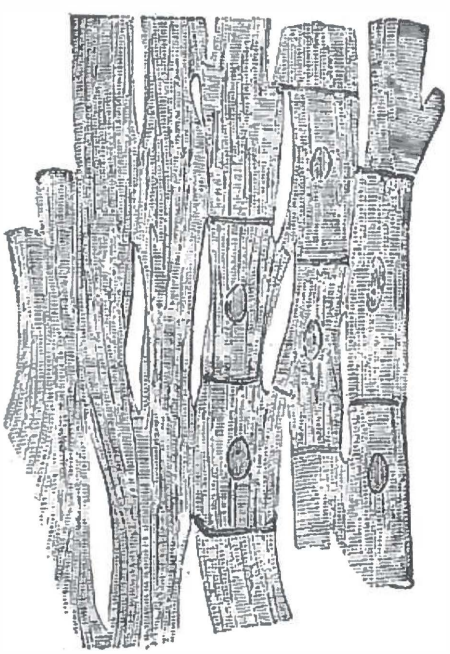


Figure 1: Example of cardiac myocyte arrangement (From Gray's anatomy of the human body)

tant. Methods resembling physical exercise or inducing a stress response (by means of a pharmacological stressor) are widely used for this indication.

The myocardium

The myocardium is composed of branching and anastomising striated muscle cells joined together in a collagen network with a capillary microcirculation (Figure 1)(2). These muscle fibers are arranged in a spiral form making it an effective pump.

Cardiac myocytes have an extreme dependence on aerobic metabolism, with less than 1% of the energy produced by anaerobic metabolism.

This also stresses the importance of adequate blood supply. The blood supply for the myocardium is delivered by the left and right coronary artery and their side branches. A significant stenosis somewhere in this coronary system can cause diminished blood supply to the myocardial distribution area of the specific coronary artery.

The question as to when a stenosis is significant can be viewed from two perspectives. From a morphological perspective a certain luminal diameter narrowing (e.g. 50 or 70%) can be assigned as significant. The best approach is probably defining a stenosis as significant when causing functional alterations to the myocardium.

Non-invasive tests for the detection of myocardial ischemia

ECG alterations, left ventricular wall motion abnormalities and perfusion abnormalities under stress conditions are all means of objectifying myocardial ischemia, which can be performed with different imaging modalities. The advantage of perfusion imaging lies in the earlier occurrence of perfusion abnormalities in the ischemic cascade (3) as compared to wall motion abnormalities or ECG changes (Figure 2).

Nevertheless, exercise ECG testing is one of the most non-invasive commonly test used for the detection of myocardial ischemia, because it is a simple, inexpensive test. The decision to perform a stress-test is in current protocols determined by the pre-test probability of disease. Age, gender, chest pain characterization, prior myocardial infarction and other risk fac-

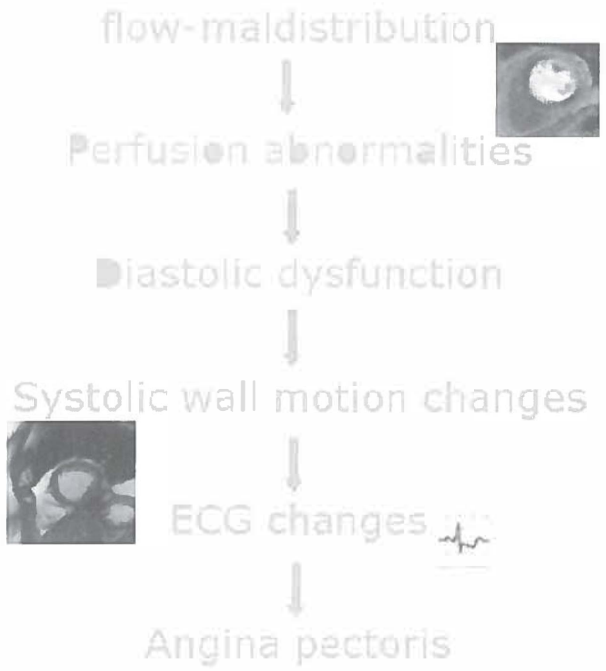


Figure 2: Ischemic cascade

tors determine this pre-test probability. It is generally believed that patients with an intermediate pre-test probability (defined as between 25-75%) are the best candidates for non-invasive testing (4;5). The underlying basis for this conviction comes from the fact that a positive test result is highly predictive of significant CAD in patients with a high pre-test probability, but a negative test result does not exclude significant CAD in these patients. On the other hand in patients with a very low pre-test probability a positive test result is likely to be a false positive result.

Besides ECG-testing, modalities like echocardiography, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) are used as non-invasive stress tests. Echocardiography under dobutamine infusion focuses on detection of wall motion abnormalities indicative of myocardial ischemia. PET and SPECT imaging rely on imaging myocardial perfusion. SPECT can be performed using either thallium-201 or sestamibi-technetium-99m as a radionuclide. This can be performed either using exercise or pharmacological stress. SPECT is currently probably

the most used non-invasive imaging modality for myocardial perfusion imaging. The diagnostic accuracies of these tests vary in patients with an intermediate pre-test likelihood of significant CAD. A meta-analysis comparing these tests reports a sensitivity of 68% and a specificity of 77% for exercise ECG testing (6). With stress echocardiography sensitivity being 76% and specificity 88%, PET results were 91% and 82% respectively for sensitivity and specificity. SPECT scored 88 and 77% respectively.

These well known stress-tests for the detection of myocardial ischemia all have one or more limitations. Exercise ECG testing has a rather poor diagnostic accuracy. Stress echocardiography, although far more accurate than exercise ECG testing, is highly operator dependent and a good acoustic window is mandatory. PET has good diagnostic accuracy, but is only available in specialized centers. SPECT-imaging uses a high radiation dose and is hampered in terms of spatial resolution. MR might be able to overcome these limitations due to its inherent higher spatial and temporal resolution.

History of MR

Jean Baptiste Joseph Fourier formed the basis for MR imaging. His focus on mathematics led to the well-know Fourier transformation, without which creating MR images would not be possible (7). In the 1920s the basics of MR were established by various scientists. Bloch (8) and Purcell (9) were the first to see the possibility of using MR for medical imaging. In 1946 they described the MR phenomenon, for which they shared a Nobel prize in physics in 1952. Another shared Nobel prize was rewarded to Lauterbur

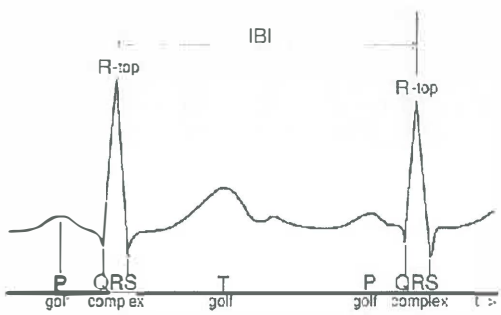


Figure 3: Example of ECG signal. R-top easily detectable for triggering with MR.

(10) and Mansfield (11) in 2003 in physiology and medicine. In 1973 Lauterbur had the first MR images on sample and in 1977 Mansfield produced the first clinical MR images. Hereafter the clinical use of MRI for various clinical indications and body parts evolved rapidly. Imaging of the heart with MR lagged behind, primarily due to the motion of the heart and to a lesser degree due to respiratory motion. Technical advances in MR, for example the use of ECG-triggering, high power gradients, phased array coils and further sequence design employing parallel imaging made it possible to acquire fast images with MR. The MR triggers data acquisition on the ECG-signal (from electrodes applied on the patient), building up images from signal arising from the same phase in the R-R interval (Figure 3).
With various types of sequences both anatomical images (with data acquisition in a fixed, relatively motionless phase in the R-R interval) and functional imaging (also referred to as cine imaging; with data acquisition during the entire or large part of the R-R interval) can be obtained.

MR stress tests

Dobutamine stress MR for wall motion analysis was the first MR stress test which was technically possible (12). Wall motion imaging with MRI provides not only morphological information about the myocardial wall, but also functional information. Three-dimensional information about global and regional myocardial function can nowadays be acquired with high accuracy and reproducibility (Figure 4).
The consistently high level of spatial and temporal resolution with which

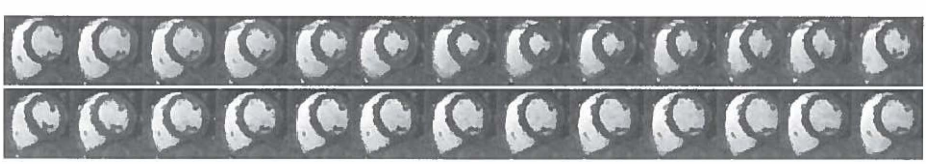


Figure 4: Complete cardiac cycle of a mid-ventricular short-axis slice acquired with retrospective gating. Representing the currently high temporal resolution of cine MR imaging, allowing for the detection of small alterations of systolic wall motion.

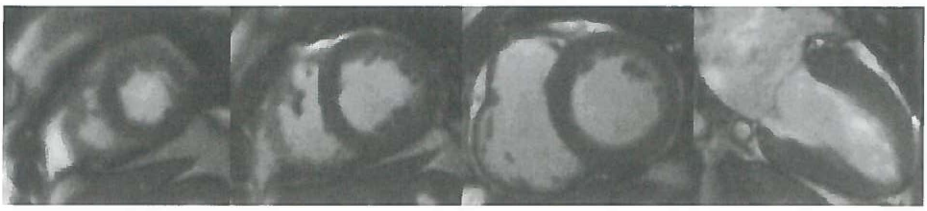


Figure 5: Cine MR series for regional wall motion analysis. Representing 3 short-axis images from the apex to the base of the heart, and one long axis image.

cine MR images can be acquired enables the detection of small alterations of systolic wall motion up to heart rates of 200 beats per minutes. This allows for analysis of regional function with cardiac MRI even under pharmacological stress conditions in multiple slice positions (Figure 5).
Imbalance between oxygen demand and supply, due to a flow-limiting coronary stenosis, will give regional contractile dysfunction in the myocardial area vascularised by the specific affected coronary artery (13). Besides being able to detect myocardial ischemia, low-dose dobutamine can be used to assess myocardial viability.
Dobutamine is a primarily β-1- adrenergic catecholamine which increases myocardial oxygen demand. It has both a positive inotropic and a chronotropic action. The hemodynamic effects are comparable with exercise. It has a low arrythmogenicity, with a half life time of approximately two minutes. The inotropic effect occurs before the chronotropic effect. This positive inotropic effect, which occurs at low doses of dobutamine, can be used for myocardial viability assessment. High dose dobutamine is used for the detection of inducible myocardial ischemia caused by significant CAD.
The purpose of dobutamine stress Cardiovascular Magnetic Resonance Imaging (CMR) in patients with chest pain suspected of significant coronary artery disease is to non-invasively detect the imaging signs of myocardial ischemia, with a diagnostic strategy which is ischemia driven. Thus detected ischemia hereby is a an indication for invasive coronary angiography and possible revascularization.

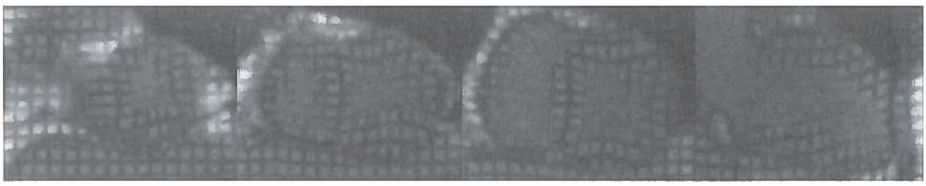


Figure 6: Cine MR series with myocardial grid-tagging. Representing 3 short-axis images and one long axis image.

Left ventricular wall motion analysis for the detection of myocardial ischemia started with a maximum stress level of 20 micrograms dobutamine per kilogram per minute (12, 14-16). This seemed feasible and showed good results, but was inadequate to detect ischemia in all patients. The use of a high dose dobutamine stress MR protocol led to a higher diagnostic accuracy, with sensitivities and specificities from 83-86% (17;18). Nagel et al. compared dobutamine stress CMR directly with dobutamine stress echocardiography in the same patients and found that detection of wall motion abnormalities by MR yielded a significantly higher diagnostic accuracy in comparison to stress echocardiography (17).

Improvements over the years with dobutamine stress CMR in general constituted improved image quality, the use of rapid high gradient MR systems (>30mT/m; SR>100), Steady State Free Precession (SSFP) and parallel imaging techniques.

Myocardial tagging, a technique using non-selective radiofrequency pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients, proved to be useful in left ventricular functional analysis (Figure 6) (19;20). Kuijpers et al. evaluated whether diagnostic accuracy, in a high dose dobutamine stress CMR protocol for the detection of myocardial ischemia, could be further increased with the use of myocardial tagging (21).

A clinical study with 194 patients and two years follow-up assessed the additional value of myocardial tagging for the detection of myocardial ischemia, defining a reduced or absent inward movement of one (subendocardial) or

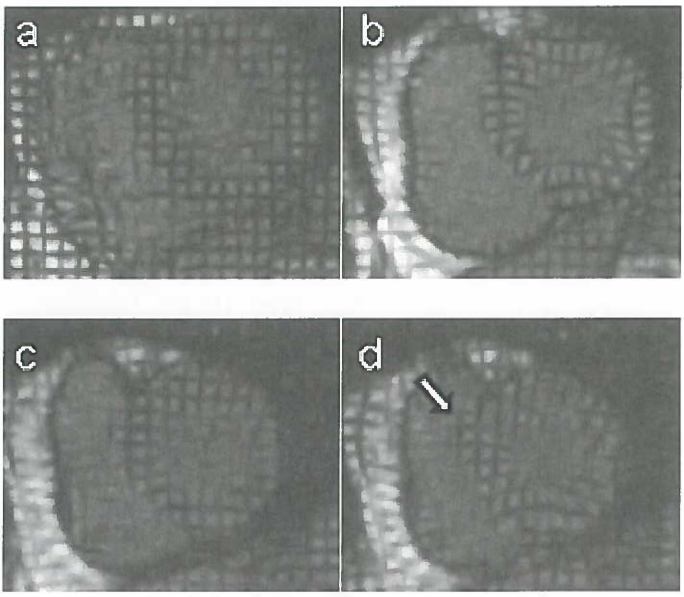


Figure 7: Short-axis basal views with grid-tagging. Diastolic (a) and systolic image (b) at rest showing a normal wall contraction pattern, tagged lines bending in all segments. Diastolic (c) and systolic image (d) under high dose dobutamine showing akinesia of the anteroseptal wall. Example of inducible myocardial ischemia in the distribution area of the Left Anterior Descending coronary artery (LAD).

more grid-lines as a sensitive marker for the detection of myocardial ischemia. Evaluation of these intra-myocardial strains was performed visually and turned out to be more sensitive than analysis of cine images alone, reaching a sensitivity of 96%.(22) Figure 7 shows an example of the use of myocardial grid tagging for the detection of myocardial ischemia.

With these innovations ischemia detection was already possible and quite accurate with MR. Further improvements in MR hardware (mainly the routine use of 1.5T MR scanners) and sequence design allowed for perfusion imaging with MR with potential advantages for MR perfusion in terms of imaging earlier in the ischemic cascade, a more favourable safety profile of adenosine (used mainly for MR perfusion imaging) over dobutamine and faster protocols.

REFERENCE LIST

(1) Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL, Jr., Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A, Jr., Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 1997 July 1;96(1):345-54.

(2) Falk E, Shah PK, Feyter de PJ. Ischemic heart disease. 2007.

(3) Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987 March 9;59(7):23C-30C.

(4) Gibbons RJ, Chatterjee K, Daley J, Douglas JS, Fihn SD, Gardin JM, Grunwald MA, Levy D, Lytle BW, O'Rourke RA, Schafer WP, Williams SV, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A, Jr., Russell RO, Ryan TJ, Smith SC, Jr. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 1999 June;33(7):2092-197.

(5) Fraker TD, Jr., Fihn SD, Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, Ferguson TB, Jr., Fihn SD, Fraker TD, Jr., Gardin JM, O'Rourke RA, Williams SV, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. Circulation 2007 December 4;116(23):2762-72.

(6) Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. Ann Intern Med 1999 May 4;130(9):719-28.

(7) Irwan R, Oudkerk M. History of Magnetic Resonance. Edelman RR, Hesselink JR, Zlatkin MB, Crues J, editors. In Clinical Magnetic Resonance Imaging. [third edition]. 2006.

(8) Bloch F. Nuclear induction. Phys rev 1946; 70:460-474.

(9) Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in solids. Phys rev 1946; 69:37-38.

(10) Lauterbur PC. Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature 1973; 242:190-191.

(11) Mansfield P, Maudsley AA. Medical imaging by NMR. Br J Radiol 1977 March;50(591):188-94.

(12) Pennell DJ, Underwood SR, Manzara CC, Swanton RH, Walker JM, Ell PJ, Longmore DB. Magnetic resonance imaging during dobutamine stress in coronary artery disease. Am J Cardiol 1992 July 1;70(1):34-40.

(13) Ross J, Jr. Regional myocardial function and microvascular dysfunction. Does the alternate cascade represent ischemia? Cardiologia 1999 September;44(9):797-9.

(14) Baer FM, Voth E, Theissen P, Schicha H, Sechtem U. Gradient-echo magnetic resonance imaging during incremental dobutamine infusion for the localization of coronary artery stenoses. Eur Heart J 1994 February;15(2):218-25.

(15) Baer FM, Voth E, Theissen P, Schneider CA, Schicha H, Sechtem U. Coronary artery disease: findings with GRE MR imaging and Tc-99m-methoxyisobutyl-isonitrile SPECT during simultaneous dobutamine stress. Radiology 1994 October;193(1):203-9.

(16) van Rugge FP, van der Wall EE, Spanjersberg SJ, de Roos A, Matheijssen NA, Zwinderman AH, van Dijkman PR, Reiber JH, Bruschke AV. Magnetic resonance imaging during dobutamine stress for detection and localization of coronary artery disease. Quantitative wall motion analysis using a modification of the centerline method. Circulation

1994 July;90(1):127-38.

(17) Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, Ellmer A, Dreysse S, Fleck E. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999 February 16;99(6):763-70.

(18) Hundley WG, Hamilton CA, Thomas MS, Herrington DM, Salido TB, Kitzman DW, Little WC, Link KM. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation 1999 October 19;100(16):1697-702.

(19) Power TP, Kramer CM, Shaffer AL, Theobald TM, Petruolo S, Reichek N, Rogers WJ, Jr. Breath-hold dobutamine magnetic resonance myocardial tagging: normal left ventricular response. Am J Cardiol 1997 November 1;80(9):1203-7.

(20) Scott CH, Sutton MS, Gusani N, Fayad Z, Kraitchman D, Keane MG, Axel L, Ferrari VA. Effect of dobutamine on regional left ventricular function measured by tagged magnetic resonance imaging in normal subjects. Am J Cardiol 1999 February 1;83(3):412-7.

(21) Kuijpers D, Ho KY, van Dijkman PR, Vliegenthart R, Oudkerk M. Dobutamine cardiovascular magnetic resonance for the detection of myocardial ischemia with the use of myocardial tagging. Circulation 2003 April 1;107(12):1592-7.

chapter 2

Introduction on protocols for MR "stress" first-pass perfusion imaging

Based on Imaging Decisions: summer 2009 (in press)
And Imaging Decisions: autumn 2006; vol 10; nr 3

INTRODUCTION

Myocardial perfusion imaging with Cardiovascular Magnetic Resonance Imaging (CMR) is a dynamic technique to analyse the first-pass of a bolus of contrast agent through the myocardium. A heavily T1-weighted perfusion sequence is used with acquiring multiple slice positions of the left ventricle with 40-60 images per slice position (Figure 1).

Early reports from the group of Edelman et al. already showed the feasibility of first-pass myocardial perfusion using CMR (1). It proved possible first in a rat and later in humans. Clear first-pass wash-in and wash-out was observed. Observations of signal enhancement after revascularization were published one year later (2). These reports stated the possibility of performing myocardial perfusion imaging with CMR in a resting condition.

In case of a normal myocardial perfusion, the myocardium of the left ventricle will homogeneously enhance after a bolus of gadolinium. Perfusion abnormalities (perfusion defects) can occur after, for instance, a myocardial infarction, and are visible as regional areas of low signal intensity, which can be related to the distribution area of a coronary artery.

Another possible explanation for a perfusion defect is a significant stenosis of a coronary artery giving rise to diminished flow and subsequent diminished perfusion of the myocardium supplied by the stenotic vessel (Figure 2), which in this regard represents myocardial ischemia.

Since only very high grade coronary stenoses give rise to perfusion defects under conditions of rest the way had to be paved for detecting myocardial ischemia related perfusion defects with MRI. In 1992, Schaefer et al. reported in Radiology that it was possible to detect regional perfusion abnormalities using pharmacological induced "stress" (Dipyridamol)(3).

The concept of stress perfusion MR imaging was born, but image quality and spatial coverage was limited; in that time only a single slice of the myocardium. Technical improvements have led to a current spatial coverage of 3 to 8 slices, (with a slice thickness of 8-12 mm) dependent on the temporal resolution.

Besides dipyridamol, dobutamine and adenosine are used as pharmacological stressors for myocardial perfusion MR imaging. Dipyridamol can be

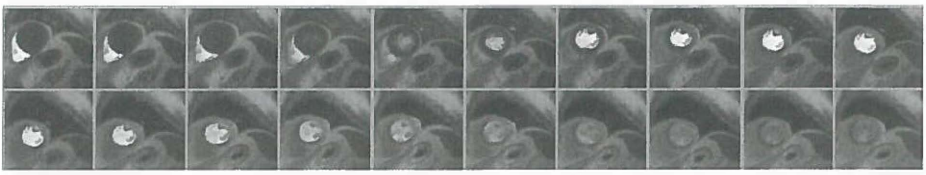


Figure 1: 20 consecutive images of the first-pass perfusion of a mid-ve Figure 1: 20 consecutive images of the first-pass perfusion of a mid-ventricular short-axis slice. Signal enhancement in the right ventricular cavity can be observed in the first image (top row). Images 4-7 (top row) display contrast arrival in the left ventricular cavity. Myocardial enhancement can be observed in the subsequent images, with the last images of the bottom row representing wash-out. Furthermore a large perfusion defect is present, see also figure 2 in which one frame is enlarged. For normal diagnostic purposes viewed in cine mode. ntricular short-axis slice. Signal enhancement in the right ventricular cavity can be observed in the first image (top row). Images 4-7 (top row) display contrast arrival in the left ventricular cavity. Myocardial enhancement can be observed in the subsequent images, with the last images of the bottom row representing wash-out. Furthermore a large perfusion defect is present, see also figure 2 in which one frame is enlarged. For normal diagnostic purposes viewed in cine mode.

used for perfusion imaging, but its important drawback is the long half life. Therefore dipyridamol has lost popularity as a pharmacological stressor in favour of adenosine.

Dobutamine a synthetic catecholamine is actually the only real pharmacological stressor (leading to a considerable increase in systolic blood pressure and heart rate). For perfusion imaging it has a limited role. As a result of the inotropic and chronotropic effect it is better suited for wall motion analysis of the left ventricle (4;5). Wall motion abnormalities under dobutamine infusion are also indicative of myocardial ischemia, but occur, as mentioned, later in the ischemic cascade. Because of the earlier occurrence of perfusion abnormalities before wall motion abnormalities, dobutamine perfusion-imaging can in potential be performed on peak dose dobutamine to further analyze an atypical wall motion abnormality.

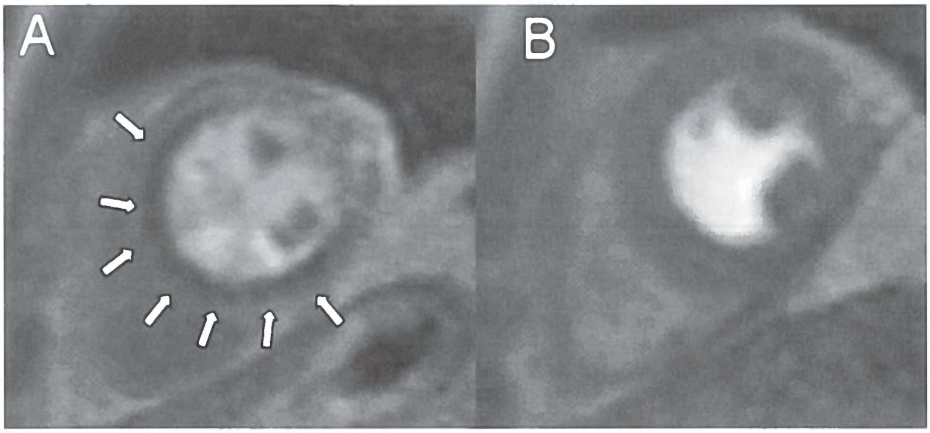


Figure 2: Two single frames of the same mid-ventricular short-axis slice of the same patient, under adenosine infusion A (frame identical to fifth image bottom row of figure 8, now enlarged) and rest perfusion B. Under adenosine infusion a large perfusion defect is present (low signal area pointed out by the arrows). Rest perfusion shows a normal homogeneous perfusion of the myocardium, combination indicating myocardial ischemia.

Adenosine is an endogenous nucleotide with strong vasodilator capabilities. It accomplishes maximal vasodilatation of normal vessels. No further dilatation of significant coronary stenoses is possible (already physiological maximal vasodilatation), thereby creating a coronary steal-effect (Figure 3). In terms of imaging, a relative hypoperfusion of the myocardium supplied by the stenotic vessels.

Adenosine is therefore not a real stressor. The term "stress" is used to indicate that it is a test to detect myocardial ischemia. It is also referred to as adenosine vasodilator stress or just adenosine perfusion. The short half life makes it very controllable in a MR environment.
"Stress" perfusion imaging with MRI is therefore currently mostly performed with adenosine as a pharmacological "stressor".

Building blocks for "stress" perfusion CMR protocols

Different strategies apply when creating a stress perfusion CMR protocol

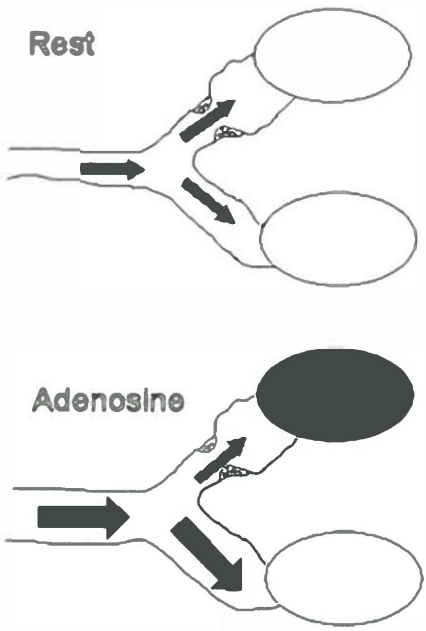


Figure 3: Graphic representation of coronary steal effect. Under adenosine maximal vasodilatation of normal vessels occurs. No further dilatation of significant coronary stenoses is possible (already physiological maximal vasodilatation), thereby creating a coronary steal-effect.

and performing the examination. The Building Blocks for these protocols are stress perfusion imaging, rest perfusion imaging, cine imaging in spare time between contrast boluses (for left ventricular functional parameter assessment) and Delayed Contrast Enhancement (DCE). Figures 4 to 6 display these protocols in images.

When performing stress and rest perfusion imaging, the stress perfusion imaging is typically performed first, because this is the most important part of the examination. This way there is no signal influence by a prior contrast bolus and if the examination has to be stopped for whatever reason at least this part of the examination is done. Between stress and rest perfusion imaging one should wait several minutes, not because of the effect of the adenosine (this effect is gone in seconds), but because of the signal influence caused by the first contrast bolus.
In this spare time typically a stack of short axis cine images of the left ven-

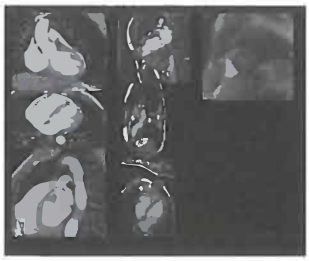


Figure 4: Stress-only protocol: after localizer images and standard cine images only under adenosine infusion.

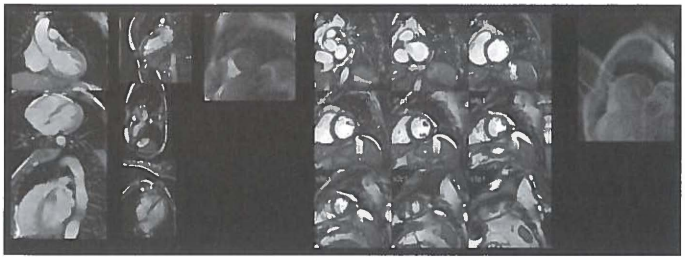


Figure 5: Stress-rest protocol: with rest perfusion after stress perfusion and cine imaging

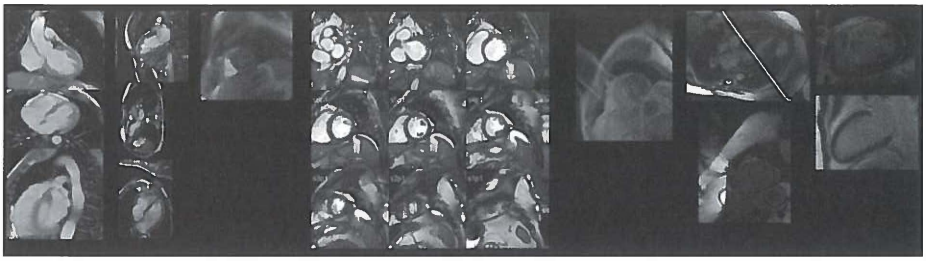


Figure 6: Stress-rest-DCE protocol. Alternative stress perfusion and DCE.

tricle can be acquired for left ventricular functional parameter assessment, which after quantification can give an idea as to parameters like ejection fraction, stroke volume, and end-diastolic and end-systolic volumes.

Wall motion imaging with cardiac MRI provides important functional information about global and regional myocardial function. Most institutions now use 1.5T MR systems for state-of-the-art MR cine imaging. For adequate wall motion analysis the entire cardiac cycle needs to be captured as well as good contrast between the myocardial wall and the blood pool. Fast imaging employing steady-state acquisition with Steady State Free Precession (SSFP) sequences resulted in improved image quality (6;7). Signal intensity in SSFP sequences is mainly related to inherent properties of the tissue, which provides inherent high contrast between blood and myocardium.(8) For this purpose no contrast agent has to be used.

The capture of the entire cardiac cycle can be obtained with retrospective ECG gating, allowing for cine-loops to be acquired. Parallel imaging allows for either reduced acquisition time or improvement of temporal resolution. Measurements comparing the proper end-diastolic frame with the end-systolic frame of consecutive short-axis slices provide information on global left ventricular function (Figure 7). The value of global left ventricular functional parameter assessment has been well established for MR imaging. However CT is also receiving a role in the assessment of left ventricular functional parameter assessment, as shown in a number of recent articles (9;10), for this purpose with CT of course a contrast agent was used (Iomeron 400 mg/ml, Bracco, Milan, Italy). Cardiac cine MR is for now considered to be the reference standard for measurements on global left ventricular function (11).

A protocol employing "stress"-only (Figure 4) has the advantage of reduced imaging time, only one contrast agent bolus, no spatial matching required between "stress" and rest perfusion and no signal influence by the first contrast agent bolus. It can in potential be used in patients without a prior myocardial infarction to determine in a short time whether there is an indication for coronary angiography, its clinical application and results

Figure 7: Consecutive short axis slices for global left ventricular functional parameter assessment. Top row represents end-diastolic frame, bottom row is end-systolic frame. Epi- and endocardial contours are drawn using QMASS v6.1.2 MEDIS, Leiden

are the focus of chapter 3. Advantages of a more comprehensive protocol which can and is used in patients with a history of myocardial infarction and a need to assess viability (Figures 5 and 6) are improved CAD detection (12) and more easily recognition of artifacts (13).

The importance of detecting viable myocardium lies in the fact that patients with regions of reversible left ventricular dysfunction due to chronic coronary artery disease may benefit from revascularization therapy, whereas non-viable myocardium does not improve after revascularization (14). Myocardial viability assessment with cardiac MRI can be performed in two ways: a morphological approach and a functional approach (low-dose dobutamine). The morphological approach uses either the end-diastolic wall thickness or the DCE technique (Figure 8) (15).

The DCE technique aims to detect regions with delayed gadolinium uptake (Figure 9) which is defined as "scarred" myocardium or factually increased interstitial space. The transmural extent of this delayed enhancement is then used to predict whether a patient can benefit from revascularization therapy..

Kaandorp et al. summarized multiple studies using this delayed enhancement technique and found an average sensitivity of 95% and a specificity of 45 % (16). The impaired specificity is mainly caused by non-transmural scars (1 to 74%). A prediction of improvement of contractile function is difficult in these circumstances with only morphological information. Wellnhofer et al. showed that in these circumstances low-dose dobutamine stress CMR (Figure 10) is superior to delayed enhancement as a predictor

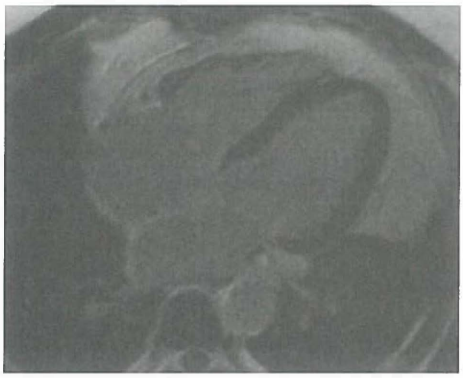


Figure 8: Four chamber view with delayed enhancement technique. Normal examination, with proper nulling of the myocardium and no areas of delayed contrast enhancement.

of recovery after revascularization (17). DCE and dobutamine stress CMR in this study provided complementary information. DCE can localize and quantify regions of delayed enhancement, whereas low-dose dobutamine is probably a better predictor of functional recovery in non-transmural scars (17). Which technique to assess viability in fact is better has yet to be established. Currently there is more validation for DCE.

A choice in the "stress" perfusion protocol regarding which building blocks to use has to be made "in our opinion" according to the presence of a prior myocardial infarction and experience. With less experience rest perfusion and DCE are probably more helpful.

Preparations for adenosine "stress" perfusion MR examination

Before scanning the patient with adenosine, some essential instructions should be given to the patient. Xanthine containing substances, such as coffee, tea, cola and chocolate block the effect of adenosine and should be stopped 24 hours prior to the examination to make it a diagnostic study. Another check-up is to whether the patient uses Dipyridamol. Dipyridamol potentiates adenosine, therefore it has to be stopped if possible or considered a contra-indication. Another precaution is to check (again) for contra-indications, such as asthma, acute coronary syndrome and recent myocardial infarction and pre-existing AV-block. Besides these contra-indications, of course general contra-indications for MR imaging, such as renal insufficiency, claustrophobia and non MR-compatible metallic implants apply.

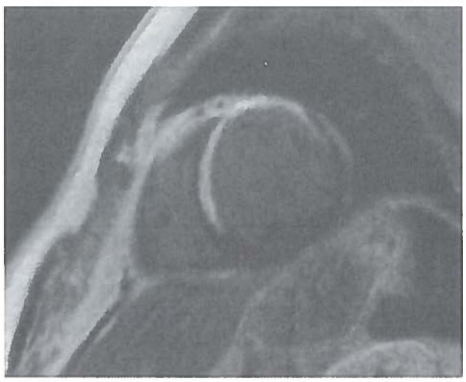


Figure 9: Mid-ventricular short-axis slice with a large almost transmural area of delayed enhancement in the anterior and septal wall.

From adenosine patients may get a flushing sensation and warmth. These possibilities should be explained to the patient as normal side-effects. Other potential side-effects are headaches, atypical chest pain, mild reductions in blood pressure, bradycardia and AV-block. These side-effects have been systematically reported in over 3000 MR examinations (18). All these side-effects were transient, resolved in a few minutes and did not require medical intervention.

Even if an AV-block occurs, the antidote is simple, namely pressing the stop button of the adenosine pump. For the patient and the doctor this pretty much means taking a deep breath. A crash-car should however be present for the theoretical chance of a serious adverse event with aminophyline as an antidote present. Regular exercise drills should be trained and a physician should be present in the MR-suite during the adenosine infusion.

After these check-ups the patient is placed on the MR table, intravenous line(s) placed, a blood pressure cuff is applied for monitoring, and of course ECG leads are placed.

Furthermore, breathing instruction for the perfusion sequence is given.

Examination

First localizer images are acquired for subsequent steps. From these images perfusion slices are planned (Figure 11).

Before starting the adenosine infusion, the next step should be to perform a perfusion dry-run. This means starting a perfusion sequence without con-

trast applied and with only a single image acquired per slice position. This way, one can make sure that the most apical slice and most basal slice are properly positioned. One should anticipate for the fact that during adenosine infusion the heart rate will increase and probably also the length axis shortening of the left ventricle, the most basal slice, may then be to basal and show parts of the left ventricular outflow tract rendering it a non diagnostic slice. Another advantage of this dry-run is to make sure that there is no disturbing back folding. In case of back folding over the left ventricle the field of view should be enlarged or positioning should be changed, with the back folding in this case over non left ventricle areas (Figure 12).

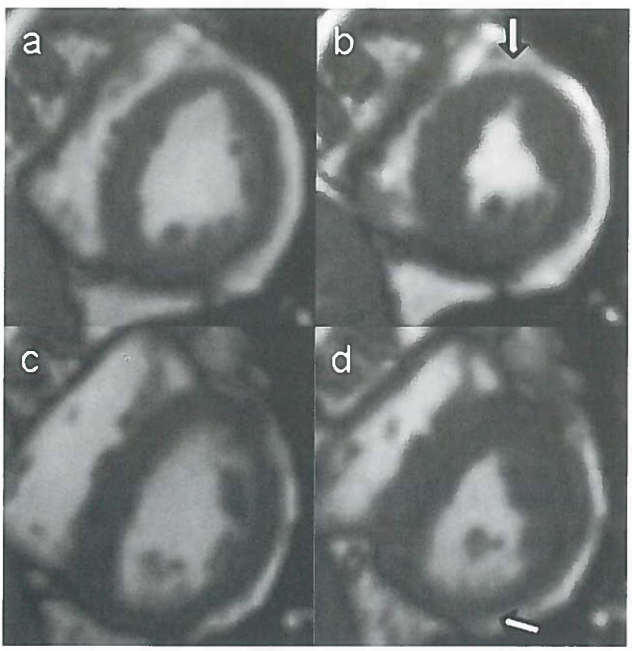


Figure 10. Example of viability assessment and detection of myocardial ischemia in the presence of Rest Wall Motion Abnormalities (RWMA). (a): diastolic image at rest. (b): mid-systolic image with hypokinesia of the anterior wall. (c): diastolic image under infusion of 10 dobutamine (μg/kg/min). (d): systolic image showing improvement of anterior wall motion and an akinetic wall motion pattern in the inferior wall. Arrows are pointing towards the wall motion abnormality or improvement.

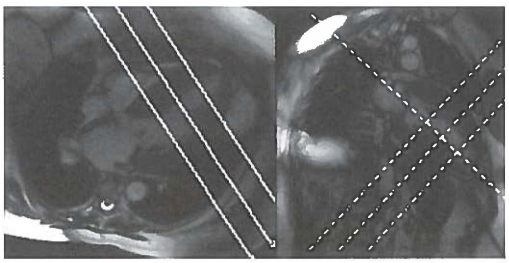


Figure 11: Acquisition steps for planning three short-axis and one long axis slice for the following perfusion sequence.

After these verifications the acquired images per slice should again be set to 40-60 and then the adenosine infusion may begin.

Adenosine is infused intravenously (140 µg/kg/min) and first-pass perfusion imaging is performed after 3 minutes of continuous adenosine infusion using a bolus of contrast agent (gadolinium-DTPA) of 0.05-0.1 mmol/kg, with a flow rate of 3-5 ml/s followed by a saline flush. For this purpose a heavily T1-weighted dynamic sequence is used, acquiring images in multiple slice positions (at least 3 to 4) consisting of 40-60 images per position in one breath hold.

In order to dynamically follow the wash-in and wash-out of a contrast agent it is important to have a high temporal resolution. Most clinically used perfusion sequences allow to acquire 3-4 slices in different positions with single heart beat resolution. This is, however, dependent on the heart rate. A heart rate of 60 Beats Per Minute (BPM) equals approximately an R-R interval of 1000 ms. An increase in heart rate decreases the R-R interval and thereby reduces possible image acquisition time and as a consequence spatial coverage. Under adenosine infusion the heart rate increases with 10-15 beats per minute, which leaves enough spatial coverage. In case of a large increase in heart rate novel parallel imaging sequences can be used.

The protocol choice should match the perfusion sequence. The choice for the sequence depends on factors like whether you want to perform a visual or quantitative analysis, the heart rate and whether you want to use a "stress"-only protocol. For a "stress"-only examination our choice is for the highest signal and contrast to noise ratio. For quantitative analysis fewer artifacts are important and for imaging at really high heart rates, novel par-

allel imaging techniques are needed to maintain enough spatial coverage. The best perfusion sequence has yet to be determined. SR-GRE-EPI, SR-FLASH and SR-SSFP are often used. SR-SSFP give higher signal to noise ratio (SNR) and contrast to noise ratio (CNR) (19), but probably also some more artifacts. A good overview of available perfusion sequences is given by Kellman et al (20).

The injection speed of the contrast agent bolus has to be between 3-5 ml/s (21;22), because a small homogeneous bolus is needed to track the first-pass of the contrast agent and resulting signal intensity changes.

The contrast dose is dependent on whether one wants to perform a visual or a (semi-) quantitative analysis. For a (semi-) quantitative approach a low dose of 0.05 mmol/kg is required to maintain a linear relationship between signal intensity change and contrast dose. Interpretation of these perfusion images is, however, most of the time performed visually or qualitatively. For routine clinical practice it is the most often used analysis. The optimal gadolinium dose for visual analysis is 0.1 mmol/kg, with significantly more artifacts at higher gadolinium doses (21;22). After contrast arrival in the left ventricle the adenosine infusion can be stopped and the examination can be further completed dependent on the chosen protocol.

During the examination a score form (Figure 13) can be filled in registering blood pressure, heart rate and symptoms. Furthermore, a first initial assessment can be made.

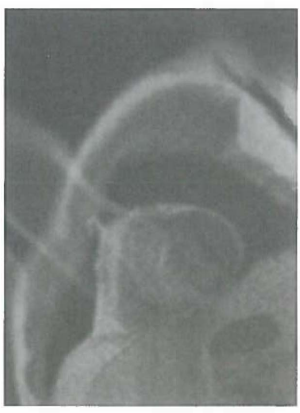


Figure 12: Example of dry-run sequence with back folding.

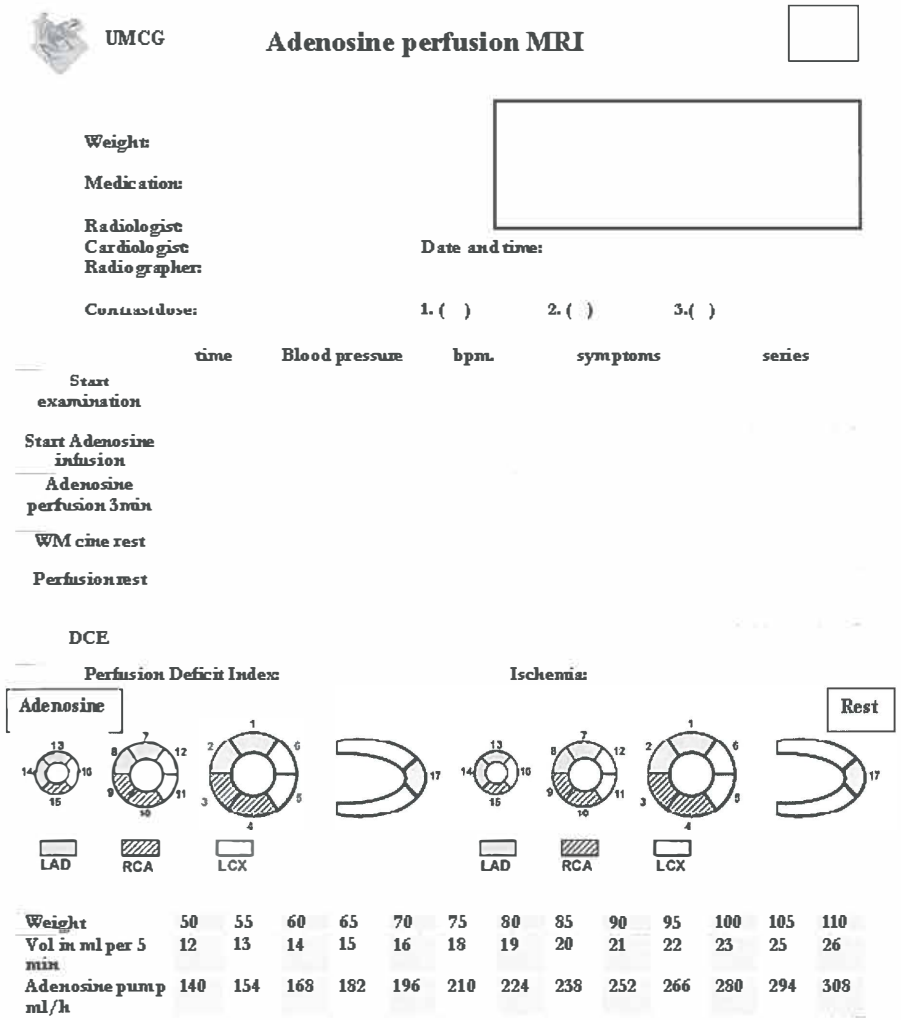


Figure 13: Score form for adenosine perfusion MR examinations

Interpretation

In the report of the analysis, the radiologist states the myocardial segments with the perfusion defect, the degree of transmurality and to which coronary artery these segments belong (Figure 14). This is merely a rough indicator, since there is regional variability of distributions areas (24;25).

Heart rate and blood pressure compared to rest are also mentioned. Left ventricular functional parameters and information regarding rest perfusion

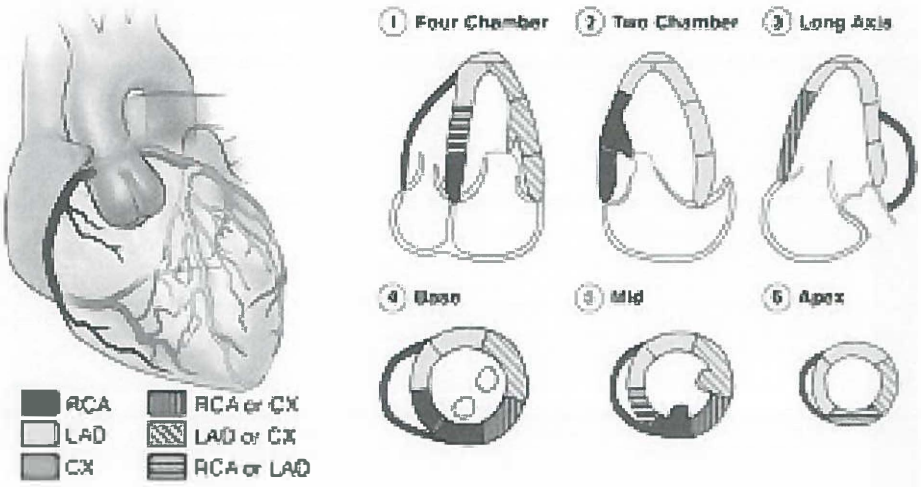


Figure 14: Coronary distribution areas. With permission to reprint from Frank A. Flachskampf (23).

or DCE is provided depending again on the protocol.

Artifacts are important to discriminate from "true" perfusion defects. They occur early, are subendocardial real focal defects, occurring during the upslope of signal intensity change and then disappearing. They are caused by high gadolinium concentrations or low spatial resolution. A quantitative analysis with MR is possible, in which at signal-intensity time curves peak signal intensity and upslope are used as parameters for hypoperfusion. For a quantitative analysis a lower dose gadolinium of 0.05 mmol/kg is used, as mentioned, to maintain a linear relationship between contrast-dose and signal intensity. Post-processing is necessary, in which endocardial and epicardial contours have to be drawn, resulting in signal intensity time curves (Figure 15).

This can be rather time consuming. Studies comparing visual analysis with a quantitative analysis show similar good results (26-28) comparable with our experience.

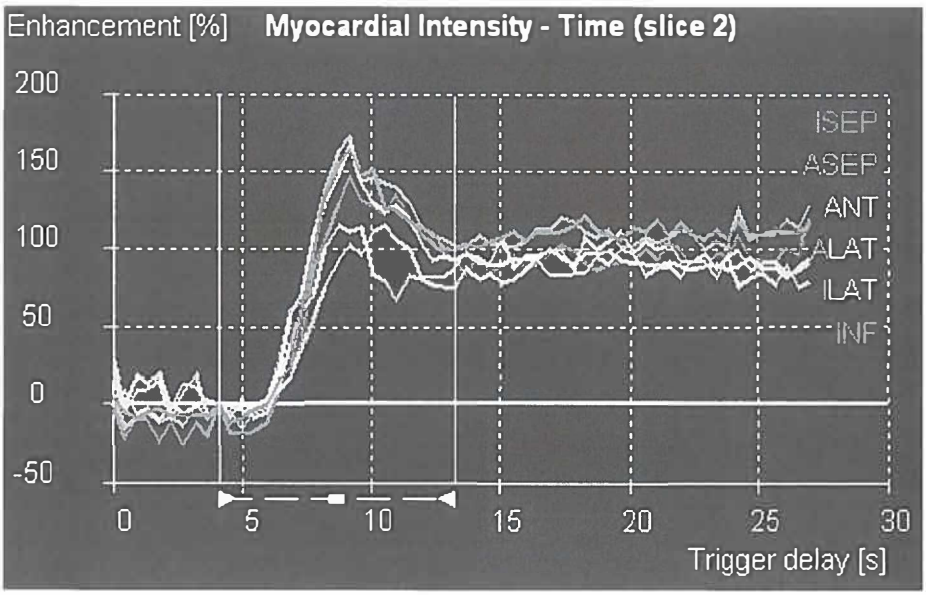


Figure 15: Graphic representation of myocardial signal intensity change (enhancement) over time after a bolus of contrast agent for 6 different myocardial segments.

Current status

In summary, a choice has to be made for the protocol and used sequences, the gadolinium dose, 0.1 for a visual analysis and 0.05 mmol/kg gadolinium for a quantitative analysis. The injection speed has to be between 3-5 ml/sec for a compact bolus. Spatial coverage should be set at least at 3-4 slices. Visual analysis is the most used analysis method in clinical practice. Quantitative analysis is probably more objective and less experience related, but still at this moment time-consuming. Besides these issues more and more validation for adenosine perfusion MR is published.

Bernhardt and co-workers for instance performed a study in which they assessed whether adenosine perfusion MR can predict the need for revascularization with CAG as a reference standard and it proved a useful prediction to guide therapy (29).

Reported diagnostic accuracies over the last three years for adenosine perfusion CMR range from 78-100% for sensitivity, 68-93% for specificity,

Negative Predictive Value (NPV) from 77-100% and Positive Predictive Value (PPV) from 71-95% (12;13;21;22;29-38). Differences in these reported accuracies are caused by differences in the studied population, the used sequence and used protocols, the contrast dose, spatial coverage and the used reference modality and the stenoses grade defined as significant.

Higher diagnostic accuracies are reached when adenosine perfusion CMR was not compared to CAG but to a functional reference standards, such as for instance Fractional Flow Reserve (FFR) (37). In this way, haemodynamically relevant stenosis could be distinguished from non- haemodynamically relevant stenosis.

The prognostic role of a normal adenosine perfusion MR examination has been investigated in a few studies (35;39;40). In a study by Ingkanisorn et al. (35), the prognosis of a negative adenosine perfusion MR study in patients presenting to the Emergency Room with stable chest pain was assessed with no events at one-year follow-up in case of a normal adenosine perfusion examination. Also the sum of the total cardiac risk factors was less predictive than the MR results.

Paetsch et al. compared adenosine stress perfusion and dobutamine stress wall motion analysis in a single examination in the same patients (41). With the highest overall accuracy for dobutamine stress wall motion analysis, but the highest sensitivity for adenosine perfusion MR. Results from the MR-impact study (a multi-centre, multi-vendor study) show that adenosine perfusion MR with a dose of 0.1 mmol/kg gadolinium is superior to SPECT imaging in a direct comparison with quantitative CAG as the reference standard (42).

The current clinical indications for adenosine perfusion CMR are therefore: the detection of myocardial ischemia in the setting of new or recurrent chest pain, prognosis and risk stratification, follow-up after interventional treatment,(43) determination of the functional significance of known angiographically determined lesions and microvascular dysfunction (44).

Future perspectives for adenosine perfusion MR examinations are the routine use of 3T imaging, (45-47) and more published results from multi-centre randomized trials. Further sequence design is ongoing, especially focus-

ing on parallel imaging. Furthermore, less time-consuming quantification is to be expected. Importantly, protocols are further optimized for the patient population allowing a more routine implementation. Heterogeneity at this time still exists between used protocols and reported accuracies. The used protocol should, to our opinion, be tailored for the patient population.

Purpose and outline of this thesis

In this thesis issues on MR perfusion in the detection of myocardial ischemia are studied. An adenosine "stress"-only approach in patients with a clinical necessity to exclude myocardial ischemia and no history of myocardial infarction is described in Chapter 3. In Chapter 4 the inter-observer variability of the visual analysis of adenosine "stress"-only images is studied in relation to experience and the systematical use of reading criteria. In patients with a history of myocardial infarction rest perfusion, DCE and cine wall motion imaging for assessment of global left ventricular function can be added to the protocol. Chapter 5 focuses on the post-processing of global left ventricular functional parameter assessment. Whether the post-processing analysis of every second short-axis slice is as accurate as analysis of consecutive slices is the focus of this study.

Ischemia detection and viability assessment can also be performed in patients with a known history of myocardial infarction with dobutamine stress MR for wall motion analysis. The additional value of performing perfusion imaging at peak dose dobutamine to assess if an atypical wall motion abnormality is indeed caused by myocardial ischemia is described in Chapter 6.

Perfusion imaging at real high heart rates, such as under peak dose dobutamine infusion, may be suffering from a limitation in spatial coverage. Chapter 7 compares two different techniques for parallel imaging in terms of signal to noise ratio (SNR) and contrast to noise ratio (CNR).

REFERENCE LIST

(1) Atkinson DJ, Burstein D, Edelman RR. First-pass cardiac perfusion: evaluation with ultrafast MR imaging. Radiology 1990 March;174(3 Pt 1):757-62.

(2) Manning WJ, Atkinson DJ, Grossman W, Paulin S, Edelman RR. First-pass nuclear magnetic resonance imaging studies using gadolinium-DTPA in patients with coronary artery disease. J Am Coll Cardiol 1991 October;18(4):959-65.

(3) Schaefer S, van TR, Saloner D. Evaluation of myocardial perfusion abnormalities with gadolinium-enhanced snapshot MR imaging in humans. Work in progress. Radiology 1992 December;185(3):795-801.

(4) Kuijpers D. Diagnosis of coronary artery disease with dobutamine-stress MRI. Eur Radiol 2005 February;15 Suppl 2:B48-B51.

(5) Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, Ellmer A, Dreysse S, Fleck E. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999 February 16;99(6):763-70.

(6) Barkhausen J, Ruehm SG, Goyen M, Buck T, Laub G, Debatin JF. MR evaluation of ventricular function: true fast imaging with steady-state precession versus fast low-angle shot cine MR imaging: feasibility study. Radiology 2001 April;219(1):264-9.

(7) Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging 2001 September;14(3):230-6.

(8) Thiele H, Nagel E, Paetsch I, Schnackenburg B, Bornstedt A, Kouwenhoven M, Wahl A, Schuler G, Fleck E. Functional cardiac MR imaging with steady-state free precession (SSFP) significantly improves endocardial border delineation without contrast agents. J Magn Reson Imaging 2001 October;14(4):362-7.

(9) van der Vleuten PA, de Jonge GJ, Lubbers DD, Tio RA, Willems TP,

Oudkerk M, Zijlstra F. Evaluation of global left ventricular function assessment by dual-source computed tomography compared with MRI. Eur Radiol 2009 February;19(2):271-7.

(10) de Jonge GJ, van Ooijen PMA, van der Vleuten PA, Lubbers DD, Kasemier JH, de Bock GH, Oudkerk M. The reliability of automatic measurement of left ventricular function with dual-source computed tomography datasets. Eur Radiol 2009. Epub ahead of print.

(11) Pennell DJ. Ventricular volume and mass by CMR. J Cardiovasc Magn Reson 2002;4(4):507-13.

(12) Klem I, Heitner JF, Shah DJ, Sketch MH, Jr., Behar V, Weinsaft J, Cawley P, Parker M, Elliott M, Judd RM, Kim RJ. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. J Am Coll Cardiol 2006 April 18;47(8):1630-8.

(13) Thomson LE, Fieno DS, Abidov A, Slomka PJ, Hachamovitch R, Saouaf R, Friedman JD, Berman DS. Added value of rest to stress study for recognition of artifacts in perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2007;9(5):733-40.

(14) Bax JJ, van der Wall EE, Harbinson M. Radionuclide techniques for the assessment of myocardial viability and hibernation. Heart 2004 August;90 Suppl 5:v26-v33.

(15) Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM, Finn JP, Judd RM. An improved MR imaging technique for the visualization of myocardial infarction. Radiology 2001 January;218(1):215-23.

(16) Kaandorp TA, Lamb HJ, van der Wall EE, de Roos A, Bax JJ. Cardiovascular MR to access myocardial viability in chronic ischaemic LV dysfunction. Heart 2005 October;91(10):1359-65.

(17) Wellnhofer E, Olariu A, Klein C, Grafe M, Wahl A, Fleck E, Nagel E. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. Circulation 2004 May 11;109(18):2172-4.

(18) Bernhardt P, Steffens M, Kleinertz K, Morell R, Budde R, Leischik R,

Kramer A, Overhoff U, Strohm O. Safety of adenosine stress magnetic resonance imaging using a mobile cardiac magnetic resonance system. J Cardiovasc Magn Reson 2006;8(3):475-8.

(19) Schreiber WG, Schmitt M, Kalden P, Mohrs OK, Kreitner KF, Thelen M. Dynamic contrast-enhanced myocardial perfusion imaging using saturation-prepared TrueFISP. J Magn Reson Imaging 2002 December;16(6):641-52.

(20) Kellman P, Arai AE. Imaging sequences for first pass perfusion --a review. J Cardiovasc Magn Reson 2007;9(3):525-37.

(21) Giang TH, Nanz D, Coulden R, Friedrich M, Graves M, Al-Saadi N, Luscher TF, von Schulthess GK, Schwitter J. Detection of coronary artery disease by magnetic resonance myocardial perfusion imaging with various contrast medium doses: first European multi-centre experience. Eur Heart J 2004 September;25(18):1657-65.

(22) Wolff SD, Schwitter J, Coulden R, Friedrich MG, Bluemke DA, Biederman RW, Martin ET, Lansky AJ, Kashanian F, Foo TK, Licato PE, Comeau CR. Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study. Circulation 2004 August 10;110(6):732-7.

(23) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, John Sutton M, Stewart W. Recommendations for chamber quantification. Eur J Echocardiogr 2006 March;7(2):79-108.

(24) Muehling OM, Jerosch-Herold M, Panse P, Zenovich A, Wilson BV, Wilson RF, Wilke N. Regional heterogeneity of myocardial perfusion in healthy human myocardium: assessment with magnetic resonance perfusion imaging. J Cardiovasc Magn Reson 2004;6(2):499-507.

(25) Pereztol-Valdes O, Candell-Riera J, Santana-Boado C, Angel J, Aguade-Bruix S, Castell-Conesa J, Garcia EV, Soler-Soler J. Correspondence between left ventricular 17 myocardial segments and coronary arteries. Eur Heart J 2005 December;26(24):2637-43.

(26) Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, Marincek B, Luscher TF, von Schulthess GK. Assessment of myo-

cardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. Circulation 2001 May 8;103(18):2230-5.

(27) Ishida N, Sakuma H, Motoyasu M, Okinaka T, Isaka N, Nakano T, Takeda K. Noninfarcted myocardium: correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. Radiology 2003 October;229(1):209-16.

(28) Chiu CW, So NM, Lam WW, Chan KY, Sanderson JE. Combined first-pass perfusion and viability study at MR imaging in patients with non-ST segment-elevation acute coronary syndromes: feasibility study. Radiology 2003 March;226(3):717-22.

(29) Bernhardt P, Engels T, Levenson B, Haase K, Albrecht A, Strohm O. Prediction of necessity for coronary artery revascularization by adenosine contrast-enhanced magnetic resonance imaging. Int J Cardiol 2006 September 20;112(2):184-90.

(30) Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. J Am Coll Cardiol 2004 December 7;44(11):2173-81.

(31) Paetsch I, Foll D, Langreck H, Herkommer B, Klein C, Schalla S, Fleck E, Nagel E. Myocardial perfusion imaging using OMNISCAN: a dose finding study for visual assessment of stress-induced regional perfusion abnormalities. J Cardiovasc Magn Reson 2004;6(4):803-9.

(32) Plein S, Radjenovic A, Ridgway JP, Barmby D, Greenwood JP, Ball SG, Sivananthan MU. Coronary artery disease: myocardial perfusion MR imaging with sensitivity encoding versus conventional angiography. Radiology 2005 May;235(2):423-30.

(33) Cury RC, Cattani CA, Gabure LA, Racy DJ, de Gois JM, Siebert U, Lima SS, Brady TJ. Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients with coronary artery disease. Radiology 2006 July;240(1):39-45.

(34) Sakuma H, Suzawa N, Ichikawa Y, Makino K, Hirano T, Kitagawa K, Takeda K. Diagnostic accuracy of stress first-pass contrast-enhanced

myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. AJR Am J Roentgenol 2005 July;185(1):95-102.

(35) Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. J Am Coll Cardiol 2006 April 4;47(7):1427-32.

(36) Pilz G, Bernhardt P, Klos M, Ali E, Wild M, Hofling B. Clinical implication of adenosine-stress cardiac magnetic resonance imaging as potential gatekeeper prior to invasive examination in patients with AHA/ACC class II indication for coronary angiography. Clin Res Cardiol 2006 October;95(10):531-8.

(37) Rieber J, Huber A, Erhard I, Mueller S, Schweyer M, Koenig A, Schiele TM, Theisen K, Siebert U, Schoenberg SO, Reiser M, Klauss V. Cardiac magnetic resonance perfusion imaging for the functional assessment of coronary artery disease: a comparison with coronary angiography and fractional flow reserve. Eur Heart J 2006 June;27(12):1465-71.

(38) Kuhl HP, Katoh M, Buhr C, Krombach GA, Hoffmann R, Rassaf T, Neizel M, Buecker A, Kelm M. Comparison of magnetic resonance perfusion imaging versus invasive fractional flow reserve for assessment of the hemodynamic significance of epicardial coronary artery stenosis. Am J Cardiol 2007 April 15;99(8):1090-5.

(39) Pilz G, Jeske A, Klos M, Ali E, Hoefling B, Scheck R, Bernhardt P. Prognostic value of normal adenosine-stress cardiac magnetic resonance imaging. Am J Cardiol 2008 May 15;101(10):1408-12.

(40) Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007 April 3;115(13):1769-76.

(41) Paetsch I, Jahnke C, Wahl A, Gebker R, Neuss M, Fleck E, Nagel E. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance

perfusion. Circulation 2004 August 17;110(7):835-42.

(42) Schwitter J, Wacker CM, van Rossum AC, Lombardi M, al Saadi N, Ahlstrom H, Dill T, Larsson HB, Flamm SD, Marquardt M, Johansson L. MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. Eur Heart J 2008 February;29(4):480-9.

(43) Fenchel M, Franow A, Stauder NI, Kramer U, Helber U, Claussen CD, Miller S. Myocardial perfusion after angioplasty in patients suspected of having single-vessel coronary artery disease: improvement detected at rest-stress first-pass perfusion MR imaging--initial experience. Radiology 2005 October;237(1):67-74.

(44) Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002 June;%20;346(25):1948-53.

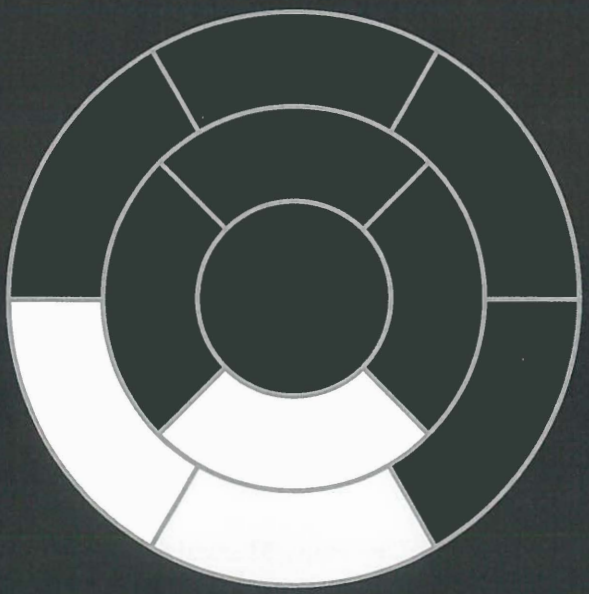
(45) Araoz PA, Glockner JF, McGee KP, Potter DD, Jr., Valeti VU, Stanley DW, Christian TF. 3 Tesla MR imaging provides improved contrast in first-pass myocardial perfusion imaging over a range of gadolinium doses. J Cardiovasc Magn Reson 2005;7(3):559-64.

(46) Gutberlet M, Noeske R, Schwinge K, Freyhardt P, Felix R, Niendorf T. Comprehensive cardiac magnetic resonance imaging at 3.0 Tesla: feasibility and implications for clinical applications. Invest Radiol 2006 February;41(2):154-67.

(47) Theisen D, Wintersperger BJ, Huber A, Dietrich O, Reiser MF, Schonberg SO. Myocardial perfusion imaging with Gadobutrol: a comparison between 3 and 1.5 Tesla with an identical sequence design. Invest Radiol 2007 July;42(7):499-506.

chapter 3

Performance of adenosine "stress-only" perfusion MRI in patients without a history of myocardialinfarction: a clinical outcome study



Submitted for publication European Heart Journal

Performance of adenosine "stress-only" perfusion MRI in patients without a history of myocardial infarction: a clinical outcome study

D.D. Lubbers, MD[1,*]
D. Rijlaarsdam - Hermsen, MD[2,*]
D. Kuijpers, MD, PhD[1,3]
M. Kerkhof, MD, PhD[4]
P.E. Sijens, PhD[1]
P.R.M. van Dijkman, MD, PhD[2]
M. Oudkerk, MD, PhD[1]

Department of Radiology[1], University Medical Center Groningen, University of Groningen. Departments of Cardiology[2] and Radiology[3], Bronovo Hospital, The Hague, The Netherlands and the Department of Epidemiology[4], University Medical Center Groningen, University of Groningen.

*Both authors contributed equally to the manuscript.

ABSTRACT

Purpose: To assess the diagnostic value of adenosine "stress-only" myocardial perfusion MR for ischemia detection as an indicator for coronary angiography in patients without a prior myocardial infarction and a necessity to exclude ischemia.

Methods : Adenosine perfusion MRI was performed at 1.5 T in 139 patients with a suspicion of ischemia and no prior myocardial infarction. After 3 minutes of adenosine infusion a perfusion sequence was started. Patients with a perfusion defect were referred to coronary angiography (CAG). Patients with a normal perfusion were enrolled in follow-up.

Results: Fourteen out of 139 patients (10.1 %) had a perfusion defect indicative of ischemia. These patients underwent a coronary angiogram, which showed complete agreement with the perfusion images.
125 patients with a normal myocardial perfusion entered follow-up (median 672 days, range 333 – 1287 days). In the first year of follow-up one Major Adverse Coronary Event (MACE) occurred and one patient had new onset chest pain with a confirmed coronary stenosis. Reaching a negative predictive value for MACE of 99.2 % and for any coronary event of 98.4 %. At two year follow-up no additional MACE occurred . Sensitivity of adenosine perfusion MR for MACE is 93.3 % and specificity and positive predictive value are 100%.

Conclusion: Adenosine myocardial perfusion MR for the detection of myocardial ischemia in a "stress-only" protocol in patients without prior myocardial infarctions, has a high diagnostic accuracy. This fast examination can play an important role in the evaluation of patients without prior myocardial infarctions and a necessity to exclude ischemia.

INTRODUCTION

Adenosine "stress" MR myocardial perfusion imaging has a proven high sensitivity and negative predictive value for the detection of myocardial ischemia (1-12). High diagnostic accuracies are reached in patient groups with relatively high prevalence of disease in studies combining rest-stress perfusion and delayed contrast enhancement. For the subgroup of patients with a history of myocardial infarction these elaborate protocols or different stress MR imaging methods are probably most appropriate. In relatively lower risk patients, those without known myocardial infarction, less comprehensive protocols may be sufficient to guide further work-up and therapy choice. In lower-risk patient groups examined by adenosine "stress-only" perfusion MR imaging the number of purely diagnostic coronary angiographies (CAG's) might thus be reduced, which would be important because CAG is an invasive test with a risk of complications and relatively expensive. Furthermore, taking into account that PCI with stent implantation is not harmless, invasive treatment should only be reserved for those patients with objectified myocardial ischemia (13;14). A non-invasive imaging technique such as an appropriately designed MR protocol, can be used as an indicator to determine which patients need to be directed to coronary angiography. With the routine implementation of adenosine perfusion MR still lagging behind, we sought to tailor a protocol designed for a specific population.

Directing the patient to the proper MR stress perfusion test or protocol, could yield diagnostic gain and time savings allowing analysis of larger patient groups.

In this study, the prognosis after a negative adenosine perfusion MR examination and the diagnostic accuracy of adenosine "stress" myocardial perfusion MR were examined in a stress-only approach, in patients without prior myocardial infarction and a clinical necessity to exclude myocardial ischemia.

MATERIALS AND METHODS

Patient population

150 consecutive patients referred between January 2005 to April 2006 from the outpatient clinic of the department of Cardiology for an adenosine perfusion MR, were included. Eleven patients were not enrolled in the final study population due to a history of myocardial infarction (3 patients), use of vasoactive medication during adenosine (2 patients), moving out of the country with loss of follow-up (3 patients) and refused consent (3 patients). The final study population therefore consisted of 139 prospectively enrolled patients. The study was approved by the medical ethical board. Pretest likelihood of these patients was determined according to Gibbons et al. (15). Patients who could not be determined according to this classification were stratified with a calcium score or considered to be at intermediate risk (for example rhythm abnormalities). Patients with a calciumscore > 90th percentile were considered to be at intermediate risk. Furthermore the percentage of patients with: hypertension, diabetes, smoking history, positive family history for coronary artery disease (CAD) and hypercholesterolemia and summary values on age, gender distribution, body weight and Body Mass Index (BMI) are displayed in Table 1.

Patients with a perfusion defect were referred for CAG. Patients with a normal adenosine perfusion examination had clinical follow-up for at least one year.

Adenosine perfusion MR

All anti-anginal medication was stopped 4 days before the adenosine perfusion MR examination. Xhantine containing products like coffee, tea, chocolate, cola had to be stopped 24 hours prior to the examination. Dypiridamol had to be stopped or was considered a contra-indication. Scanning was performed at 1.5 T using a magnetom Avanto MRI system (Siemens Medical Solutions, Erlangen, Germany). After the patient was positioned on the scanning table, intravenous access was established via an anticubital vein. Vector ECG monitoring leads, a phased-array surface coil covering the heart, and a brachial blood pressure cuff were applied. A single lead

ECG signal was continuously monitored on the MRI-console. Systolic and diastolic blood pressures and heart rate were recorded at baseline and during adenosine infusion.

After 3 minutes of adenosine infusion (0.140 mg/kg/min) during the first pass of 0.1 mmol/kg gadopentetate dimeglumine with a flow rate of 5 ml/s flushed with 15 ml 0.9% NaCL (flow rate 5ml/s) a perfusion sequence was started: TrueFisp: TR, 150.5/163.1 ms; TE 1.03 ms; TI 100/103 ms; α 45/50°; FOV 300 X 300; slice-thickness 6 mm; matrix 76 X 128; iPAT 2. During the examination a radiologist and a cardiologist were present in the MR suite, to monitor the condition of the patient and to evaluate the images immediately. Total duration of the protocol was approximately 15 minutes.

Image analysis

Perfusion series were visually analysed by an experienced radiologist and cardiologist in consensus, using a 16 segment model. A perfusion abnormality in at least two segments at consecutive planes of the left ventricle or one segment of the most apical slice, was used as an indication for CAG. Patients with a perfusion defect were examined by CAG within 3 weeks.

Analysis of the coronary angiograms was performed by an experienced cardiologist, blinded to the MR results. A significant coronary lesion was defined as a narrowing of >50%. The decision for a PCI or CABG was made in regular consultation with cardiac surgeons and interventional cardiologists.

Follow-up

Follow-up was completed in October 2008. The status of the patient was determined by review of the hospital records, contacting the patient's general physician or by a questionnaire after informed consent. Reported clinical events were confirmed by contact with the treating hospital. The date of the hospital visit, last visit to the general physician or the date of returning the questionnaire was used to calculate follow-up time.

Patients were observed for occurrence of MACE and MACE including

coronary artery revascularization after objectified ischemia as composite end point and classified as composite MACE. Occurrence of noncardiac mortality was documented: such cases were censored for MACE evaluation at the time of death.

Primary outcome

The aim of this study was to assess the diagnostic accuracy of an adenosine "stress-only" perfusion MR examination in patients without a prior myocardial infarction as a clinical indicator for coronary angiography and to determine the prognosis after a normal adenosine perfusion MR examination. Confirmation of the adenosine perfusion MR results was done by detection of a significant coronary stenosis on CAG or with at least one year follow-up in case of a normal adenosine perfusion MR examination.

Statistics

Sensitivity, specificity, negative and positive predictive values were calculated, with confidence intervals. Baseline characteristics are given as mean or median with standard deviation or range for continuous variables and as number (%) for categorical variables.

RESULTS

139 consecutive patients entered the study. Mean age 60.7 ± 10.5 years, 54% male. Demographic and hemodynamic data are listed in table 1. During adenosine perfusion MR no major adverse reactions were seen in this patient group.

Fourteen out of 139 patients (10.1 %) had a perfusion abnormality indicative for myocardial ischemia, figure 1.

On a per patient basis significant coronary artery disease was demonstrated by CAG in all fourteen patients, followed by revascularization in 10 patients (1 CABG, 9 PCI, in 4 patients revascularization was not feasible).

The 125 patients with a negative (normal) adenosine perfusion MR examination were followed up for a median period of 672 days (range 333 – 1287 days). There was one MACE during the first follow-up year (0.8 %) due

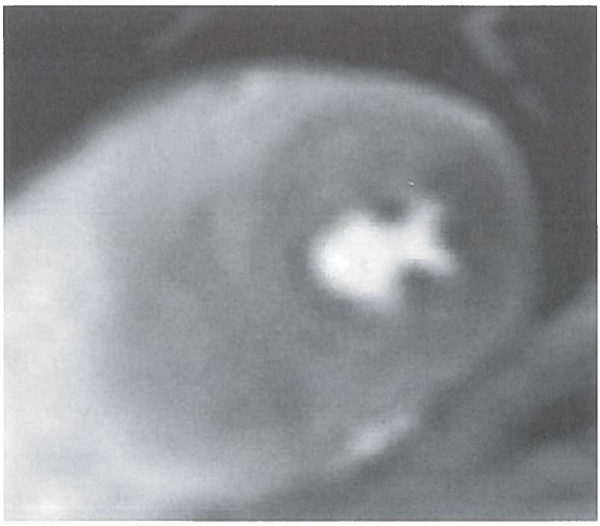


Figure 1: Mid-ventricular short-axis single frame with perfusion defect in the distribution area of the LCX.

to an acute coronary syndrome complicated by ventricular fibrillation, 12 months after the adenosine perfusion MR examination. There was one case of new onset chest pain 10 months after the adenosine perfusion MR examination with subsequent stent implantation , giving a composite MACE rate of 1.6%. Both patients had a low pre-test likelihood.

In the second follow-up year two additional revascularizations were performed (17 and 18 months after the adenosine perfusion MR and no additional MACE,.

Diagnostic values calculated for MACE for sensitivity are 93.3 % (CI: 0.68 – 0.99), specificity 100% (CI: 0.97 – 1.00), Negative Predictive Value (NPV) 99.2 (CI: 0.96 – 1.00), and Positive Predictive Value (PPV) of 100% (CI: 0.77 – 1.00) Only 6 out of 32 patients (18.8%) with a high pre-test likelihood had a positive adenosine perfusion MR examination.

Distribution of the pre-test likelihood of significant coronary artery disease is listed in figure 2 and presented in table 1.

DISCUSSION

The main results of this study are that prognosis after a negative adenosine perfusion MR examination is good in this patient group and justifies conservative treatment rather than performing an invasive examination.

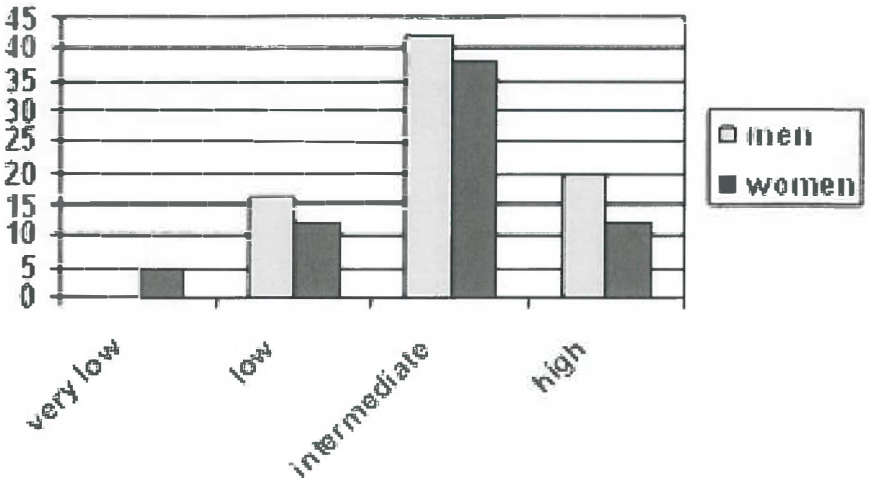


Figure 2: Distribution of patients' pre-test likelihood of significant coronary artery disease.

Second, comparison between positive adenosine perfusion MR examinations and CAG is good on a per patient basis, and could be used in the preselection of patients to be examined by coronary angiography.

Diagnostic performances reported of adenosine perfusion MR studies, vary widely depending on the pulse-sequence, contrast dose, the modality used as a reference standard, the studied patient population and the used protocol. Besides this, coronary artery disease is a progressive disease, which to some extent explains the relative late occurrence of MACE or composite MACE after a negative adenosine perfusion MR in the few patients in this study. Results should in this regard also be seen as ongoing disease and not by definition as a false negative examination.

For a visual, qualitative approach to adenosine perfusion MR, one needs an imaging protocol approach. A good, but extensive approach has been proposed by Klem et al. (7), starting analysis with delayed contrast imaging, followed by rest and stress perfusion images. For a specific population without prior myocardial infarction we propose an imaging strategy that focuses on the adenosine stress perfusion MR series, to answer the question

Table 1: Demographic and hemodynamic data.

Variable	Mean or %
Age, years	60.7 ± 10.5
Male, %	54
Body Mass Index, kg, mean	26.3 ± 3.9
Hypercholesterolaemia, %	86.1
Hypertension, %	46.3
Diabetes, %	14.9
Current smokers, %	18.8
Former smokers, %	44.2
Positive family history, %	52.1
Pre-test likelihood	
Very low, %	2.2
Low, %	19.4
Intermediate, %	55.4
High, %	23.0
Resting diastolic blood pressure, mmHg, mean	83.1 ± 10.2
Diastolic blood pressure under adenosine , mmHg, mean	87.6 ± 10.0
Resting systolic blood pressure, mmHg, mean	153.3 ± 25.2
Systolic blood pressure under adenosine, mmHg, mean	146.4 ± 23.1
Resting heart rate, bpm, mean	76.6 ± 16.0
Heart rate under adenosine, bpm, mean	88.5 ± 17.5

Values are expressed as mean ± SD, range or percentage

if there is a need for coronary angiography. In a relatively lower prevalence population the adenosine perfusion MR examination can exclude myocardial ischemia in a large group of patients with a normal adenosine "stress-only" perfusion examination, saving considerable imaging time and thus allowing analysis of larger patient groups. The importance of this study is underlined by a recent assessment by Nandalur et al. (16) that relatively little knowledge is available on the use of stress perfusion imaging in lower pre-test probability groups such as in patients without prior myocardial in-

farction.

CAG, an invasive, expensive test with a risk of complications, can in this strategy be reserved for patients with objectified ischemia. In this way adenosine perfusion MR can be used to reduce the number of pure diagnostic CAG's.

The few long-term follow-up studies published so far (1;12;17), found good prognosis for a negative adenosine perfusion MR examinations, results we can confirm with our study in this patient group. To the best of our knowledge this is the first study to assess the long term follow-up of an adenosine "stress-only" approach.

Different imaging modalities can serve as a gatekeeper for further invasive examinations. Exercise ECG testing results are less accurate than believed. A meta-analysis of 147 published reports with in total 24074 patients reports a mean sensitivity of exercise ecg-testing of 68% and a mean specificity of 77% (15). Diagnostic accuracy is even lower when the test is performed only in patients without a previous myocardial infarction.

Nuclear imaging modalities play an important role in many centers and a lot of experience and validation is present, but they do have some important drawbacks regarding limited spatial and temporal resolution, attenuation artefacts and the use of radiation. All issues that can be overcome with adenosine perfusion MR, but for MR to be able to compete with nuclear and other stress imaging modalities, imaging time needs to be short, images easily interpretable and protocols optimised for the patient population, taking into account the presence of a prior myocardial infarction, and the need for assessment of viable myocardium. On indication a rest perfusion MR examination or delayed contrast enhancement can be performed. The optimal population for an adenosine perfusion MR examination is in our opinion found in the patient group without a prior myocardial infarction. For patients with a prior myocardial infarction viability imaging may also be required.

Diagnostic performance of dobutamine stress MR examinations in this respect has shown good results, with a good long term prognosis (17-19). Assessment of viability can be performed in the same examination in a

functional way, without increasing imaging time significantly and may be more reliable than quantification of scar tissue (20). In a patient group without prior myocardial infarction absence of myocardial ischemia can be determined with a normal, homogeneous, adenosine perfusion MR series, with an imaging time of only fifteen minutes.

Some earlier studies have reported moderately high specificities, due to the fact that perfusion MR was not able to discriminate between perfusion defects caused by ischemia or other causes (2;10). Specificity is probably also high in this study probably due to examining patients without a prior history of myocardial infarction.

The use of CAG as a reference standard might be a limitation, because CAG may be a "flawed" gold standard. CAG fails to account for the effect of diffuse disease, length of diseased segments and serial stenoses, and the functional effects in terms of perfusion for the myocardium (21). Higher levels of diagnostic accuracy are observed when adenosine perfusion MR was compared with PET (22) or FFR measurements as the reference standard (23). Current clinical practice regarding risk stratification and therapy guidance is however directed by the CAG, which makes it a clinically relevant reference standard.

Rather than performing a quantitative analysis, we optimized the imaging protocol for a robust, visual approach. This can be regarded as a limitation, but previous studies have shown that quantitative and qualitative, visual assessment of myocardial perfusion to have similar good correlations with CAG (22;24;25). Delayed contrast enhancement imaging or rest perfusion imaging was not routinely performed. This may provide additional valuable diagnostic information, but mostly in a post-infarct setting. This might therefore be regarded as a limitation, but was a choice made for a broad application of adenosine perfusion MR in a specific population in which we doubt that it is of additional value. Prior myocardial infarction, as stated earlier, was used as an exclusion criterion in this study.

CONCLUSIONS

Adenosine perfusion MR, in a"stress"-only approach has a high diagnostic accuracy and may have a distinct clinical role in patients without previous myocardial infarctions as an examination which can reliably determine the necessity for coronary angiography in a total protocol time of only 15 minutes.

ACKNOWLEDGEMENTS

The authors thank Bernadette Blom and colleagues for image acquisition, Stella Noach for critically reviewing the paper and dr J. Frederiks for analysing the CAG's.

REFERENCE LIST

(1) Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. J Am Coll Cardiol 2006 April 4;47(7):1427-32.

(2) Sakuma H, Suzawa N, Ichikawa Y, Makino K, Hirano T, Kitagawa K, Takeda K. Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. AJR Am J Roentgenol 2005 July;185(1):95-102.

(3) Plein S, Radjenovic A, Ridgway JP, Barmby D, Greenwood JP, Ball SG, SivananthanMU. Coronary artery disease: myocardial perfusion MR imaging with sensitivity encoding versus conventional angiography. Radiology 2005 May;235(2):423-30.

(4) Giang TH, Nanz D, Coulden R, Friedrich M, Graves M, Al-Saadi N, Luscher TF, von Schulthess GK, Schwitter J. Detection of coronary artery disease by magnetic resonance myocardial perfusion imaging with various contrast medium doses: first European multi-centre experience. Eur Heart J 2004 September;25(18):1657-65.

(5) Paetsch I, Foll D, Langreck H, Herkommer B, Klein C, Schalla S, Fleck E, Nagel E. Myocardial perfusion imaging using OMNISCAN: a dose finding study for visual assessment of stress-induced regional perfusion abnormalities. J Cardiovasc Magn Reson 2004;6(4):803-9.

(6) Bernhardt P, Engels T, Levenson B, Haase K, Albrecht A, Strohm O. Prediction of necessity for coronary artery revascularization by adenosine contrast-enhanced magnetic resonance imaging. Int J Cardiol 2006 September 20;112(2):184-90.

(7) Klem I, Heitner JF, Shah DJ, Sketch MH, Jr., Behar V, Weinsaft J, Cawley P, Parker M, Elliott M, Judd RM, Kim RJ. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. J Am Coll Cardiol 2006 April 18;47(8):1630-8.

(8) Pilz G, Bernhardt P, Klos M, Ali E, Wild M, Hofling B. Clinical impli-

cation of adenosine-stress cardiac magnetic resonance imaging as potential gatekeeper prior to invasive examination in patients with AHA/ACC class II indication for coronary angiography. Clin Res Cardiol 2006 October;95(10):531-8.

(9) Cury RC, Cattani CA, Gabure LA, Racy DJ, de Gois JM, Siebert U, Lima SS, Brady TJ. Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients with coronary artery disease. Radiology 2006 July;240(1):39-45.

(10) Wolff SD, Schwitter J, Coulden R, Friedrich MG, Bluemke DA, Biederman RW, Martin ET, Lansky AJ, Kashanian F, Foo TK, Licato PE, Comeau CR. Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study. Circulation 2004 August 10;110(6):732-7.

(11) Plein S, Greenwood JP, Ridgway JP, Cranny G, Ball SG, Sivananthan MU. Assessment of non-ST-segment elevation acute coronary syndromes with cardiac magnetic resonance imaging. J Am Coll Cardiol 2004 December 7;44(11):2173-81.

(12) Pilz G, Jeske A, Klos M, Ali E, Hoefling B, Scheck R, Bernhardt P. Prognostic value of normal adenosine-stress cardiac magnetic resonance imaging. Am J Cardiol 2008 May 15;101(10):1408-12.

(13) Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 2001 June 19;103(24):2928-34.

(14) Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, Higano ST, Lim MJ, Meuwissen M, Piek JJ, Pijls NH, Siebes M, Spaan JA. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: a scientific statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. Circulation 2006 September 19;114(12):1321-41.

(15) Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froe-

licher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL, Jr., Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A, Jr., Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation 1997 July 1;96(1):345-54.

(16) Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. J Am Coll Cardiol 2007 October 2;50(14):1343-53.

(17) Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007 April 3;115(13):1769-76.

(18) Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI. Part II. Risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004 November;14(11):2046-52.

(19) Hundley WG, Hamilton CA, Thomas MS, Herrington DM, Salido TB, Kitzman DW, Little WC, Link KM. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation 1999 October 19;100(16):1697-702.

(20) Wellnhofer E, Olariu A, Klein C, Grafe M, Wahl A, Fleck E, Nagel E. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. Circulation 2004 May 11;109(18):2172-4.

(21) Crean A, Merchant N. MR perfusion and delayed enhancement imaging in the heart. Clin Radiol 2006 March;61(3):225-36.

(22) Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR, Marincek B, Luscher TF, von Schulthess GK. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a

comparison with positron emission tomography and coronary angiography. Circulation 2001 May 8;103(18):2230-5.

(23) Rieber J, Huber A, Erhard I, Mueller S, Schweyer M, Koenig A, Schiele TM, Theisen K, Siebert U, Schoenberg SO, Reiser M, Klauss V. Cardiac magnetic resonance perfusion imaging for the functional assessment of coronary artery disease: a comparison with coronary angiography and fractional flow reserve. Eur Heart J 2006 June;27(12):1465-71.

(24) Ishida N, Sakuma H, Motoyasu M, Okinaka T, Isaka N, Nakano T, Takeda K. Noninfarcted myocardium: correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. Radiology 2003 October;229(1):209-16.

(25) Chiu CW, So NM, Lam WW, Chan KY, Sanderson JE. Combined first-pass perfusion and viability study at MR imaging in patients with non-ST segment-elevation acute coronary syndromes: feasibility study. Radiology 2003 March;226(3):717-22.

chapter 4

Inter-observer variability of visual analysis of "stress"-only adenosine first-pass myocardial perfusion imaging in relation to clinical experience and reading criteria

Submitted for publication European Radiology

Inter-observer variability of visual analysis of "stress"-only adenosine first-pass myocardial perfusion imaging in relation to clinical experience and reading criteria

D.D. Lubbers[1], MD
D. Kuijpers[2], MD, PhD
R. Bodewes[1], MD
P. Kappert[1],
M. Kerkhof[3], MD, PhD
P.M.A. van Ooijen[1], PhD
M. Oudkerk[1], MD, PhD

Department of Radiology[1], University Medical Center Groningen, University of Groningen, The Netherlands. Department of Radiology[2], Bronovo Hospital, The Hague, The Netherlands. Department of epidemiology[3], University Medical Center Groningen, University of Groningen, The Netherlands

ABSTRACT

Purpose: To assess the inter-observer agreement of adenosine "stress"-only visual analysis of perfusion MR images in relation to experience and reading criteria.

Method and materials: One-hundred and six adenosine perfusion cardiac MR examinations out of 350 examinations, 46 consecutive positive examinations and 60 randomly selected negative examinations were visually analysed by four individual readers with different levels of experience: Two residents with, respectively, two years and two months of experience, and one technician. These readings were compared with the expert reading of an experienced radiologist (more than five years experience). Readings were performed blinded for clinical information and using "stress"-only adenosine perfusion images. After 3 minutes of adenosine infusion (0.140 mg/kg/min) during the first pass of 0.1 mmol/kg gadolinium (infusion rate 5 ml/s), a perfusion sequence was started acquiring three short-axis slices. After at least a month the examinations were presented again in a random order without knowledge of the performance of the first reading. This time readings were performed with the systematical use of reading criteria.

Results: Agreement with the expert reading was good for the resident with two years of experience (k = 0.88). Kappa was 0.48 for the resident with two months of experience, and 0.57 for the technician. After the second reading using all proposed reading criteria inter-observer agreement increased to 0.9, 0.68 and 0.77 respectively. Overall Fleiss kappa increased from 0.59 to 0.71 between both readings. The systematic use of reading criteria significantly improved the performance of the least experienced observer (p=0.01).

Conclusion: Visual analysis of adenosine "stress"-only first-pass perfusion cardiac MR images is feasible with moderate to very good agreement. Performance is experience related, but the systematical use of reading criteria significantly increased performance for the least experienced observer.

INTRODUCTION

Adenosine stress first-pass perfusion imaging is increasingly used for the detection of myocardial ischemia. Diagnostic accuracies in recently published papers are good (1-7). There is however still considerable heterogeneity in used clinical protocols, among others the use of (semi-) quantitative analysis or a more robust visual reading, which is more often used in clinical routine. Previous studies have shown that quantitative analysis of perfusion imaging and a visual reading both have a similar good correlation to coronary angiography (CAG) (8-11). A visual reading is robust and straight forward and with currently possible resolutions it might also be easily performed by less experienced observers. There is however wide variability in used and proposed criteria for visual assessment of perfusion abnormalities (1;2;4-7;10;12-24), ranging from no pre-defined criteria to in part contradictory criteria.

The assessment of adenosine "stress" perfusion imaging only, for a visual reading, has a number of advantages. Imaging time is reduced as well as analysis time. There is no waiting time between stress and rest perfusion, and a second bolus of contrast media can be avoided. Therefore no influence of the first contrast administration on the signal intensity of the second perfusion images exists. Using only stress perfusion imaging also eliminates the necessity to spatially match stress and rest perfusion imaging. Unfortunately perfusion imaging may suffer from artefacts, which may sometimes resemble ischemic perfusion defects (25).

The aim of this study is to assess the inter-observer variability of a visual reading of adenosine stress-only perfusion imaging. Additionally the impact of experience and the use of systematic reading criteria was assessed.

MATERIALS AND METHODS

Patient population

Forty six consecutive patients with a positive adenosine first-pass myocardial perfusion MR examination, together with 60 randomly selected patients with a negative adenosine first-pass myocardial perfusion MR examination were included. These patients were selected out of 355 patients that were

referred to our institution between January 2005 and May 2007.
The studied population consisted of 59 men and 47 women; mean age 61.2 ± 9.9 years. All patients had a clinical necessity to exclude myocardial ischemia and patients did not have a prior myocardial infarction. Exclusion criteria were: patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120), CMR-incompatible metallic implants, known claustrophobia, asthma, chronic obstructive pulmonary disease and patients using dipyridamol.

MR imaging protocol

All anti-anginal medication was stopped 4 days before the adenosine perfusion MR examination. Scanning was performed at 1.5T using a Magnetom Avanto MRI system (Siemens Medical Solutions, Erlangen, Germany). After the patient was positioned on the scanning table, intravenous access was established via an anticubital vein. ECG monitoring leads, a phased-array surface coil covering the heart and a brachial blood pressure cuff were applied. A single lead ECG was continuously monitored on the MRI-console. Systolic and Diastolic blood pressures were recorded using an automatic device (Welch-Allyn, Emro-medical) at baseline and during adenosine infusion. Blood pressure and heart rate were recorded.After 3 minutes of adenosine infusion (0.140 mg/kg/min) during the first pass of 0.1 mmol/kg gadopentetate dimeglumine Omniscan® with a flow rate of 5 ml/s flushed with 15 ml 0.9% NACL (flow rate 5ml/s) a perfusion sequence was started: TrueFisp: TR, 150.5; TE 1.03 ms; TI 100ms; □ 45°; FOV 300 X 300; slice-thickness 6 mm; matrix 76 X 128; iPAT 2. or TSENSE: TR, 163.1 ms; TE 1.03 ms; TI 103 ms; □ 50°; FOV 300 X 300; slice-thickness 6 mm; matrix 76 X 128; iPAT 2. During the examination a radiologist and a cardiologist were present in the MR suite, to monitor the condition of the patient and to evaluate the images directly.

Image analysis

Perfusion series were visually analysed by an experienced radiologist, using a 16 segment model, defining a relevant perfusion defect as a perfusion abnormality in at least two segments at consecutive planes of the left ventricle or one segment of the most apical slice.

The selected examinations were archived and viewed on a dedicated workstation (ViewPro versie 3.2.0.12, Rogan Delft, Veenendaal, the Netherlands). The examinations were anonimized and randomized. Three observers with different levels of experience performed a visual reading of the examinations (two residents, one with two years, one with two months of experience did a visual reading, and a reading was performed by a technician). The observers were fully blinded to clinical information, CAG results and adenosine stress MR related information. The observers had to state whether there was a perfusion abnormality indicative of myocardial ischemia. The observers were blinded to the results obtained by the other observers. Furthermore studies were presented to the observers in a different, random order. No prior joint training session was organized. All individual readings were compared to the expert reading. After the first reading all examinations were presented again, this time using the systematic reading criteria as proposed in the literature(1;2;4-7;10;12-24), see table 1, Readers were kept uninformed regarding there results and there was at least one month between both readings.

Statistical analysis

Summary values are expressed as mean with standard deviation.

Agreement was measured between readers and consensus reading using Cohen's Kappa. Fleiss kappa (26) was used to evaluate overall agreement. Grading of Kappa values was set at poor for 0 – 0.2; fair for 0.21 – 0.41; moderate for 0.41 – 0.6; good for 0.61 – 0.8 and very good for 0.81 – 1.0. Comparison for statistical significance between both readings for all observers was performed with the McNemar test ($p<0.05$). Data analysis was performed using SPSS 14.0 for windows and R (version 2.5.0) for Fleiss kappa calculations

Table 1. Reading criteria

Important reading criteria proposed in the literature
• Perfusiondefect (PD) more than 1/3 of wall thickness (more than subendocardium)
• At least two neighbouring segments involved
• > 5 heartbeats after maximum signal intensity in LV cavity
• PD definetely darker than surrounding myocardium
• > 3 heartbeats after peak enhancement of most normal appearing region
• PD is region of interest with lowered peak signal intensity
• Focal region of myocardium with lowered contrast enhancement
• PD in at least two segments
• PD more than 50% of wall thickness
• 4 point scale (0 normal; 1 probably normal; 2 probably abnormal; 3 abnormal)
• Hypo-enhancement in coronary flow areas
• Ischemic PD does not fluctuate in signal intensity
• Lowered signal intensity in at least one segments
• Perfusion defects persits beyond the point of peak enhancement

RESULTS

Clinical and haemodynamic data of all patients is presented in table 2. Mean heart rate at the time of adenosine stress perfusion imaging was 88.3, compared to 75,3 in rest. Systolic blood pressure at the time of adenosine perfusion imaging is 146.1, compared to 152.4 in rest. This is a normal and expected reaction to the adenosine, making it diagnostic studies.

Overall Average Fleisch kappa coefficient of reading adenosine stress-only perfusion images, regarding the question if there is a perfusion abnormal-

ity suggestive of myocardial ischemia was 0.59 for all readers and average Cohen's kappa was 0.64. Individual kappa values were 0.88 for the most experienced resident, 0.48 for the less experienced resident and 0.57 for the technician.

Then a second reading was performed, this time with the systematical use of all the reading criteria as proposed in the literature, table 1. Overall Fleiss kappa value after this reading was 0.71 Individual readings: 0.90 for the most experienced resident, 0.68 for the less experienced and 0.77 for the technician. In total 30 mismatches were present out of 318 readings.

Figures 1 to 3 illustrates different scenarios of agreement on visual analysis of adenosine stress first-pass perfusion imaging.

Comparison between the first and second reading of all observers showed no significant difference for the most experienced observer (p=1.00) and the technician (p=0.186). The least experienced observer however significantly improved (p=0.01).

Table 2. Clinical and haemodynamic data

Variable	Mean or %
Age, years	61,2 ± 9,94
Male, %	56
Body weight, kg	77,4 ± 14,3
Resting diastolic blood pressure	87,0 ± 11,1
Adenosine diastolic blood pressure, mmHg	83,4 ± 10,3
Resting systolic blood pressure, mmHg	152,4 ± 25,7
Adenosine systolic blood pressure, mmHg	146,1 ± 22,4
Resting heart rate, bpm	75,3 ± 16,8
adenosine heart rate, bpm	88,3 ± 16,5

Values are expressed as mean ± SD or percentage

Figure 1: Three images from a basal short-axis perfusion run. With contrast arrival in the LV cavity on the left. Myocardial enhancement in the middle image and washout in the last image. Clear perfusion defect in the lateral wall identified correctly by all observers.

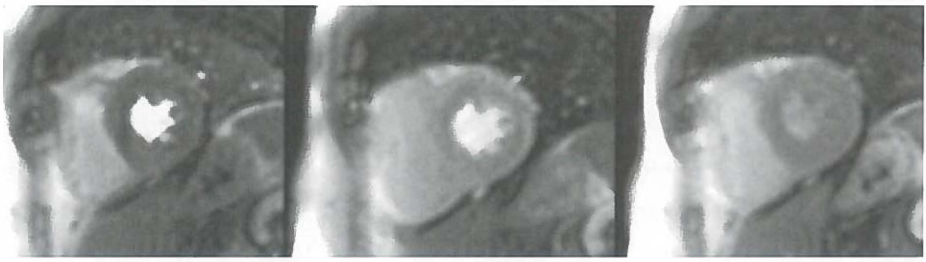


Figure 2: Normal Myocardial perfusion identified correctly by all observers despite small artefact.

Figure 3: Adenosine-stress first pass perfusion images with discrepancy between readers. Image with motion artefact and some what larger susceptibility artefact, occuring early.

DISCUSSION

The main finding of this study is that visual assessment of adenosine stress-only first-pass myocardial perfusion imaging has moderate to very good agreement. This agreement is experience related and increases with the systematical use of reading criteria for less experienced observers. More experienced readers probably already use more of the criteria published in the literature that help differentiate between real perfusion defects and artefacts. This does imply that visual analysis of adenosine stress-only images is easily learned and may help increase clinical implementation. To the best of our knowledge this is the first study to specifically look at the inter-observer variability of adenosine stress- only first pass myocardial perfusion imaging.

Standardized visual reading criteria need to be set, due to the only moderate overall agreement. This is supported by the fact that agreement increases considerably after the second reading using the proposed criteria to an overall good agreement. This compares quite favorably with other sreening methods, like for instance mammography (27-29).

Some proposed reading criteria presented in the literature may not always be applicable, for instance defining that a perfusiondefects indicative of myocardial ischemia has to be present in more than one segment fails to detect a significant distal stenosis of the left circumflex (LCX). Similar results have been found in nuclear stress perfusion imaging (30).

This study was set-up for relatively less experienced readers to little experience. It can be assumed that this lowered overall agreement. However for an examination to be easily implemented in to routine clinical practice and more widespread acceptance an examination also needs to be interpretable for less experienced readers. With the use of specific reading criteria and training by more experienced readers it can be assumed that overall agreement will increase.

Delayed contrast enhancement imaging (DCE) was not routinely performed. We believe stress-only analysis should be reserved for patients with unknown CAD, and no previous myocardial infarctions. As proposed by Klem et al. (5), image analysis should when, DCE clinically indicated, be-

gin with DCE images. In other patient categories, like the one studied in this paper, image analysis should start with the adenosine stress first-pass perfusion imaging, since this will save unnecessarily prolongation of the examination for patients. Stress perfusion analysis can in this regard be used as an arbiter for additional series. If normal, with noticeable effect of the adenosine, a rest perfusion is unnecessary.

Results from the second reading may be influenced by a general learning effect, to minimize this effect we used a relatively large data set and there was at least one month between both readings. Images were presented in a different order on both occasions. Furthermore observers were kept uninformed regarding their results of the first reading.

CONCLUSION

With relative little experience in the visual interpretation of stress perfusion MR images there is only moderate overall agreement, the use of systematic reading criteria considerably increases agreement with an expert reading, making the examination available for less experienced readers.

ACKNOWLEDGEMENTS

The authors thank Bernadette Blom and colleagues for image acquisition and Stella Noach for critically reviewing the paper.

REFERENCE LIST

(1) Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. J Am Coll Cardiol 2006 April 4;47(7):1427-32.

(2) Sakuma H, Suzawa N, Ichikawa Y, Makino K, Hirano T, Kitagawa K, Takeda K. Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. AJR Am J Roentgenol 2005 July;185(1):95-102.

(3) Plein S, Radjenovic A, Ridgway JP, Barmby D, Greenwood JP, Ball SG, Sivananthan MU. Coronary artery disease: myocardial perfusion MR imaging with sensitivity encoding versus conventional angiography. Radiology 2005 May;235(2):423-30.

(4) Bernhardt P, Engels T, Levenson B, Haase K, Albrecht A, Strohm O. Prediction of necessity for coronary artery revascularization by adenosine contrast-enhanced magnetic resonance imaging. Int J Cardiol 2006 September 20;112(2):184-90.

(5) Klem I, Heitner JF, Shah DJ, Sketch MH, Jr., Behar V, Weinsaft J, Cawley P, Parker M, Elliott M, Judd RM, Kim RJ. Improved detection of coronary artery disease by stress perfusion cardiovascular magnetic resonance with the use of delayed enhancement infarction imaging. J Am Coll Cardiol 2006 April 18;47(8):1630-8.

(6) Pilz G, Bernhardt P, Klos M, Ali E, Wild M, Hofling B. Clinical implication of adenosine-stress cardiac magnetic resonance imaging as potential gatekeeper prior to invasive examination in patients with AHA/ACC class II indication for coronary angiography. Clin Res Cardiol 2006 October;95(10):531-8.

(7) Cury RC, Cattani CA, Gabure LA, Racy DJ, de Gois JM, Siebert U, Lima SS, Brady TJ. Diagnostic performance of stress perfusion and delayed-enhancement MR imaging in patients with coronary artery disease. Radiology 2006 July;240(1):39-45.

(8) Schwitter J, Nanz D, Kneifel S, Bertschinger K, Buchi M, Knusel PR,

Marincek B, Luscher TF, von Schulthess GK. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. Circulation 2001 May 8;103(18):2230-5.

(9) Ishida N, Sakuma H, Motoyasu M, Okinaka T, Isaka N, Nakano T, Takeda K. Noninfarcted myocardium: correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. Radiology 2003 October;229(1):209-16.

(10) Chiu CW, So NM, Lam WW, Chan KY, Sanderson JE. Combined first-pass perfusion and viability study at MR imaging in patients with non-ST segment-elevation acute coronary syndromes: feasibility study. Radiology 2003 March;226(3):717-22.

(11) 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 June;11(6):607-15.

(12) Sensky PR, Samani NJ, Horsfield MA, Cherryman GR. Restoration of myocardial blood flow following percutaneous coronary balloon dilatation and stent implantation: assessment with qualitative and quantitative contrast-enhanced magnetic resonance imaging. Clin Radiol 2002 July;57(7):593-9.

(13) Fenchel M, Franow A, Stauder NI, Kramer U, Helber U, Claussen CD, Miller S. Myocardial perfusion after angioplasty in patients suspected of having single-vessel coronary artery disease: improvement detected at rest-stress first-pass perfusion MR imaging--initial experience. Radiology 2005 October;237(1):67-74.

(14) Crean A, Merchant N. MR perfusion and delayed enhancement imaging in the heart. Clin Radiol 2006 March;61(3):225-36.

(15) Klassen C, Nguyen M, Siuciak A, Wilke NM. Magnetic resonance first pass perfusion imaging for detecting coronary artery disease. Eur J Radiol 2006 March;57(3):412-6.

(16) Paetsch I, Foll D, Langreck H, Herkommer B, Klein C, Schalla S, Fleck

E, Nagel E. Myocardial perfusion imaging using OMNISCAN: a dose finding study for visual assessment of stress-induced regional perfusion abnormalities. J Cardiovasc Magn Reson 2004;6(4):803-9.

(17) Takase B, Nagata M, Kihara T, Kameyawa A, Noya K, Matsui T, Ohsuzu F, Ishihara M, Kurita A. Whole-heart dipyridamole stress first-pass myocardial perfusion MRI for the detection of coronary artery disease. Jpn Heart J 2004 May;45(3):475-86.

(18) Gebker R, Paetsch I, Neuss M, Schnackenburg B, Bornstedt A, Jahnke C, Gomaa O, Fleck E, Nagel E. Determinants of myocardial response in CMR perfusion imaging using Gd-BOPTA (Multihance). J Cardiovasc Magn Reson 2005;7(3):565-72.

(19) Panting JR, Gatehouse PD, Yang GZ, Jerosch-Herold M, Wilke N, Firmin DN, Pennell DJ. Echo-planar magnetic resonance myocardial perfusion imaging: parametric map analysis and comparison with thallium SPECT. J Magn Reson Imaging 2001 February;13(2):192-200.

(20) Elkington AG, Gatehouse PD, Prasad SK, Moon JC, Firmin DN, Pennell DJ. Combined long- and short-axis myocardial perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2004;6(4):811-6.

(21) Plein S, Ridgway JP, Jones TR, Bloomer TN, Sivananthan MU. Coronary artery disease: assessment with a comprehensive MR imaging protocol--initial results. Radiology 2002 October;225(1):300-7.

(22) Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J, Christian TF, Balaban RS, Arai AE. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. Circulation 2003 February 4;107(4):531-7.

(23) Wolff SD, Schwitter J, Coulden R, Friedrich MG, Bluemke DA, Biederman RW, Martin ET, Lansky AJ, Kashanian F, Foo TK, Licato PE, Comeau CR. Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study. Circulation 2004 August 10;110(6):732-7.

(24) Wintersperger BJ, Penzkofer HV, Knez A, Weber J, Reiser MF. Multislice MR perfusion imaging and regional myocardial function analy-

sis: complimentary findings in chronic myocardial ischemia. Int J Card Imaging 1999 December;15(6):425-34.

(25) Di Bella EV, Parker DL, Sinusas AJ. On the dark rim artifact in dynamic contrast-enhanced MRI myocardial perfusion studies. Magn Reson Med 2005 November;54(5):1295-9.

(26) Fleiss JL. Measuring nominal scale agreement among many raters. Psychological Bulletin. 1971. 76: 378-2.

(27) Elmore JG, Wells CK, Lee CH, Howard DH, Feinstein AR. Variability in radiologists' interpretations of mammograms. N Engl J Med 1994 December 1;331(22):1493-9.

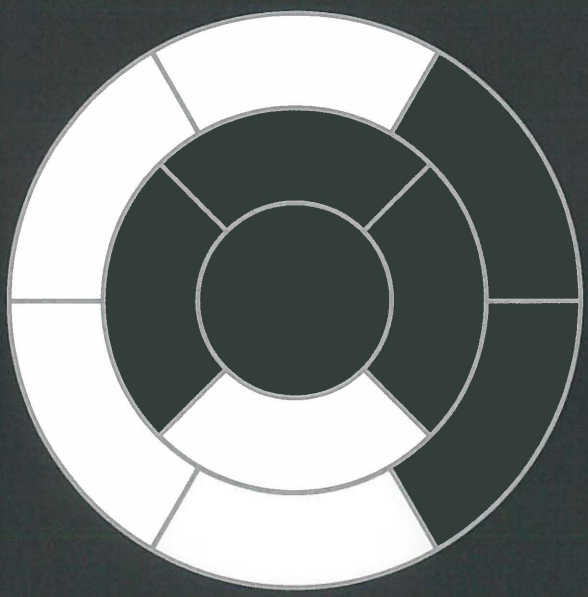
(28) Duijm LE, Louwman MW, Groenewoud JH, van de Poll-Franse LV, Fracheboud J, Coebergh JW. Inter-observer variability in mammography screening and effect of type and number of readers on screening outcome. Br J Cancer 2009 March 24;100(6):901-7.

(29) Jackson SL, Taplin SH, Sickles EA, Abraham L, Barlow WE, Carney PA, Geller B, Berns EA, Cutter GR, Elmore JG. Variability of interpretive accuracy among diagnostic mammography facilities. J Natl Cancer Inst 2009 June 3;101(11):814-27.

(30) Wackers FJ, Bodenheimer M, Fleiss JL, Brown M. Factors affecting uniformity in interpretation of planar thallium-201 imaging in a multicenter trial. The Multicenter Study on Silent Myocardial Ischemia (MSSMI) Thallium-201 Investigators. J Am Coll Cardiol 1993 April;21(5):1064-74.

chapter 5

Assessment of global left ventricular functional paramaters; analysis of every second short-axis magnetic resonance imaging slices is as accurate as analysis of consecutive slices



Int J Cardiovasc Imaging 2008; 24: 185-191

Assessment of global left ventricular functional paramaters; analysis of every second short-axis magnetic resonance imaging slices is as accurate as analysis of consecutive slices

D.D. Lubbers[1], MD
T.P. Willems[1], MD, PhD
P.A. van der Vleuten[2], MD
J. Overbosch[1], MD
M.JW. Götte[2], MD, PhD
D. van Veldhuisen[2], MD, PhD
M. Oudkerk[1], MD, PhD

Departments of Radiology[1] and Cardiology[2], University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, the Netherlands

ABSTRACT

Purpose: To assess whether accurate global left- ventricular (LV) functional parameters can be obtained by analyzing every second short-axis magnetic resonance imaging cine serie instead of consecutive slices, in order to reduce post-processing time.

Materials and methods: Forty patients, were scanned on a 1.5 T MRI-system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany) using a steady-state free precession (SSFP) sequence. A stack of short-axis cine series from above the mitral valve through the apex was acquired. Post-processing was started at the most basal slice of the left ventricle, in which at least 50% of the circumference was myocardium. End-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), ejection fraction (EF) and LV mass (LVM), were calculated. Data analysis was repeated, but now only every second slice was analyzed.

Results: Bland-Altman analysis showed slightly lower values for all LV parameters when only every second slice was analyzed, ranging from 1.7% difference for EF (limits of agreement -3.5 to 5.0) to 4.6% for SV (limits of agreement -7.2 to 15.0).

Conclusion: Analysis of every second slice for quantification of global LV function is time-saving and as accurate as analysis of consecutive slices.

INTRODUCTION

LV functional parameter analysis is performed in a variety of cardiovascular diseases. It provides direct quantitative information about the patients' current cardiovascular health status and may be useful as a prognostic marker. A diminished LV function or a LV hypertrophy is associated with an increased risk of cardiovascular mortality (1;2).

Echocardiography is currently the most widely used imaging modality for assessment of LV functional parameters, but it is limited by its operator dependency, acoustic window, poor contrast, and requires a geometric model. MR does not require geometrical assumptions and is at present considered to be the reference standard for functional imaging (3-10). As a consequence the number of patients referred for LV functional parameter analysis by MR is increasing.

Reduction in scanning-time has been achieved over the years, and visually good recognisable endocardial borders for contour delineation are provided by steady state free precession (SSFP) (11-14). Post-processing still takes considerable time, up to 30 minutes. Therefore, time-saving methods can be useful in clinical practice.

Since short-axis cine MR series can be obtained in subsequent slices with a 3D representation no geometric assumptions have to be made. Analyzing every second slice might still give accurate measurements. The purpose of this study is to assess whether accurate LV functional parameters can be obtained by analyzing every second short-axis magnetic resonance images series in order to reduce post-processing time.

MATERIALS AND METHODS

Study population

Forty consecutive patients (22 men, mean age 45 years, range 15-72) were referred for analysis of LV function. All patients had a history of cardiac disease: 13 patients had a congenital heart disease, 9 patients had a previous myocardial infarction, 10 patients had cardiomyopathy, and 8 patients were referred after an impaired LV function was found by echocardiography.

Image acquisition

Image acquisition was performed on a 1.5 T MRI-system (Magnetom Sonata, Siemens Medical systems, Erlangen, Germany) using a steady state free precession (SSFP) sequence, with the following parameters: 2.8/1.28 (repetition time ms/echo time ms), 35.8 ms temporal resolution. Flip angle 80°, field of view 320, matrix 156 x 192, voxelsize 1.7 x 1.7 x 6, bandwidth 930, half Fourier acquisition, 25 phases per cycle, using retrospective ECG-triggering. In case of an irregular rhythm prospective ECG-triggering was used with the following parameters: 3.1/1.55 (repetition time ms/echo time ms), 47.5 ms temporal resolution. Flip angle 58°, field of view 340, matrix 164 x 256, voxelsize 1.7 x 1.3 x 6, bandwidth 930, half Fourier acquisition. Slice thickness was set at 6 mm, with an inter-slice gap of 4 mm. Images were acquired at repeated end-expiratory breath-holds. A standard two by six channel body coil was used.

In order to plan the short-axis views, first standard survey images were acquired. The short-axis volume set was planned using the vertical long axis (VLA) and the four-chamber view (4CV), ensuring that the imaging plane runs parallel to the mitral valve annulus. ECG gated short-axis cine series were acquired subsequently. A full stack of short axis images was always acquired in order to look for myocardial dyssynchrony, or an abnormal shaped heart.

Post-processing: Software analysis

The short-axis cine series were analyzed using commercially available software (QMASS version 6.1.2, Medis Medical Imaging Systems, Leiden, The Netherlands). The end-diastolic phase was defined as the phase with the greatest visually estimated luminal cavity, and the systolic phase as the phase with the smallest luminal cavity. Analysis was started at the most basal slice of the left ventricle in which at least 50% of the circumference was myocardium. A difference of one section position was possible between the most basal slice in end-diastolic phase and end-systolic phase due to the influence of through-plane motion (15). Epi- and endocardial contours for the left-ventricle were drawn manually in all slices. Papillary muscles and trabeculae

were included in the lumen of the left ventricle.

The same procedure was repeated but only every second slice was analyzed, starting again from the most basal slice in which both end-diastolic and end-systolic phase contours could be drawn. every second slice was analysed towards the apex of the heart. Analysis was essentially performed on 6 mm slices, skipping 14 mm. Figure 1 gives a representation of both methods.

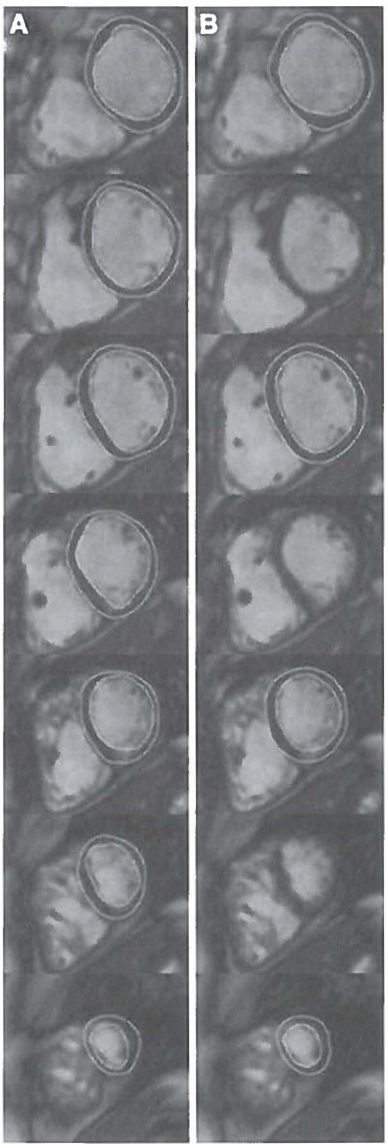


Figure 1: End-diastolic short-axis images. Representation when consecutive slices are analyzed (A) en when every second slice is analyzed (B).

Left ventricular functional parameters

The obtained parameters of the left ventricle consisted of the end-diastolic volumes (EDV) and end-systolic volumes (ESV) of all slices, and the EDV and ESV when every second slice was selected. From these parameters stroke volumes (SV) and ejection fraction (EF) were calculated for all slices and the every second slice analysis method respectively. Stroke volume was calculated by subtracting the end-systolic volume from the end-diastolic volume (SV=EDV-ESV). The ejection fraction was calculated by dividing the stroke volume with the end-diastolic volume, multiplied with 100% (EF= (SV/EDV) * 100 %). Left ventricular mass (LVM) measurements were calculated from the area between epicardial and endocardial contours in the end-diastolic phase. These parameters were directly calculated by QMASS software. Analysis of all slices and analysis of every second slice was performed by a single experienced investigator. Length of time necessary for analysis of all slices versus analysis of every second slice was measured.

Statistical analysis

Data from all functional parameters are presented as mean ± SD. The mean differences between both analyzing methods are presented together with SD. Mean differences were calculated by measurements of all slices minus measurements from analysis of every second slice, and expressed in ml for the EDV, ESV, and SV. EF is expressed as a percentage and LVM in grams The Bland-Altman method was used to assess the agreement between both methods.(16) A percentage difference is described and the limits of agreement are given. Length of time necessary for analysis was measured in minutes. Mean duration was calculated for both methods, and compared using student's T-test, in which $p < .01$ is considered to indicate a significant difference between both methods. Results are expressed as mean duration of analysis ± 2SD. It can be hypothesised that a method needing more geometrical assumptions may be flawed in the case of locally defined wall motion abnormalities. Therefore, a sub-analysis is performed, without patients in which regional wall motion abnormalities are present or can be

expected. For instance: regional akinetic regions, left or right bundle branch blocks and ventricle septumdefect.

RESULTS

Average number of slices in post-processing analyzed for "the all slices-method" is 9.2 ± 1.2. Number of slices analyzed with post-processing every second slice is 5.0 ± 0.6.

Data from all functional parameters and SD's are shown in table 1, which also shows the percentage differences and the limits of agreement.

Figure 2 shows the Bland-Altman plots for all functional parameters.

Mean EDV for analysis of all slices is 198.0 ml, for every second slice 192.2 ml. The absolute difference is 5.8 ml. Mean ESV for analysis of all slices is 113.3 ml, for every second slice 111.4 ml. The absolute difference is 1.9 ml. Mean SV is 84.7 ml for analysis of all slices, and 80.8 ml for every second slice. The absolute difference for SV is 3.9 ml. Mean EF when all slices are analyzed is 45.2 %, whereas analysis of every second slice resulted in a mean of 44.4%. The absolute difference is 0.76%. LVM measurement for analysis of all slices is 112.9 g, and 108.8 g for analysis of every second slice. The absolute difference is 4.1 g.

Table 1: Measurements of left ventricular functional parameters.

Parameter*	All slices	Alternate slices	Absolute differences	Percentage difference	Limits of agreement
EF (%)	45.1 ± 11.4	44.4 ± 12.5	0.76 ± 2.2	1.7	-3.5 to 5.0
SV (ml)	84.7 ± 25.1	80.8 ± 27.3	3.9 ± 5.7	4.6	-7.2 to 15.0
M (g)	112.9 ± 39.4	108.8 ± 37.6	4.1 ± 4.8	3.5	-5.3 to 13.5
EDV (ml)	198.0 ± 66.5	192.2 ± 64.7	5.8 ± 5.7	2.9	-5.4 to 16.9
ESV (ml)	113.3 ± 59.2	111.4 ± 59.0	1.9 ± 3.8	1.7	-5.5 to 9.2

Data for both analysing methods, and the absolute difference are presented as the mean ± SDs. EF = ejection fraction, SV = stroke volume, M = mass, EDV = end-diastolic volume, ESV = end-systolic volume

Table 2 shows a sub analysis when patients with akinetic regions, left or right bundle branch and ventricle septum defects are excluded.
On average analysis of all slices takes 13 min ± 2.5, whereas analyzing every second slice takes 8 min ± 2 ($p<0.01$).

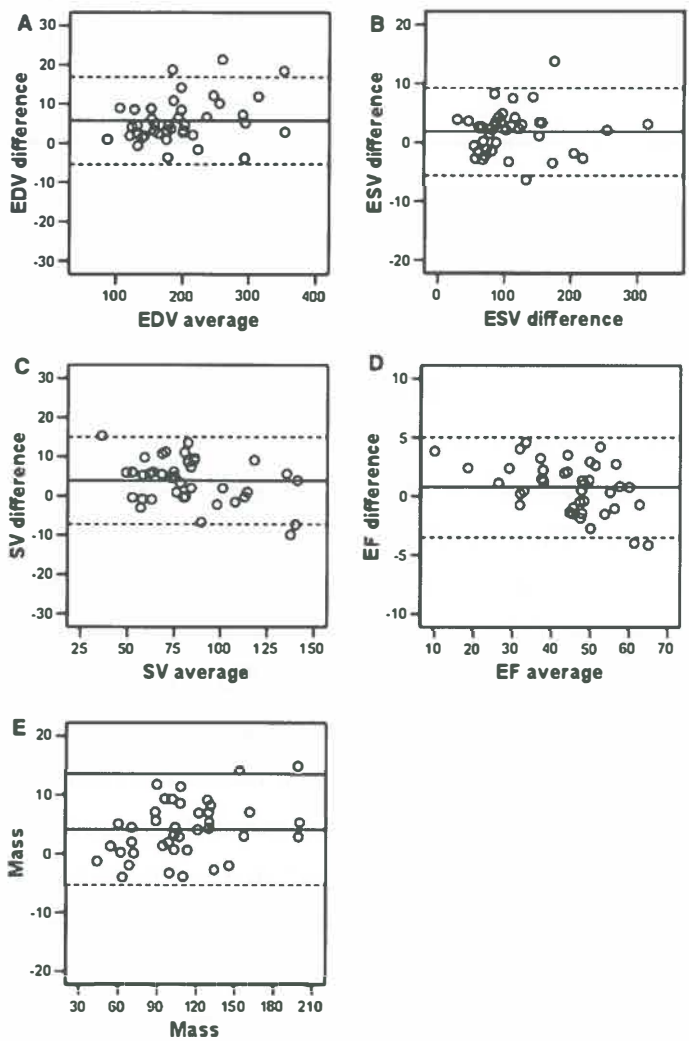


Figure 2: Bland-Altman plots depict agreement between analysis of all slices versus every second slices. Solid lines on plot represent the average between analyzing all slices versus every second slices, for: EDV (2a), ESV (2b), SV (2c), EF (2d), Mass (2e). Dotted lines represent ± 2 SDs. EF = ejection fraction, SV = stroke volume, EDV = end-diastolic volume, ESV = end-systolic volume.

Table 2: Measurements of left ventricular functional parameters, after exclusion of patients with myocardial dyssynchrony or regional deformities from analysis (n=33)

Parameter*	Absolute differences	Percentage difference	Limits of agreement
EF (%)	0.55 ± 1.9	1.2	-3.2 to 4.3
SV (ml)	3.6 ± 5.2	4.1	-6.6 to 13.8
M (g)	4.4 ± 5.0	3.9	-5.4 to 14.2
EDV (ml)	5.3 ± 5.6	2.7	-5.7 to 16.3
ESV (ml)	2.2 ± 3.7	2.1	-5.1 to 9.5

Data are presented as the mean ± SDs. EF = ejection fraction, SV = stroke volume, M = mass, EDV = end-diastolic volume, ESV = end-systolic volume

DISCUSSION

This study demonstrates that analysis of every second slices is as accurate as analysis of consecutive slices, although it slightly underestimates LV functional parameters. The mean difference for EF, which clinically is the most important variable, is less than 1%, with narrow limits of agreement. The results for the other left ventricular functional parameters are also small, and may not be of clinical relevance. Agreement between both methods is high. As proposed by Bland and Altman we have not performed a test of significance, because this is not relevant for the question of agreement. Results show that the limits of agreement are small. Image acquisition with an intersection gap 5-10 mm did not result in a significant loss of accuracy in a homogeneous population (17). To the best of our knowledge this is the first study to describe that analysis of every second obtained short-axis slices is accurate and reduces post-processing time.

Results are obtained in a clinical population with a wide range of cardiac diseases and are therefore applicable in clinical use. Results differed more in case of a myocardial dyssynchrony or an abnormal shaped heart, due to the method used. Therefore, consecutive slices should be acquired, and time reduction preserved for post-processing only. Acquiring every other short

axis slice would also save considerable imaging time, but in this way one is not informed qualitatively on all short axis slices. Limitation of our study is the fact that measurements were obtained by one observer, but reported intra- and inter-observer variability in the literature are small (18-21). Besides this analysis was performed on 6 mm slices, with a 4 mm gap, the acquisition protocol in our routine clinical practice. It might be worth acquiring contiguous images between 6-10 mm, but this will prolong imaging time. This study aimed solely at time savings in post-processing.

Another limitation is that the study was not blinded for the observer, which could influence the time needed for analysis. On the other hand, measuring the time necessary for analysis is almost certainly observer dependent, and dependent on the time-point from which analysis is started. Therefore, emphasis should not be on the absolute time one can save by analyzing every second slices, but on the fact that accurate measures can be obtained by analyzing half the slices, which would certainly save time.

Attempts to reduce post-processing time have focused on (semi) automatic contour detection of endocardial borders (22-24). Until now, manual or semi-automatic contour detection is still preferred to automatic contour detection. Although promising, automatic contour detection requires a large learning data-set, and is not feasible in all circumstances (22;23). Another attempt to reduce post-processing time is inclusion of trabeculae in the cavity volume. This indeed has shown to reduce post-processing time considerably (24;25). Even though it affects the absolute measure, it has increased the reproducibility (25;26). Still, on average 9.2 $\pm$ 1.2 short-axis series need to be analyzed

In conclusion, accurate determination of left ventricular functional parameters can be obtained by analyzing every second short-axis slice in approximately half of the time compared to analysis of all slices.

REFERENCE LIST

(1) Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992 November 15;117(10):831-6.

(2) Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990 May 31;322(22):1561-6.

(3) Sechtem U, Pflugfelder PW, Gould RG, Cassidy MM, Higgins CB. Measurement of right and left ventricular volumes in healthy individuals with cine MR imaging. Radiology 1987 June;163(3):697-702.

(4) Debatin JF, Nadel SN, Paolini JF, Sostman HD, Coleman RE, Evans AJ, Beam C, Spritzer CE, Bashore TM. Cardiac ejection fraction: phantom study comparing cine MR imaging, radionuclide blood pool imaging, and ventriculography. J Magn Reson Imaging 1992 March;2(2):135-42.

(5) Higgins CB. Which standard has the gold? J Am Coll Cardiol 1992 June;19(7):1608-9.

(6) Rominger MB, Bachmann GF, Pabst W, Rau WS. Right ventricular volumes and ejection fraction with fast cine MR imaging in breathhold technique: applicability, normal values from 52 volunteers, and evaluation of 325 adult cardiac patients. J Magn Reson Imaging 1999 December;10(6):908-18.

(7) Dulce MC, Mostbeck GH, Friese KK, Caputo GR, Higgins CB. Quantification of the left ventricular volumes and function with cine MR imaging: comparison of geometric models with three-dimensional data. Radiology 1993 August;188(2):371-6.

(8) Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP, Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson 1999;1(1):7-21.

(9) Thiele H, Paetsch I, Schnackenburg B, Bornstedt A, Grebe O, Welln-

hofer E, Schuler G, Fleck E, Nagel E. Improved accuracy of quantitative assessment of left ventricular volume and ejection fraction by geometric models with steady-state free precession. J Cardiovasc Magn Reson 2002;4(3):327-39.

(10) Bellenger NG, Grothues F, Smith GC, Pennell DJ. Quantification of right and left ventricular function by cardiovascular magnetic resonance. Herz 2000 June;25(4):392-9.

(11) Carr JC, Simonetti O, Bundy J, Li D, Pereles S, Finn JP. Cine MR angiography of the heart with segmented true fast imaging with steady-state precession. Radiology 2001 June;219(3):828-34.

(12) Barkhausen J, Ruehm SG, Goyen M, Buck T, Laub G, Debatin JF. MR evaluation of ventricular function: true fast imaging with steady-state precession versus fast low-angle shot cine MR imaging: feasibility study. Radiology 2001 April;219(1):264-9.

(13) Lee VS, Resnick D, Bundy JM, Simonetti OP, Lee P, Weinreb JC. Cardiac function: MR evaluation in one breath hold with real-time true fast imaging with steady-state precession. Radiology 2002 March;222(3):835-42.

(14) Plein S, Bloomer TN, Ridgway JP, Jones TR, Bainbridge GJ, Sivananthan MU. Steady-state free precession magnetic resonance imaging of the heart: comparison with segmented k-space gradient-echo imaging. J Magn Reson Imaging 2001 September;14(3):230-6.

(15) Marcus JT, Gotte MJ, DeWaal LK, Stam MR, van der Geest RJ, Heethaar RM, van Rossum AC. The influence of through-plane motion on left ventricular volumes measured by magnetic resonance imaging: implications for image acquisition and analysis. J Cardiovasc Magn Reson 1999;1(1):1-6.

(16) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986 February 8;1(8476):307-10.

(17) Cottin Y, Touzery C, Guy F, Lalande A, Ressencourt O, Roy S, Walker PM, Louis P, Brunotte F, Wolf JE. MR imaging of the heart in patients after myocardial infarction: effect of increasing intersection gap on

measurements of left ventricular volume, ejection fraction, and wall thickness. Radiology 1999 November;213(2):513-20.

(18) Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W, Neubauer S, Hahn D. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. Eur Radiol 2000;10(3):438-42.

(19) Semelka RC, Tomei E, Wagner S, Mayo J, Kondo C, Suzuki J, Caputo GR, Higgins CB. Normal left ventricular dimensions and function: interstudy reproducibility of measurements with cine MR imaging. Radiology 1990 March;174(3 Pt 1):763-8.

(20) Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging 2003 March;17(3):323-9.

(21) Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004 February;147(2):218-23.

(22) van der Geest RJ, Lelieveldt BP, Angelie E, Danilouchkine M, Swingen C, Sonka M, Reiber JH. Evaluation of a new method for automated detection of left ventricular boundaries in time series of magnetic resonance images using an Active Appearance Motion Model. J Cardiovasc Magn Reson 2004;6(3):609-17.

(23) Baldy C, Douek P, Croisille P, Magnin IE, Revel D, Amiel M. Automated myocardial edge detection from breath-hold cine-MR images: evaluation of left ventricular volumes and mass. Magn Reson Imaging 1994;12(4):589-98.

(24) Angelie E, de Koning PJ, Danilouchkine MG, van Assen HC, Koning G, van der Geest RJ, Reiber JH. Optimizing the automatic segmentation of the left ventricle in magnetic resonance images. Med Phys 2005 February;32(2):369-75.

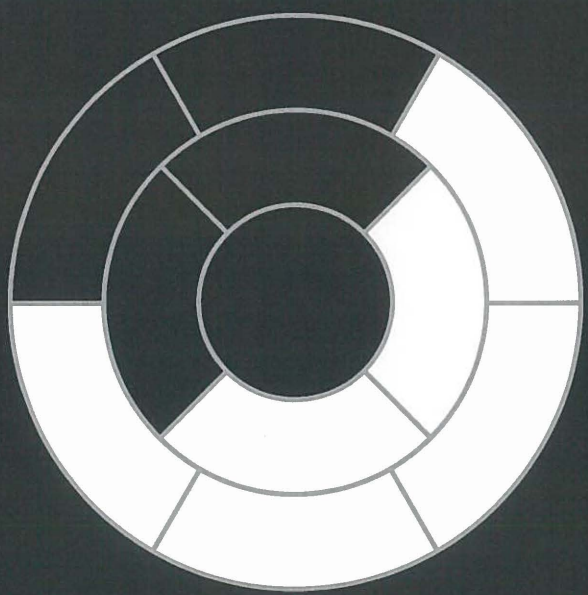
(25) Papavassiliu T, Kuhl HP, Schroder M, Suselbeck T, Bondarenko O, Bohm CK, Beek A, Hofman MM, van Rossum AC. Effect of en-

docardial trabeculae on left ventricular measurements and measurement reproducibility at cardiovascular MR imaging. Radiology 2005 July;236(1):57-64.

(26) Sievers B, Kirchberg S, Bakan A, Franken U, Trappe HJ. Impact of papillary muscles in ventricular volume and ejection fraction assessment by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2004;6(1):9-16.

chapter 6

The additional value of first-pass myocardial perfusion imaging during peak dose of dobutamine stress cardiac MRI for the detection of myocardial ischemia



Int J Cardiovasc Imaging 2008; 24: 69-76

The additional value of first-pass myocardial perfusion imaging during peak dose of dobutamine stress cardiac mri for the detection of myocardial ischemia

D.D. Lubbers[1], MD,
C.H.C. Janssen[1], MD,
D. Kuijpers[1,2], MD, PhD ,
P.R.M. van Dijkman[3], MD, PhD,
J. Overbosch[1], MD,
T.P. Willems[1], MD, PhD,
M. Oudkerk[1], MD, PhD

Department of Radiology[1], University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, the Netherlands
Department of Radiology[2] and Cardiology[3], Bronovo Hospital, Bronovolaan 1, P.O.Box 96900, 2597 AX, The Hague, the Netherlands

ABSTRACT

Purpose: To assess the additional value of first pass myocardial perfusion imaging during peak dose of dobutamine stress Cardiac-MR (CMR).

Materials and methods: Dobutamine Stress CMR was performed in 115 patients with an inconclusive diagnosis of myocardial ischemia on a 1.5 T system (Magnetom Avanto, Siemens Medical Systems). Three short-axis cine and grid series were acquired during rest and at increasing doses of dobutamine (maximum 40μg/kg/min). On peak dose dobutamine followed immediately by a first pass myocardial perfusion imaging sequence. Images were graded according to the sixteen-segment model, on a four point scale.

Results: Ninety-seven patients showed no New (Induced) Wall Motion Abnormalities (NWMA). Perfusion imaging showed absence of perfusion defects in 67 of these patients (69%). Perfusion deficits attributable to known previous myocardial infarction were found in 30 patients (31%). Eighteen patients had NWMA, indicative for myocardial ischemia, of which 14 (78%) could be confirmed by a corresponding perfusion defect. Four patients (22%) with NWMA did not have perfusion defects. In these four patients NWMA were caused by a Left Bundle Branch Block (LBBB). They were free from cardiac events during the follow-up period (median 13.5 months; range 6-20).

Conclusion: Addition of first-pass myocardial perfusion imaging during peak dose dobutamine stress CMR can help to decide whether a NWMA is caused by myocardial ischemia or is due to an (inducible) LBBB, hereby preventing a false positive wall motion interpretation.

INTRODUCTION

Dobutamine stress Cardiac MRI (CMR) is used to detect myocardial ischemia of the left ventricle by means of wall motion analysis during the infusion of high-dose dobutamine (1-4). Previous studies have reported a broad range of sensitivity (83-91%) and specificity (80-86%) of dobutamine stress CMR for the detection of myocardial ischemia (1;3;5;6). It has been proven to be more accurate than dobutamine stress echocardiography. The addition of myocardial tagging even further increased the sensitivity (96%) of dobutamine stress CMR (4). False positive dobutamine stress CMR's were described for left bundle branch block (LBBB) or an incidental low interpretability. (4) Means to overcome for these false-positive dobutamine stress CMR's could increase specificity even further.

Assessment of myocardial perfusion is used to provide information on the hemodynamic significance of a coronary artery stenosis. Segments with New Wall Motion Abnormalities (NWMA) detected with dobutamine stress CMR should also show perfusion defects, since perfusion abnormalities precede wall motion abnormalities in the ischemic cascade (6).

Normal stress perfusion SPECT-results predict a less than 1% annual risk of cardiac death or myocardial infarction, thereby yielding a high negative predictive value (7-10). High negative predictive values are also reported for MR perfusion imaging combined with MRI cine-angiography (100%) in a small study of 15 patients (11).

The addition of a perfusion sequence on peak-dose dobutamine may further enhance the interpretation of dobutamine stress CMR, by ruling out false positive findings, through the combined strength of both methods.

The purpose of this study is to assess whether the addition of perfusion imaging to dobutamine stress CMR at peak-dose dobutamine reduces the number of false-positive dobutamine stress CMR examinations.

MATERIALS AND METHODS

Patient population

Between September 2004 and April 2006, 124 consecutive patients were referred from the department of Cardiology for a dobutamine stress CMR.

The study was approved by the local ethical committee. Informed consent was obtained prior to the study, after the nature of the procedure had been explained. All patients had chest pain and an inconclusive diagnosis of coronary artery disease by means of history, ECG recordings at rest and, if performed, during a bicycle exercise test. Patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120), CMR-incompatible metallic implants or known claustrophobia were not eligible.

Protocol for dobutamine stress CMR with myocardial perfusion on peak-dose dobutamine

To ensure cardiac response to dobutamine, all anti-anginal medication was stopped 4 days before the dobutamine stress CMR examination. After the patient was positioned on the scanning table, intravenous access was established via an anticubital vein. ECG monitoring leads, a phased-array surface coil covering the heart, and a brachial blood pressure cuff were applied. A single lead ECG was continuously monitored on the MRI-console. Systolic and diastolic blood pressures were recorded using an automatic device (Welch-Allyn, Emro-medical) at baseline and every 3 minutes throughout the procedure. Blood pressure and heart rate were recorded. The imaging methodology of dobutamine stress CMR has been described in detail previously (4). Dobutamine stress CMR was performed on a 1.5 T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany). Three short-axis cine breath-hold CMR images of the left ventricle, with and without myocardial tagging, were acquired at rest and during incremental dosage of dobutamine up to 40 μg/kg/min. An ECG-triggered segmental gradient-echo pulse sequence was used: TrueFisp: TR 57.64, ms; TE, 1.1 ms; α, 59°; FOV, 284 X 350 mm; slice-thickness 6 mm; and matrix 125 X 192; iPAT 2. Tagging was performed with a standard FLASH grid-sequence: TR, 46 ms; TE, 3.8 ms; α, 14°; FOV, 284 X 350 mm; slice-thickness 6 mm and matrix 141 X 256. The basal plane was taken 1.5 cm below the mitral valves. The midventricular and apical short-axis views were divided equally over the remaining part of the left ventricle. When a wall motion abnormality (WMA) was detected at baseline, infusion was started at 5 μg/kg/min,

after which the dose of dobutamine was increased to 10, 20, 30 and 40 μg/kg/min. Starting dose of dobutamine was 10 μg/kg/min when no WMA was detected at baseline. Imaging started 6 minutes after each dose increase and required 3 minutes per dose increase.

Termination criteria for dobutamine stress CMR were the development of new wall motion abnormalities (NWMA) or worsening WMA, a fall of systolic blood pressure of more than 40 mmHg, marked hypertension above 240/120 mmHg, severe chest pain, ventricular arrhythmias and intolerable side effects. NWMA are indicative of myocardial ischemia.

On peak dose dobutamine a bolus injection of 0.1 mmol/kg gadolinium-DTPA (Omniscan®) was given and a perfusion sequence was started: True-Fisp: TR, 150.5 or 163.1 ms; TE 1.03 ms; TI 100/103 ms; α 45/50°; FOV 300 X 300; slice-thickness 6 mm; matrix 76 X 128; iPAT 2. The same three slices as the cine and tagging series were acquired.

During the examination a radiologist and a cardiologist were present in the MR suite, to monitor the condition of the patient and to visually evaluate the images. When NWMA's with a corresponding perfusion defect were seen, a coronary angiography (CAG) was performed within 3 weeks. Patients with NWMA's and a normal first pass perfusion on peak stress entered follow-up.

Image analysis

Wall motion was scored on six segments of the basal plane, six on the midventricular plane and four on the apical plane. Segmental wall motion was qualitatively graded as 1 = normal or hyperkinesis; 2 = hypokinesis; 3 = akinesis; and, 4 = dyskinesis. Myocardial ischemia was defined as a new (induced) or worsening WMA in at least two segments at consecutive planes of the left ventricle during infusion of dobutamine. Analysis was performed using both cine and tagging images as described in detail previously (4).

Wall Motion Score Index (WMSI) was derived as the mean score of all segments of all short-axis images. WMSI data from the combined analysis of the cine and tagging images were determined from baseline and peak stress

images.

The first pass perfusion images on peak dose dobutamine were visually analyzed by an experienced radiologist and cardiologist in a consensus reading after the wall motion analysis by the same physicians. A perfusion abnormality, corresponding to the coronary artery distribution areas, in at least two segments at consecutive short-axis slices or one segment of the most apical slice of the left ventricle was defined as myocardial ischemia.

Follow-up

Follow-up data were obtained in September 2006. The present status of the patient was determined by review of the hospital records or contacting the patient's general physician. The date of the last review was used to calculate follow-up time.

Evaluated end points were nonfatal myocardial infarction (angina of >30 minutes duration and either 2 mm ST segment elevation in two consecutive ECG leads or a rise in creatine kinase level and its myoglobine fraction two times the upper limit of normal), cardiac death (death in the presence of acute myocardial infarction, significant cardiac arrhythmias or refractory congestive heart failure) and coronary revascularization.

RESULTS

Patient population

From the 124 consecutively included patients, in nine patients the examination could not be completed due to: intolerable side effects (nausea, vomiting) in four patients, claustrophobia in three patients. Two patients were excluded due to insufficient image quality, one of whom had an irregular rhythm with triggering difficulties, and the other patient was unable to sustain breath holds.

Therefore, 115 patients all with good image quality were analysed (93%) with a mean age 61±11 years, 20 women (30%). Demographic and hemodynamic data are listed in table 1.

Table 1: demographic and hemodynamic data

Variable	Mean or %
Age, years	61 ±11
Female, %	29.6
Previous myocardial infarction, %	38.0
Revascularization, %	31.0
Rest wall motion abnormalities (RWMA)	40.9
Body weight, kg	78 ±12
Resting diastolic blood pressure, mmHg	87 ±11
Peak diastolic blood pressure, mmHg	78 ±12
Resting systolic blood pressure, mmHg	152 ±26
Peak systolic blood pressure, mmHg	151 ±31
Resting heart rate, bpm	79 ±15
Peak heart rate, bpm	119 ±21
Rate-pressure product* at rest	12,030 ±3545
Rate-pressure product at peak stress	17,935 ±4807
Wall Motion Score Index (WMSI) at baseline	1.18 ±0.32
Wall Motion Score Index (WMSI) at peak dose	1.21 ±0.34

*Demographic and Hemodynamic Data Values are expressed as mean ± SD or percentage . *Rate-pressure product=(heart rate)x(systolic blood pressure) RWMA = Rest Wall Motion Abnormality; WMSI = Wall Motion Score Index*

Dobutamine stress CMR with myocardial perfusion on peak-dose dobutamine

Eighteen of the 115 patients (16%) had NWMA of whom 14 (78%) showed perfusion deficits on peak dose dobutamine in the corresponding segments. Four patients (22%) with NWMA did not have a perfusion defect. In these four patients, NWMA were attributable to a LBBB as could be confirmed with an independent (stress) ECG. Two of these were inducible LBBB, not known prior to the examination. CAG was positive for the corresponding segments in the 14 patients (100%) with NWMA and a corresponding perfusion deficit.

Ninety-seven patients (84%) had no NWMA. The perfusion images on peak dose dobutamine showed absence of perfusion defects in 67 of these 97 patients (69%) and perfusion defects in 30 (31%). Of these patients 29 (97%) were attributable to a known previous myocardial infarction in the patients history combined with the presence of RWMA's and 1 patients (3%) had a small perfusion defect inferior which could not be assigned to a known previous event in the patients history. Figure 1 illustrates the course and outcome of the study.

In figure 2 the additional value of cine or grid tagging images combined with stress first-pass perfusion images is illustrated.

Follow-up results (median 13,5 months, range 6-20 months) were obtained from all patients with NWMA's and a normal first-pass perfusion. None of these patients had cardiac events or revascularizations at follow-up.

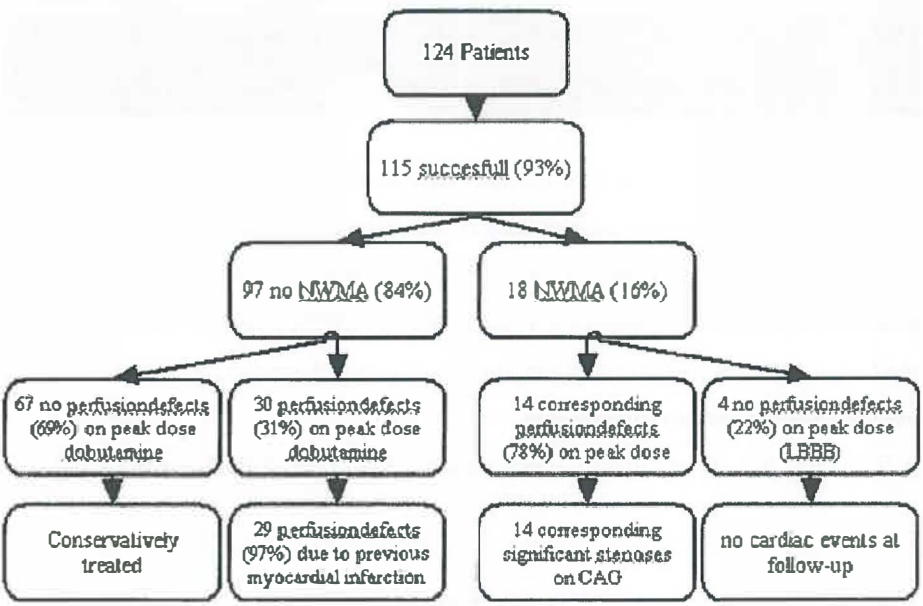


Figure 1: Flow chart illustrating course of the study and outcome.
NWMA = New Wall Motion Abnormality; LBBB = Left Bundle Branch Block; CAG = Coronary angiogram

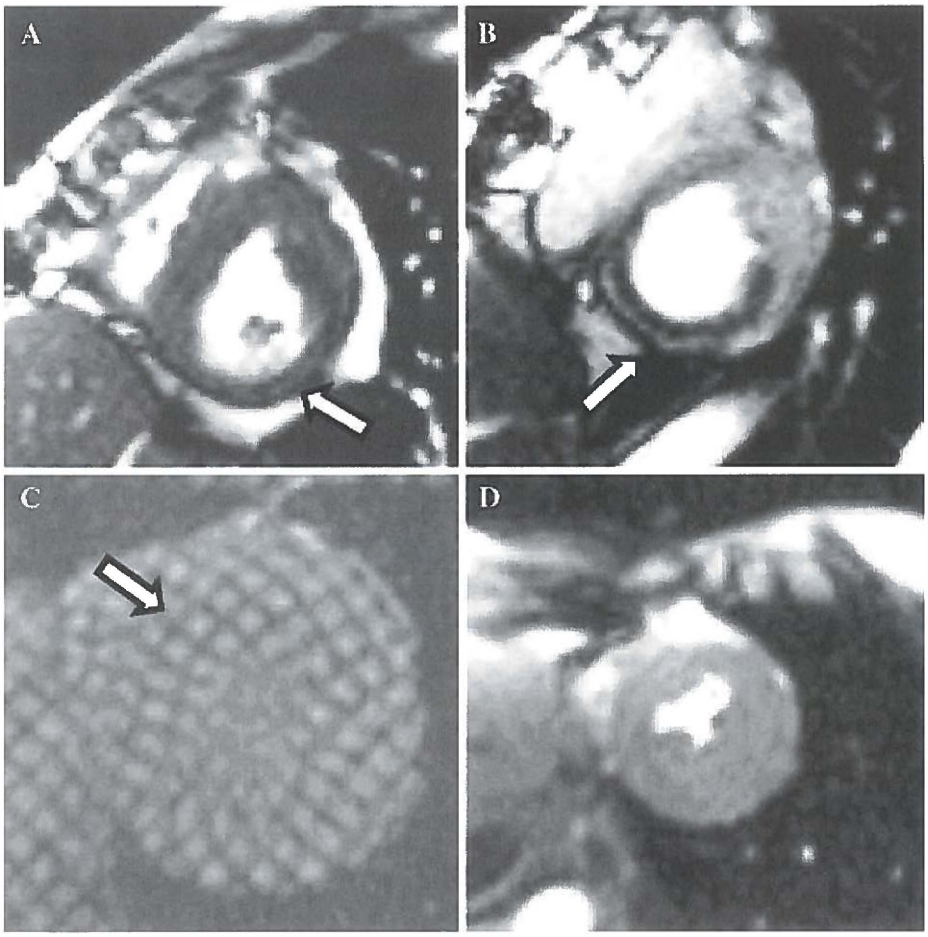


Figure 2: Short axis views at peak-dose dobutamine. Cine image illustrating a NWMA inferior (A). 2A. Perfusion abnormality in the corresponding segment (B). Dyskinetic septal wall in another patient (C). No perfusion abnormalities in the corresponding segment (D). Dyskinetic septal wall in C was due to a LBBB, this differentiation could be made by a perfusion sequence on peak dose dobutamine. Arrows indicate the wall motion abnormality or perfusion abnormality.

NWMA = New Wall Motion Abnormality; LBBB = Left Bundle Branch Block

DISCUSSION

This study demonstrates that adding first-pass myocardial perfusion imaging during peak-dose dobutamine has direct clinical relevance for the interpretation of dobutamine stress CMR examinations, by increasing the

interpretation of possible wall motion abnormalities (NWMA) of the left ventricle. The addition of first pass perfusion relies on the conceptual use of the ischemic cascade. Ischemic wall motion abnormalities are preceded by perfusion abnormalities, therefore a visualized NWMA due to myocardial ischemia should also show perfusion abnormalities. A normal perfusion study is used to identify wall motion abnormalities not due to myocardial ischemia, and an abnormal corresponding perfusion deficit is used to confirm NWMA, indicative for myocardial ischemia.

This is the first study to assess the additional value of a first pass myocardial perfusion imaging sequence on peak-dose dobutamine during a dobutamine stress CMR. Previous studies have reported a broad range of sensitivity and specificity for dobutamine stress CMR in the detection of myocardial ischemia (4). In this protocol we have chosen for a prolonged infusion time of dobutamine from 3 to 6 minutes without atropine and the use of the target heart rate rule, as described before (4;12-17).

The use of the target heart rate rule from a physical exercise based concept can not be generalized to a pharmacological stress setting and has been questioned in several reports (12-14;18) It has also been shown that the target heart rate rule can not be extrapolated to a pharmacological stress examination (19). In a recent overview of published dobutamine stress CMR examinations by Strach et al. (20) , the approach we used (4) showed to provide the highest diagnostic accuracy for significant coronary artery disease defined by a > 50% luminal stenosis on a coronary angiogram. Specificity, although already high, was lowered, according to our opinion, in part due to LBBB. This could be overcome with a perfusion sequence, taking into account the high negative predictive value of normal myocardial perfusion imaging. The additional value of myocardial perfusion MRI could be used for this purpose and may add significant diagnostic information.

In this study we added a perfusion sequence on peak dose dobutamine in all patients. The results show a good agreement between the absence of NWMA and myocardial perfusion. The main purpose of this study was to assess the additional value of first-pass perfusion imaging in the presence of NWMA. Our recommendation for future clinical use is to add a

first pass perfusion sequence on indication, namely if there is doubt on whether a NWMA is due to myocardial ischemia. In this way, the specificity of dobutamine stress CMR can be even further increased. By combining dobutamine stress CMR with myocardial perfusion, one still has the opportunity to examine for viability, which seems even superior to scar quantification (24).

Absolute specificity values can not be given with this study, because a CAG was not performed in case of a negative dobutamine stress CMR examinations. The outcome of the dobutamine stress CMR and myocardial perfusion on peak dose dobutamine was used as a direct arbiter for subsequent clinical follow-up. In this respect follow-up was considered the reference standard. None of the patients with NWMA's and a normal myocardial perfusion had an adverse outcome at follow-up. Therefore, it is reasonable to state that adding first pass myocardial perfusion imaging on peak-dose dobutamine increases the specificity of dobutamine stress CMR in this patient group.

Our data could have been influenced by a referral bias, but in light of previous results, we found it not justifiable to perform a CAG in case of a negative examination (12). Furthermore, the high negative predictive value of dobutamine stress CMR examination without perfusion imaging has been proven before (12;22). Mahrholdt et al. (23) examined 139 patients with a LBBB. All 139 patients had fixed perfusion defects with SPECT, 19 could not be confirmed with CAG. Rest wall motion analysis and myocardial perfusion (between 5 and 30 minutes after contrast administration) was performed on these 19 patients using MRI. All 19 patients showed septal wall motion abnormalities, but none showed subendocardial or transmural contrast enhancement. This also indicates that contrast enhanced imaging can help differentiate between WMA on the basis of coronary artery disease or a LBBB.

Long term follow-up will provide information about the case in which a small perfusion abnormality was seen inferior without NWMA. Whether this abnormality is a "true" abnormality or an artefact is unclear. This patient did not have any adverse cardiac event at 14 months follow-up.

Another limitation of our study is the fact that images were analysed semi-quantitatively. Quantitative wall motion analysis could possibly provide additional information, but due to the time-consuming nature this is not yet feasible in clinical practice. Furthermore, no decisions can be made during the examination, which we believe is crucial, since overstressing may lead to serious complications (13).

Visual analysis of wall motion and perfusion images was performed in a consensus reading by an experienced radiologist and cardiologist. This can be regarded as a limitation since the observers are not blinded for the previous wall motion images. However, this does represent routine clinical practice and is fundamental to the underlying concept of using first-pass perfusion imaging in the presence of NWMA. In recent studies the inter-observer agreement of dobutamine stress CMR were investigated and good agreement was found (24;25).

In a clinical post-infarct setting, delayed contrast enhancement imaging may provide valuable diagnostic information. To our opinion, this would in our study not have provided additional information regarding the fact whether a NWMA was caused by myocardial ischemia or a non-ischemic cause, and guide the necessity for an invasive coronary angiogram. Cine and grid tagging images were acquired at rest to look for rest wall motion abnormalities. New wall motion abnormalities in this setting would represent myocardial ischemia (whether or not in the presence of a previous myocardial infarction). Delayed contrast enhancement imaging was therefore not performed in this protocol.

In this protocol we only acquired stress first-pass perfusion images. Perfusion imaging at rest may be very useful in stress-rest perfusion imaging studies, but the main focus in this protocol is on a normal perfusion in case of NWMA. A rest perfusion exam would in this context not provide additional information (the rest perfusion exam will also be normal). In this way the protocol is not unnecessarily prolonged and a second bolus injection of gadolinium-DTPA can be omitted.

CONCLUSION

Good agreement exists between the absence of NWMA and a normal myocardial perfusion. Furthermore, a perfusion sequence on peak-dose dobutamine can help decide whether a NWMA is caused by ischemia or is due to a LBBB. First pass myocardial perfusion during peak-dose dobutamine can be used as an additional tool to reduce the number of false-positive NWMA's, to improve the detection of myocardial ischemia.

ACKNOWLEDGEMENTS

The authors thank Stella Noach for critically reviewing the paper. Hester van der Zaag-Loonen for statistical advice and Bernadette Blom and colleagues for image acquisition.

REFERENCE LIST

(1) Pennell DJ, Underwood SR, Manzara CC, Swanton RH, Walker JM, Ell PJ, Longmore DB. Magnetic resonance imaging during dobutamine stress in coronary artery disease. Am J Cardiol 1992 July 1;70(1):34-40.

(2) Nagel E, Lehmkuhl HB, Bocksch W, Klein C, Vogel U, Frantz E, Ellmer A, Dreysse S, Fleck E. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. Circulation 1999 February 16;99(6):763-70.

(3) Hundley WG, Hamilton CA, Thomas MS, Herrington DM, Salido TB, Kitzman DW, Little WC, Link KM. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. Circulation 1999 October 19;100(16):1697-702.

(4) Kuijpers D, Ho KY, van Dijkman PR, Vliegenthart R, Oudkerk M. Dobutamine cardiovascular magnetic resonance for the detection of myocardial ischemia with the use of myocardial tagging. Circulation 2003 April 1;107(12):1592-7.

(5) van Rugge FP, van der Wall EE, Spanjersberg SJ, de Roos A, Matheijssen NA, Zwinderman AH, van Dijkman PR, Reiber JH, Bruschke AV. Magnetic resonance imaging during dobutamine stress for detection and localization of coronary artery disease. Quantitative wall motion analysis using a modification of the centerline method. Circulation 1994 July;90(1):127-38.

(6) Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987 March 9;59(7):23C-30C.

(7) Schinkel AF, Elhendy A, Bax JJ, van Domburg RT, Huurman A, Valkema R, Biagini E, Rizzello V, Feringa HH, Krenning EP, Simoons ML, Poldermans D. Prognostic implications of a normal stress technetium-99m-tetrofosmin myocardial perfusion study in patients with a healed myocardial infarct and/or previous coronary revascularization. Am J

Cardiol 2006 January 1;97(1):1-6.

(8) Elhendy A, Schinkel AF, van Domburg RT, Bax JJ, Valkema R, Huurman A, Feringa HH, Poldermans D. Risk Stratification of Patients with Angina Pectoris by Stress 99mTc-Tetrofosmin Myocardial Perfusion Imaging. J Nucl Med 2005 December;46(12):2003-8.

(9) Schinkel AF, Elhendy A, van Domburg RT, Bax JJ, Vourvouri EC, Bountioukos M, Rizzello V, Agricola E, Valkema R, Roelandt JR, Poldermans D. Incremental value of exercise technetium-99m tetrofosmin myocardial perfusion single-photon emission computed tomography for the prediction of cardiac events. Am J Cardiol 2003 February 15;91(4):408-11.

(10) Hachamovitch R, Hayes S, Friedman JD, Cohen I, Shaw LJ, Germano G, Berman DS. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? J Am Coll Cardiol 2003 April 16;41(8):1329-40.

(11) Wintersperger BJ, Penzkofer HV, Knez A, Weber J, Reiser MF. Multislice MR perfusion imaging and regional myocardial function analysis: complimentary findings in chronic myocardial ischemia. Int J Card Imaging 1999 December;15(6):425-34.

(12) Kuijpers D, van Dijkman PR, Janssen CH, Vliegenthart R, Zijlstra F, Oudkerk M. Dobutamine stress MRI. Part II. Risk stratification with dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004 November;14(11):2046-52.

(13) Kuijpers D, Janssen CH, van Dijkman PR, Oudkerk M. Dobutamine stress MRI. Part I. Safety and feasibility of dobutamine cardiovascular magnetic resonance in patients suspected of myocardial ischemia. Eur Radiol 2004 October;14(10):1823-8.

(14) Kuijpers D. Diagnosis of coronary artery disease with dobutamine-stress MRI. Eur Radiol 2005 February;15 Suppl 2:B48-B51.

(15) Janssen CH, Kuijpers D, Vliegenthart R, Overbosch J, van Dijkman PR, Zijlstra F, Oudkerk M. Coronary artery calcification score by multislice computed tomography predicts the outcome of dobu-

tamine cardiovascular magnetic resonance imaging. Eur Radiol 2005 June;15(6):1128-34.

(16) van Dijkman PR, Kuijpers DA, Blom BM, van Herpen G. Dobutamine stress magnetic resonance imaging: a valuable method in the noninvasive diagnosis of ischemic heart disease. J Electrocardiol 2002;35 Suppl:57-9.

(17) van Dijkman PR, Kuijpers TJ, Blom BM, van Herpen G. [Dobutamine stress magnetic resonance imaging (DS-MRI), a valuable tool for the diagnosis of ischemic heart disease]. Ned Tijdschr Geneeskd 2002 July 13;146(28):1327-32.

(18) Elhendy A, van Domburg RT, Bax JJ, Nierop PR, Geleijnse ML, Ibrahim MM, Roelandt JR. The functional significance of chronotropic incompetence during dobutamine stress test. Heart 1999 April;81(4):398-403.

(19) Arsenault M, Bergeron S, Dumesnil JG, Fortin MP, Poirier P. Anginal threshold between stress tests: exercise versus dobutamine stress echocardiography. Med Sci Sports Exerc 2005 January;37(1):18-23.

(20) Strach K, Meyer C, Schild H, Sommer T. Cardiac stress MR imaging with dobutamine. Eur Radiol 2006 December;16(12):2728-38.

(21) Wellnhofer E, Olariu A, Klein C, Grafe M, Wahl A, Fleck E, Nagel E. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. Circulation 2004 May 11;109(18):2172-4.

(22) Hundley WG, Morgan TM, Neagle CM, Hamilton CA, Rerkpattanapipat P, Link KM. Magnetic resonance imaging determination of cardiac prognosis. Circulation 2002 October 29;106(18):2328-33.

(23) Mahrholdt H, Zhydkov A, Hager S, Meinhardt G, Vogelsberg H, Wagner A, Sechtem U. Left ventricular wall motion abnormalities as well as reduced wall thickness can cause false positive results of routine SPECT perfusion imaging for detection of myocardial infarction. Eur Heart J 2005 October;26(20):2127-35.

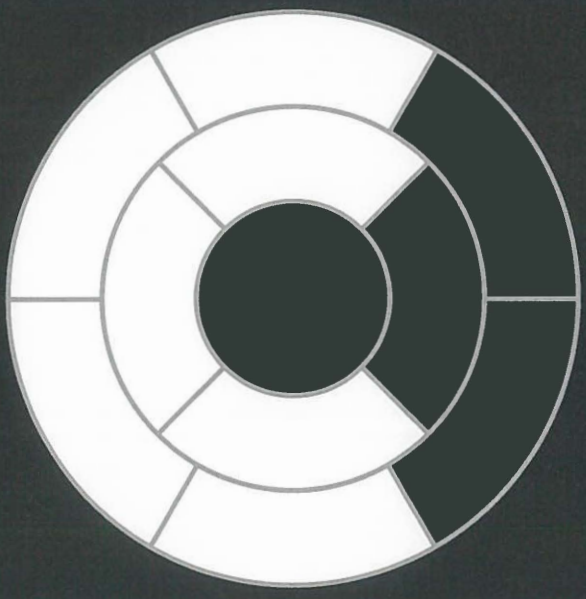
(24) Syed MA, Paterson DI, Ingkanisorn WP, Rhoads KL, Hill J, Cannon RO, III, Arai AE. Reproducibility and inter-observer variability of dob-

utamine stress CMR in patients with severe coronary disease: implications for clinical research. J Cardiovasc Magn Reson 2005;7(5):763-8.

(25) Paetsch I, Jahnke C, Ferrari VA, Rademakers FE, Pellikka PA, Hundley WG, Poldermans D, Bax JJ, Wegscheider K, Fleck E, Nagel E. Determination of interobserver variability for identifying inducible left ventricular wall motion abnormalities during dobutamine stress magnetic resonance imaging. Eur Heart J 2006 June;27(12):1459-64.

chapter 7

Parallel imaging for first-pass myocardial perfusion



Magnetic Resonance Imaging 2007; 25: 678-683

Parallel imaging for first-pass myocardial perfusion

R. Irwan[1], PhD
D.D. Lubbers[1], MD
P.A. van der Vleuten[2], MD
P. Kappert[1]
M.J.W. Götte[2], MD, PhD
P.E. Sijens[1], PhD

Department of Radiology,[1] University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands
Department of Cardiology[2], University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands

ABSTRACT

Purpose: Two parallel imaging methods used for first-pass myocardial perfusion imaging were compared in terms of signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) and image artifacts.

Materials and methods: One used adaptive Time-adaptive SENSitivity Encoding (TSENSE) and the other used GeneRalized Autocalibrating Partially Parallel Acquisition (GRAPPA), which are both applied to a gradient-echo sequence. Both methods were tested on 12 patients with coronary artery disease. The order of perfusion sequences was inverted in every other patient. Image acquisition was started during the administration of a contrast bolus followed by a 20-ml saline flush (3 ml/s), and the next perfusion was started at least 15 min thereafter using an identical bolus. An acceleration rate of 2 was used in both methods, and acquisition was performed during breath-holding.

Results: Significantly higher SNR, CNR and image quality were obtained with GRAPPA images than with TSENSE images. GRAPPA, however, did not yield a higher CNR when applied after the second bolus. GRAPPA perfusion imaging produced larger differences between subjects than did TSENSE.

Conclusion: Compared to TSENSE, GRAPPA produced significantly better CNR on the first bolus. More consistent SNR and CNR were obtained from TSENSE images than from GRAPPA images, indicating that the diagnostic value of TSENSE may be better.

INTRODUCTION

The use of myocardial perfusion imaging in cardiology is gaining more and more interest (1). Magnetic resonance imaging (MRI) is an attractive tool with potentially high spatial and temporal resolutions that is used for the coverage of the entire heart during first-pass contrast-enhanced MRI with a single heartbeat. Two contradicting factors limiting the widespread clinical application of perfusion MRI are its speed and spatial resolution, which is primarily due to constraints on the signal-to-noise ratio (SNR). Recently, an integrated parallel acquisition technique (iPAT) based on temporal low-pass filtering and spatial sensitivity encoding with multicoil arrays [Time-adaptive SENSitivity Encoding (TSENSE)] has been applied to first-pass contrast-enhanced cardiac magnetic resonance to provide coverage of the heart with a single-heartbeat temporal resolution (2). This acceleration is realized by reducing the number of acquired phase-encoding lines to combine temporally interleaved k-space lines (Figure 1) to generate coil sensitivity maps directly from image data.

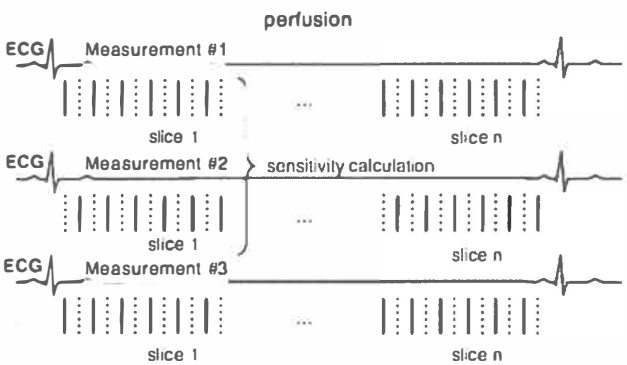


Figure 1: An example of a rate of 2 for TSENSE acquisition (Q. Zhang, private communication, 2005, MR R&D Siemens, Chicago). Solid lines represent acquired phase-encoding lines, and dotted lines represent those not acquired. A series of image frames is sequentially acquired, alternately sampling even and odd lines of k-spaces. Coil sensitivity is calculated from a number of combined frames, while only even or odd k-space lines are used to reconstruct any particular image. A sliding window method is used to update the coil sensitivity estimation for every frame.

Another well-known parallel imaging method, called GeneRalized Autocalibrating Partially Parallel Acquisition (GRAPPA) (3), on the other hand, reduces the number of acquired phase-encoding lines and reconstructs images by still fully sampling central k-space lines. Sampling these additional central k-space lines reduces, however, the effective acceleration rate.

Thus, with respect to GRAPPA, TSENSE offers the advantage of reconstructing images with high temporal resolution. However, evaluations of image quality and artifacts are still to be performed. The purpose of the present study was to compare image quality in terms of SNR, contrast-to-noise ratio (CNR) and the presence of artifacts in gradient-echo sequences between TSENSE and GRAPPA for cardiac perfusion imaging, in conjunction with perfusion order.

The study was set up for both methods to produce the number of slices currently used for clinical purposes in our institution. The ability of TSENSE to achieve greater spatial coverage has not been utilized in this study in order to keep experimental results as similar as possible.

MATERIALS AND METHODS

Study population

First-pass myocardial perfusion MRI was performed in 12 patients with documented coronary artery disease who were scheduled for percutaneous transluminal coronary angioplasty (six men, six women; mean age, 65 years; age range, 41–78 years). Prior to scanning, intravenous access was established with the catheterization of an antecubital vein. Written informed consent was acquired in advance from all 12 patients.

MRI

Cardiac MRI was performed on all 12 patients with a 1.5-T whole-body MR scanner (Magnetom Sonata; Siemens Medical Systems, Germany) equipped with high-performance gradients (maximum amplitude, 40 mT/m; slew rate, 200 T/m/s). Patients were positioned headfirst in supine position. Cardiac MRI signals were received by a standard coil system for cardiac imaging (a 2×6-channel body array). Fast scout images were acquired during breath-

holding to determine the true short axis of the left ventricle. Then, first-pass perfusion imaging was planned as follows: three short-axis and one long-axis first-pass perfusion MR images were obtained (TR=158/172 ms, TE=1.3 ms, flip angle=100, slice thickness=12 mm, bandwidth=460/490 Hz/pixel) using prospective electrocardiography triggering. An in-plane data acquisition matrix of 192×115 was used, with a maximum field of view of 40×40 cm2, which yielded a resolution of 3.4×2.1×12 mm3.

Image acquisition was started upon the administration of a half dosage of contrast bolus (Dotarem, 0.2 mmol/kg, 3 ml/s) followed by a 20-ml saline flush to prevent blood coagulation in the catheter. Acquisitions were performed during breath-holding for as long as possible, followed by shallow breathing for a total acquisition time of 60–80 s. After completing a first-pass perfusion imaging study, the second half of the bolus was administered at least 15 min after the first administration, and a second perfusion imaging sequence was started. This time interval was necessary to obtain the greatest amount of contrast agent washed out of the myocardium at the time of the second dose (4).

The order of perfusion sequences was inverted in every other patient. In both sequences, an acceleration rate of 2 was used to obtain a 128-line resolution using 64 phase encodes acquired in a single heartbeat. For TSENSE,

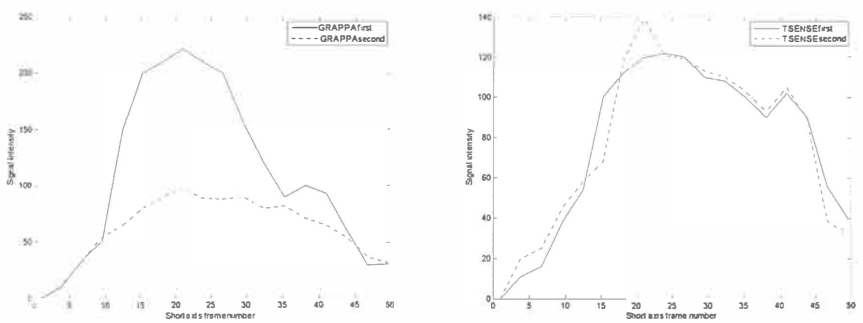


Figure 2: (A) GRAPPA curve depicting signal intensity as a function of midventricular short-axis slices measured within the lumen. (B) TSENSE curve depicting signal intensity as a function of midventricular short-axis slices measured within the lumen.

a sliding window over eight 64-phase-encoded measurements was used to derive SENSE coefficients, which were then used to obtain a full 128-line resolution image. A GRAPPA factor of 2 was used to reduce data acquisition. Both iPAT techniques were applied to a gradient-echo sequence fast low-angle shot.

SNR and CNR measurements

Quantitative analysis was based on measurements of SNR and CNR. First, the maximum mean intensity of the lumen was searched through images using slice–intensity curves, as shown in figure 2. The SNR and CNR values on the image were then measured with the maximum mean intensity of the lumen. In this study, we used the maximum mean intensity of the three short-axis sections to define the maximum contrast. The purpose of this approach was twofold: (a) to avoid signal intensity variations across slices; and (b) to minimize the effects of different blood circulation times in both sequences.

For SNR evaluation, the mean signal intensity within the left ventricular myocardium (Smyo) was measured within a single region(s) of interest (ROI). Noise was measured from the mean±standard deviation (S.D.) of pixel values from small ROI placed within ghost-free regions of background outside the patient (Figure 3). The average S.D. from these noise regions was used in the calculation of SNR and CNR.

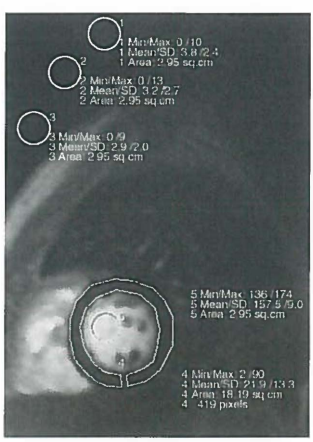


Figure 3: Short-axis image found using the maximum mean intensity criterion. The circles (ROI1, ROI2 and ROI3) in the image indicate the ROI for the measurement of noise outside the body. The ROI within the myocardium is used for the measurement of signal intensity. The contrast is measured by subtracting the mean intensity of the myocardium (ROI4) from that of the lumen (ROI5).

For CNR, the mean blood signal (Sblood) was measured in the lumen of the ventricular cavity of midventricular short-axis images, again by using the maximum mean intensity. The ROI was placed within the boundaries of the ventricular cavity. Contrast was then defined as the mean difference between the lumen and myocardium signal intensities. Based on these data, SNR and CNR were calculated as

$$(1)\quad SNR = \frac{S_{myo}}{N_{air}}$$

$$(2)\quad CNR = \frac{S_{blood} - S_{myo}}{N_{air}}$$

where Nair is the mean±S.D. of the signal in air derived from ROI positioned anterior to the chest wall, as demonstrated in Figure 3. The order of perfusion was alternated, and measurements were classified into two experiments. Mean±S.D. values were computed for both experiments. Comparing the outcome of the total variation between the first experiment and the second experiment allowed us to draw conclusions on the effects of perfusion order on image quality.

RESULTS

As an illustration, Figure 4 depicts 12 (of 50) short-axis cine images acquired using TSENSE, where a perfusion defect in the left circumflex artery (LCX) flow area is shown. Figure 5A and B shows short-axis images

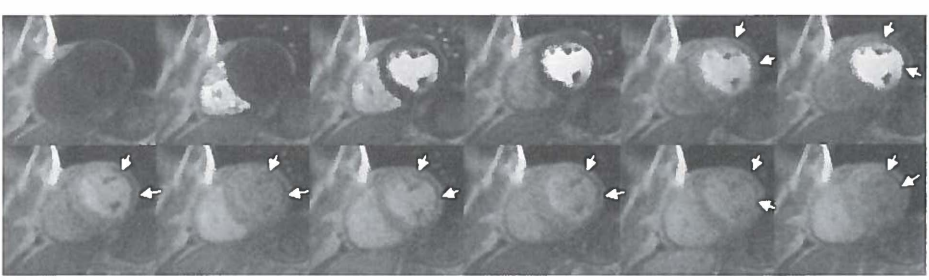


Figure 4: Twelve of 50 first-pass myocardial perfusion short-axis images at the midventricular level of a 50-year-old male patient with LCX occlusion. Arrows indicate perfusion defects in the LCX flow area.

obtained with GRAPPA and TSENSE, respectively. Note the slight (visual) improvement in contrast with better depiction of the myocardium on the GRAPPA image (Figure 5A).

Table 1A and B summarizes the SNR and CNR measurements for both methods in two different perfusion orders. A paired t test was performed to determine significant differences between measurements, with P being the measure of significance level. The calculations for SNR and CNR comparisons are summarized below

(1) $\left.\frac{SNR_{GRAPPA}}{SNR_{TSENSE}}\right|_{GRAPPA\ first} = \frac{23.8}{17.4} = 1.35;$ not significant

(2) $\left.\frac{SNR_{GRAPPA}}{SNR_{TSENSE}}\right|_{TSENSE\ first} = \frac{28.0}{16.4} = 1.71;$ $P<.02$

(3) $\left.\frac{CNR_{GRAPPA}}{CNR_{TSENSE}}\right|_{GRAPPA\ first} = \frac{95.5}{54.5} = 1.75;$ $P<.0001$

(4) $\left.\frac{CNR_{GRAPPA}}{CNR_{TSENSE}}\right|_{TSENSE\ first} = \frac{67.2}{61.0} = 1.1;$ not significant

Some things are worth noting. First, the S.D. of CNR tended to grow for both methods when it was used on the second bolus. Second, the S.D. of

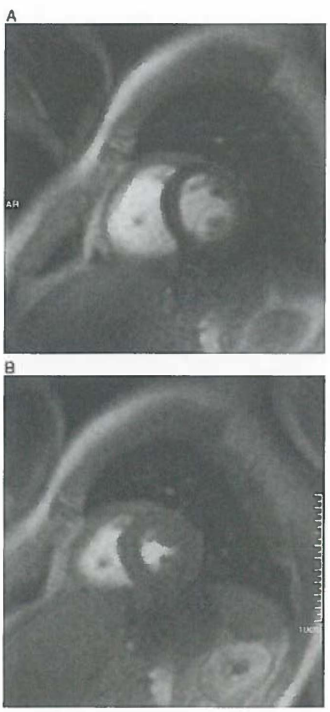


Figure 5: Short-axis slice of a midventricular slice of a patient with septal myocardial infarction. First-pass perfusion imaging with (A) GRAPPA and (B) TSENSE.

SNR, in contrast, tended to decrease when the method was used on the second bolus.

Figure 2A and B also shows that measurements in Table 1 agree with the signal intensity in the lumen across slices for both methods. Significant differences between sequences used for the first time and sequences used for the second time are obvious on a GRAPPA image (Figure 2A), while a TSENSE image gives more consistent signal intensities (Figure 2B).

Comparing the artifact levels of both scans, a distinct reduction of image artifacts is observed in TSENSE images, as depicted in Figure 6. This image artifact, known as ghost artifact, occurred in almost every TSENSE data series caused by local signal modulation in amplitude or phase between different phase-encoding processes (5) and (6).

DISCUSSION

In the current study, we compared two parallel imaging methods and investigated the influence of perfusion order. The main findings are outlined below.First, although TSENSE lowers SNR, it produces a more consistent signal distribution across an image. This finding was based on the fact that TSENSE produced significantly lower S.D. than did GRAPPA, as demonstrated in Figure 2. A possible explanation for this is that the background noise is generally correlated in a parallel imaging scheme, which contributes to the low scatter in SNR and CNR measurements. In addition, for practical

Figure 6: Ghosting artifact (arrows) caused by local signal modulation in amplitude and phase between different phase-encoding steps.

Table 1: Quantitative results of GRAPPA and TSENSE in SNR and CNR in two different perfusion orders: (A) GRAPPA followed by TSENSE; (B) TSENSE followed by GRAPPA

A	GRAPPA		TSENSE	
Patient	SNR	CNR	SNR	CNR
1	36.0	97.4	17.8	59.1
2	27.9	105.5	16.3	67.6
3	22.5	98.4	18.8	53.4
4	19.4	107.3	16.5	54.3
5	20.1	104.5	16.8	56.8
6	15.1	60.0	18.2	35.6
Mean	23.5	95.5*	17.4	54.5
SD	7.4	17.8	1.0	10.6

B	TSENSE		GRAPPA	
Patient	SNR	CNR	SNR	CNR
1	16.5	69.8	32.6	53.4
2	16.7	66.7	43.1	79.9
3	16.3	61.2	33.4	79.2
4	15.4	47.8	20.5	70.8
5	17.5	62.1	20.1	60.2
6	15.8	58.2	18.2	59.5
Mean	16.4	61.0	28.0*	67.2
SD	0.7	7.7	9.9	11.1

** P<.02.*

*** P<.0001.*

in vivo implementation at high heart rates, the latter is suboptimal because of its poor time resolution.

The SNR of TSENSE was at least 30% lower than that of GRAPPA with the same acceleration factor. This percentage was expected as SNR loss would be approximately R, where R is the acceleration rate (7), while GRAPPA achieved gains due to central k-space lines.

Second, TSENSE is desirable because it provides reasonable acquisition times and minimizes the effects of patient motion. This acquisition scheme, however, is more sensitive to EPI ghosts (7) caused by both temporal and spatial low-pass filtering than it is to GRAPPA ghosts (Figure 6). These image artifacts were not unexpected as Kellman et al. (7) have reported that one of the drawbacks of an adaptive method for coil sensitivity estimation was that k-space acquisition was optimized for speed rather than for image quality.

Third, the effect of the order of bolus administration on image quality has played an important role in the determination of CNR. From Table 1A, it can be seen that, when GRAPPA was started first, CNR values were found to be higher than average. This phenomenon can be viewed from two different perspectives: (a) GRAPPA is more sensitive to the blood signal difference between the presence of contrast and the absence of contrast; and/or (b) GRAPPA performs suboptimally when the contrast has been first passed through the heart even after a washout period of at least 15 min. This is the first association to report on the effect of perfusion order on image quality.

Lastly, one may argue that the high S.D. values in Table 1 could possibly be due to the different amounts of contrast bolus administrated to each patient, as this amount is weight-dependent. However, the S.D. of the weights of all patients in this study was <1.0, indicating that this factor could be neglected.

Our results suggest that TSENSE may be an attractive myocardial perfusion MRI technique that allows simultaneous acquisition at high heart rates with sufficient spatial coverage for clinical evaluation. Additionally, TSENSE yields robust high-quality data irrespective of the study performed beforehand.

A major advantage of iPAT used in TSENSE over GRAPPA is that the former allows faster image acquisition at the same acceleration factor by deriving coil sensitivity maps from acquired data rather than from additionally sampled central k-space lines (Q. Zhang, private communication, 2005, MR R&D Siemens, Chicago). For demonstration purposes, we simulated

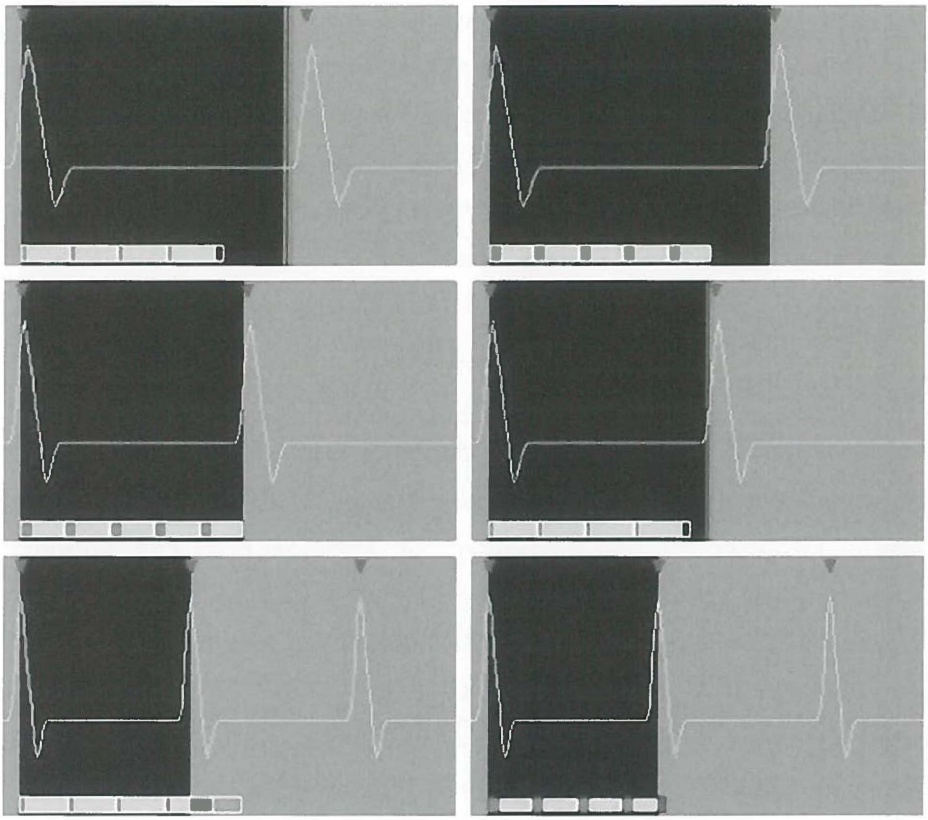


Figure 7: Four k-space measurements within several R–R *intervals: 1000 ms (top), 800 ms (middle) and 600 ms (bottom) using GRAPPA (left) and TSENSE (right), both with the same acceleration factor* R=2. *Red bars show a part of the measurement that did not fit into the* R–R *interval.*

three R–R intervals using the pulse sequence software package Integrated Development Environment for Applications (8) on our MRI scanner, as illustrated in Figure 7: 1000 ms (top), 800 ms (middle) and 600 ms (bottom). Four measurements were then performed using GRAPPA (left) and TSENSE (right), both with an acceleration factor R=2. With respect to GRAPPA, it can be seen that TSENSE requires substantially less time to perform four measurements within one R–R interval. Moreover, at a very short R–R interval of 600 ms (Figure 7, bottom), TSENSE would still do

the job reasonably as GRAPPA would fail, as the red bar shows the part of the measurement that did not fit into the R–R interval. Acquisition at short R–R intervals is especially of importance for stress perfusion imaging.
It is also worth noting that TSENSE may achieve approximately twice the spatial coverage (7) of GRAPPA — a point that certainly adds clinical value to the assessment of any heart disease.

CONCLUSION

Gradient-echo-based sequences, with and without coil sensitivity, for first-pass myocardial perfusion imaging purposes were compared. Regardless of acquisition time, one may consider using GRAPPA for better image quality. However, the major advantage of TSENSE is its high temporal resolution and spatial coverage, which are approximately twice as high as those of GRAPPA, implying that TSENSE still performs well at high heart rates (shorter R–R intervals) when GRAPPA would fail. Particularly for stress perfusion imaging, TSENSE shows excellence. When used for the first time, GRAPPA produced significantly better CNR than did TSENSE, but showed insignificant differences in SNR. In contrast, when GRAPPA was applied after the second bolus, it produced insignificant differences in CNR. Further studies are required to investigate the added value of higher temporal resolution and/or greater spatial coverage for clinical use.

ACKNOWLEDGMENTS

We are grateful to J. Overbosch for setting up the clinical protocol and to Q. Zhang (MR R&D Siemens) for helpful discussions.

REFERENCE LIST

(1) Wolff SD, Schwitter J, Coulden R, Friedrich MG, Bluemke DA, Biederman RW, Martin ET, Lansky AJ, Kashanian F, Foo TK, Licato PE, Comeau CR. Myocardial first-pass perfusion magnetic resonance imaging: a multicenter dose-ranging study. Circulation 2004 August 10;110(6):732-7.

(2) Kellman P, Epstein FH, McVeigh ER. Adaptive sensitivity encoding incorporating temporal filtering (TSENSE). Magn Reson Med 2001 May;45(5):846-52.

(3) Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, Kiefer B, Haase A. Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn Reson Med 2002 June;47(6):1202-10.

(4) 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 July 29;108(4):432-7.

(5) Winkelmann R, Bornert P, Dossel O. Ghost artifact removal using a parallel imaging approach. Magn Reson Med 2005 October;54(4):1002-9.

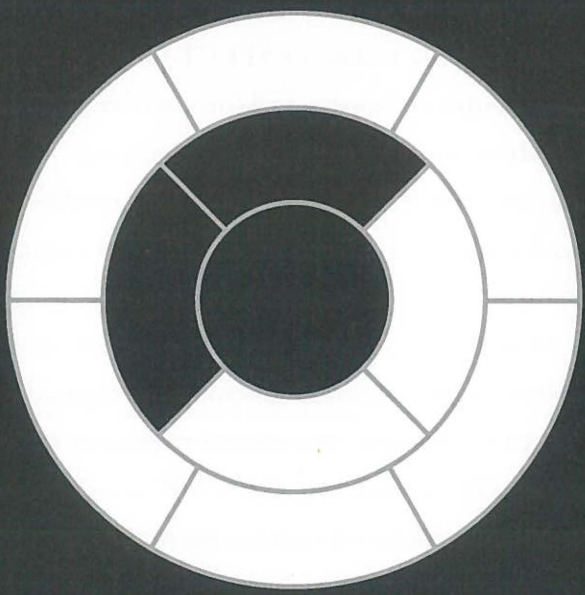
(6) Kellman P, McVeigh ER. Ghost artifact cancellation using phased array processing. Magn Reson Med 2001 August;46(2):335-43.

(7) Kellman P, Derbyshire JA, Agyeman KO, McVeigh ER, Arai AE. Extended coverage first pass perfusion imaging using slice-interleaved TSENSE. Magn Reson Med 2004 January;51(1):200-4.

(8) Integrated Development Environment for Applications (IDEA), Siemens AG, Medical Solutions, Magnetic Resonance, Erlangen, Germany.

chapter 8

Summary



Chest pain accounts for a large number of patients seeking care from a physician. The differential diagnosis, however, can be broad. The need to diagnose or exclude ischemic heart disease is important in this respect. Severity and extent of myocardial ischemia are for instance directly related to prognosis. Besides, coronary revascularization is guided not only by coronary stenosis morphology but also by its hemodynamic consequences. Of course in a large number of cases myocardial ischemia can be made improbable by means of history, physical examination and resting ECG.

This still leaves a large number of patients with stable chest pain for whom the existence of significant coronary artery disease (CAD) or the severity and extent of myocardial ischemia is unclear. Non-invasive methods determine the need for invasive coronary angiography (CAG) combined with revascularization, thereby reducing the pure number of diagnostic CAG's. In this respect, the assessment of function has incremental value over morphology alone. Methods resembling physical exercise or inducing a stress response (by means of a pharmacological stressor) are widely used for this indication.

Wellknown "stress"-tests for the detection of myocardial ischemia, such as for instance bicycle exercise testing or SPECT-imaging are limited in their diagnostic accuracy, radiation burden and/or spatial resolution. The current status of MRI enables us to overcome these problems.

ECG alterations, left ventricular wall motion abnormalities and perfusion abnormalities under stress conditions are all means of objectifying myocardial ischemia, which can be performed with different imaging modalities. The advantage of perfusion imaging lies in the earlier occurrence of perfusion abnormalities in the ischemic cascade as compared to wall motion abnormalities or ECG changes. Myocardial perfusion imaging with Cardiovascular Magnetic Resonance Imaging (CMR) is a dynamic technique to analyse the first-pass of a bolus of contrast agent through the myocardium. A heavily T1-weighted perfusion sequence is used, acquiring multiple slice positions of the left ventricle, with 40-60 images per slice position. Reported diagnostic accuracies over the last three years for adenosine perfusion CMR range from 78-100% for sensitivity, 68-93% for specificity, Negative

Predictive Value (NPV) from 77-100% and Positive Predictive Value (PPV) from 71-95%. Differences in these reported accuracies are caused by differences in the studied population, the used sequence and used protocols, the contrast dose, spatial coverage and the used reference modality and the stenoses grade defined as significant.

Different strategies apply when creating a stress perfusion CMR protocol and performing the examination. The building blocks for these protocols are stress perfusion imaging, rest perfusion imaging, cine wall motion imaging and Delayed Contrast Enhancement (DCE).

Choices have to be made concerning the pharmacological stressor, the perfusion sequence, contrast dose and injection speed and, very importantly, the used protocol in relation to the patient population.

Protocol improvements and considerations for Cardiac "stress" MR perfusion examinations are the object of study in this thesis.

The use of an adenosine "stress"-only approach in patients without a prior myocardial infarction and a clinical necessity to exclude significant myocardial ischemia is described in **Chapter 3**. The study analyses 134 consecutive patients referred for an adenosine perfusion MR examination. The patients with a perfusion defect suspected to be caused by myocardial ischemia were referred for a CAG, which confirmed a significant stenosis of a coronary artery. The patients with a normal or negative adenosine 'stress"-only examination were followed for at least a year. With a Negative Predictive Value of 99.2%, this justifies, in our opinion, not performing an invasive examination or extended MR perfusion protocol for this selected patient group.

Besides a continuous infusion of adenosine for three minutes, a bolus of gadolinium is necessary to detect a relevant perfusion defect. The contrast dose for a perfusion examination is dependent on whether one wants to perform a visual or a (semi-) quantitative analysis. For a (semi-) quantitative approach a low dose of 0.05 mmol/kg is required to maintain a linear relationship between signal intensity change and contrast dose. Interpretation of these perfusion images is however most of the time performed visually or qualitatively. For routine clinical practice this is the most often used

analysis. The optimal gadolinium dose for visual analysis is 0.1 mmol/kg, with significantly more artefacts at higher gadolinium doses.

Artefacts are important to discriminate from "true" perfusion defects. They occur early and are subendocardial real focal defects, occurring during the upslope of signal intensity change, after which they disappear. They are caused by a high gadolinium concentrations or low spatial resolution.

Chapter 4 assesses the inter-observer variability of visual analysis of adenosine "stress"-only perfusion examinations in relation to experience and the systematic use of reading criteria. The readings of three different observers, with varying degree of experience and knowledge concerning perfusion examinations, are compared to an expert reading. 106 perfusion examination were read twice by all observers. After the first reading there was moderate to good agreement compared to the expert reading, depending on the level of experience. Readers were kept blind for their performance and after at least a month a second reading was performed, this time with the systematical use of reading criteria as proposed in the literature. By using a systematic visual analysis one can differentiate between a normal perfusion, a defect caused by myocardial ischemia, and an artefact. This includes a systematical analysis for a relationship with a coronary distribution area, whether it involves neighboring segments. Changes in signal intensity are looked for, knowing that especially artefacts may cause these fluctuations and assessment to whether the defect persists after peak enhancement is an important criterium, which is more suggestive for a "true" perfusion defect. The systematic use of these reading criteria improved agreement with the expert reading for all observers, most for the least experienced observer.

Besides using adenosine perfusion MR for patients without a prior myocardial infarction (and a possible need for viability assessment), it can be used in a post-infarct setting. In this respect, the comparison with a rest perfusion examination and/or Delayed Contrast Enhancement (DCE) is important. This approach, using a comprehensive Adenosine perfusion MR examination, has been studied thoroughly in the literature. It is important to realize that between both perfusion series (adenosine perfusion and rest perfusion) there is a "waiting time" to allow for the signal intensity influ-

ences of the first contrast bolus to decrease. This time is usually filled with the acquisition of a stack of short-axis cine (wall motion) images to allow for the determination of global left ventricular functional parameter assessment, which can provide additional prognostic information. **Chapter 5** focuses on the post-processing of global left ventricular functional parameter assessment. Hypothesizing that the analysis (drawing of epicardial and endocardial contours with dedicated software) of every second short-axis slice is as accurate as analysing consecutive short-axis slices. Bland-Altman analysis shows narrow limits of agreement, confirming that in the post-processing stage, analysing every second short-axis slice is as accurate as analysing consecutive short-axis slices in a normal shaped heart, hereby reducing post-processing time with approximately 50%.

Viability assessment and ischemia detection can, besides by a comprehensive adenosine perfusion MR examination, be performed with a Dobutamine Stress MR examination (focussing on wall motion abnormalities). Contra-indications for adenosine or dobutamine and local expertise can be a reason to choose for either one. Because of perfusion abnormalities occur before wall motion abnormalities, perfusion-imaging can be performed on peak dose dobutamine in case of an atypical wall motion abnormality to confirm that it is indeed myocardial ischemia, or not. **Chapter 6** focuses on this issue, in which a perfusion series is performed at peak dose dobutamine in 115 patients. It proved technically possible and furthermore showed that the addition of first-pass myocardial perfusion imaging at peak dose dobutamine can help prevent a false positive wall motion analysis for myocardial ischemia.

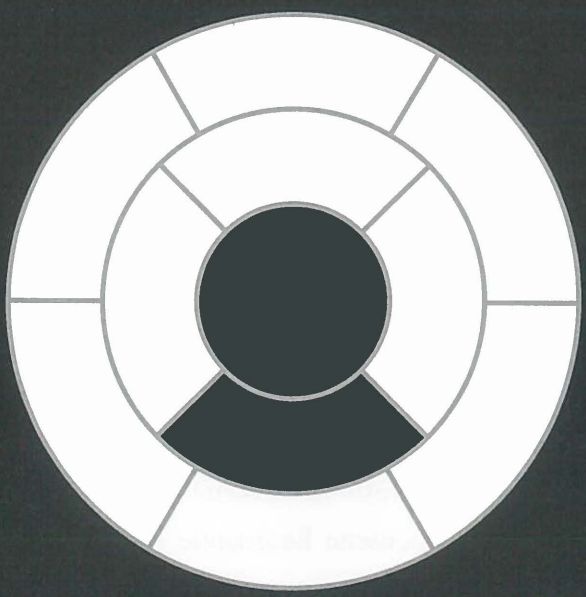
When performing perfusion imaging at really high heart rates, such as under peak dose dobutamine infusion, perfusion series can be compromised by limited spatial coverage. The single shot acquisition technique of a perfusion sequence allows the acquisition of a slice position in a certain point in the R-R interval, with the acquisition of different slice positions in other points of the same R-R interval. Shortening of the R-R interval (such as when the heart rate increases) therefore potentially decreases the number of possible slice positions which can be acquired with single heart beat

temporal resolution, hence spatial coverage. Shortening of data acquisition time per slice position, such as with parallel imaging techniques, might overcome this problem. **Chapter 7** compares a novel parallel imaging technique for first-pass perfusion imaging (TSENSE), which allows data acquisition with higher temporal resolution and potentially more spatial coverage, with a "conventional" parallel imaging sequence (GRAPPA). In 12 patients both perfusion sequences were performed (rest perfusion), in inverted order in every other patient. Perfusion series were then analysed in terms of signal to noise ratio (SNR) and contrast to noise ratio (CNR). Higher SNR, CNR and image quality, were obtained with the GRAPPA technique, but more consistent SNR and CNR with TSENSE. These results, combined with the possibility of acquiring more spatial coverage, gives TSENSE a roll in performing perfusion imaging at high heart rates.

In conclusion, this thesis focuses on MR perfusion in the detection of myocardial ischemia and used protocols in this respect. In patients with no prior myocardial infarction, a fast adenosine "stress"-only technique can reliably exclude significant myocardial ischemia in a large patient group in a protocol time of only 15-20 minutes. Using systematic reading criteria for a visual analysis of perfusion images considerably improves agreement with an expert reader. In a post-infarct setting, either with a comprehensive adenosine MR examination or a dobutamine stress MR examination, improvements in time can be achieved by reducing post-processing of a stack of short-axis cine images by analysing only every second short-axis series for global left ventricular functional parameter assessment. In this respect, specificity of a dobutamine stress MR examination can be increased by performing a perfusion sequence on peak dose dobutamine. For imaging at higher heart rates, a TSENSE first-pass perfusion sequence may play a role to maintain enough spatial coverage.
Taking these issues into account, as well as the benefits of MR over current stress tests in terms of increased diagnostic accuracy and resolution and no radiation burden, a more widespread use and implementation into routine clinical can be anticipated and suggested.

chapter 9

Samenvatting



Pijn op de borst, oftewel angina pectoris, is voor velen aanleiding om de hulp te zoeken van een arts. De differentiaal diagnose van angina pectoris is echter groot. De noodzaak om ischemisch hartlijden aan te tonen, danwel uit te sluiten is erg belangrijk bij deze klacht. Daarnaast wordt een eventuele revascularisatie van een coronair arterie niet alleen bepaald door de morfologie van een coronair stenose, maar ook door de haemodynamische gevolgen voor het myocardium. Bij een groot aantal patiënten wordt ischemie van het myocardium onwaarschijnlijk geacht naar aanleiding van anamnese, lichamelijk onderzoek en rust ECG.

Desondanks blijft een aanzienlijk aantal patiënten over met stabiele angina pectoris voor wie het bestaan danwel de significantie van eventueel coronairlijden onduidelijk is. Non-invasieve aanvullende onderzoeken bepalen de noodzaak voor een invasief coronair angiogram (CAG) en een eventuele revascularisatie. Hiermee wordt het aantal puur diagnostische CAG's gereduceerd. In deze context heeft de bepaling van functie toegevoegde waarde over alleen morfologie. Methoden waarbij fysieke inspanning wordt nagebootst, danwel een farmacologische stress respons wordt opgewekt, worden veelvuldig gebruikt voor deze indicatie.

Bekende "stress"-testen voor de detectie van ischemie van het myocardium, zoals bijvoorbeeld de fietsergometrie of SPECT worden beperkt door hun diagnostische accuraatheid, stralingsbelasting en/of spatiële resolutie. De huidige status van MRI technologie maakt het mogelijk deze beperkingen te overkomen. ECG afwijkingen, wandbewegingsstoornissen van de linker ventrikel en perfusie afwijkingen onder (farmacologische) stress zijn allen methoden om myocardischemie te objectiveren. Het voordeel van beeldvorming van perfusie ligt in het eerder ontstaan van perfusie afwijkingen in de ischemische cascade in vergelijking met wandbewegingsstoornissen en ECG veranderingen. Perfusie beeldvorming, oftewel perfusie imaging met Cardiovasculaire Magnetische Resonantie Imaging (CMR) is een dynamische techniek om de eerste passage (first-pass) van een bolus contrast middel te vervolgen bij de passage door het myocardium. Hiervoor wordt een sterk T1-gewogen sequentie gebruikt, waarbij meerdere slice posities worden verkregen van de linker ventrikel met 40-60 beelden per slice

positie. Gerapporteerde diagnostische accuraatheid voor adenosine perfusie CMR loopt van 78-100% voor sensitiviteit, 68-93% voor specificiteit, negatief voorspellende waarde (Negative Predictive Value; NPV) tussen 77-100 % en een positief voorspellende waarde (PPV) tussen de 71-95%. Verschillen in deze gerapporteerde diagnostische accuraatheid worden veroorzaakt door verschillen in de studie populatie, de gebruikte sequentie en protocol, de contrastdosis, spatiële "coverage" en de gebruikte modaliteit als referentiestandaard en ook de stenosegraad die gedefinieerd is als significant. Verschillende strategieën zijn mogelijk bij het creeëren van een "stress" perfusie CMR protocol en het uitvoeren van het onderzoek. De bouwstenen voor het protocol zijn: stress perfusie imaging, rust perfusie imaging, cine wandbeweging imaging en late aankleuring (Delayed Contrast Enhancement, DCE). Keuzes moeten gemaakt worden wat betreft de gebruikte farmacologische stressor, de perfusie sequentie, contrast dosis, infusie snelheid en heel belangrijk het gebruikte protocol in relatie tot de patiëntenpopulatie. Deze protocol verbeteringen en overwegingen zijn onderwerp van studie in dit proefschrift.

Het gebruik van een adenosine "sress-only" benadering bij patiënten zonder een voorgeschiedenis van een myocardinfarct en een klinische noodzaak om myocardischemie uit te schakelen wordt beschreven in **hoofdstuk 3**. Deze studie analyseert een groep van 134 opeenvolgende patiënten verwezen voor een adenosine perfusie MR onderzoek. De patiënten met een perfusiedefect suspect voor myocard ischemie werden verwezen voor een CAG. Welke in alle gevallen een significante stenose bevestigde. De patiënten met een normaal oftewel negatief adenosine "stress-only"onderzoek kwamen in de follow-up gedurende minimaal 1 jaar. Met een negatief voorspellende waarde van 99.2 % rechtvaardigt dit naar onze mening het niet verrichten van een invasief onderzoek of uitgebreider MR perfusie protocol in deze patiëntengroep.

Naast een continue adenosine infusie gedurende drie minuten is een bolus paramagnetisch contrastmiddel (extrahuppelpup gadolineum verbindingen) nodig om relevante perfusiedefecten te detecteren. De contrastdosis is afhankelijk van of men een visuele danwel een (semi-) kwantitatieve analyse

wil uitvoeren. Voor een (semi-) kwantitatieve benadering is een lage dosis van 0.05 mmol/kg nodig om een lineaire relatie te behouden tussen signaalintensiteitsveranderingen en contrastdosis. Interpretatie van deze perfusie beelden wordt over het algemeen echter visueel oftewel qualitatief gedaan. Voor routinematig klinisch gebruik is het de meest gebruikte methode. De optimale dosis voor een visuele analyse bedraagt 0.1 mmol/kg, met significant meer artefacten bij een hogere gadolineum dosis.

Het is belangrijk om artefacten te discrimineren van "reeële" perfusiedefecten. Artefacten ontstaan vroeg en zijn zeer focale subendocardiale laag sginaalgebieden. Ze ontstaan gedurende de zogeheten "upslope" van de signaalintensitieitsveranderingen en verdwijnen daarna. Deze artefacten worden veroorzaakt door een plaatselijk hoge gadolineumconcentratie danwel lagere spatiële resolutie. **Hoofdstuk 4** behandelt de inter-observer variabiliteit van visuele analyse van adenosine "stress-only" perfusie onderzoeken in relatie tot ervaring en het systematisch gebruik van beoordelingscriteria. De beoordelingen van drie verschillende beoordeelaars met een verschillende mate van ervaring wordt vergeleken met het oordeel van een expert. 106 perfusie onderzoeken werden twee maal beoordeeld door alle beoordeelaars. Na de eerste beoordeling was er een matig tot goede overeenkomst in vergelijking met de expert, afhankelijk van de mate van ervaring. Beoordeelaars werden geblindeerd voor hun prestatie en na minimaal 1 maand werd een tweede beoordeling gedaan, ditmaal met het systematisch gebruik van beoordelingscriteria zoals gesuggereerd in de literatuur. Door middel van een systematische visuele analyse is het mogelijk om te differentiëren tussen een normale perfusie, een defect veroorzaakt door myocardischemie en een artefact. Er wordt hierbij systematisch gekeken naar een relatie met een coronair stroomgebied, of het naburige segmenten betreft met een defect. Verder wordt er gekeken naar veranderingen in signaalintensiteit, wetende dat artefacten fluctuaties in signaalintensiteit geven. Daarnaast is het persisteren van een defect na piekaankleuring vooral suggestief voor een perfusiedefect veroorzaakt door ischemie. Het systematisch gebruiken van deze beoordelingscriteria verbeterde de mate van overeenkomst met de expert voor alle beoordelaars en het meest voor de

minst ervaren beoordeelaar.

Naast het gebruik van adenosine perfusie MR bij patiënten zonder een myocardinfarct (en een mogelijke noodzaak om vitaliteit aan te tonen) in de voorgeschiedenis, kan het onderzoek worden ingezet in de post-infarct setting. In dit verband is een vergelijk met rust perfusie en/of DCE van belang. Deze benadering met een uitgebreider adenosine perfusie CMR protocol is uitgebreid bestudeerd in de literatuur. Het is hierbij van belang om zich te realiseren dat tussen beide perfusie series (rust en stress) er een "wachttijd" is om er voor te zorgen dat de signaalintensiteits- invloeden van de eerste contrastbolus verminderen. Deze tijd wordt doorgaans opgevuld met de acquisitie van elkaar opvolgende korte as cine opnamen, waarmee globale linker ventrikel functionele parameter bepalingen kunnen worden gedaan, welke additionele prognostische informatie kunnen geven. **Hoofdstuk 5** richt zich op de post-processing van globale linker ventrikel functionele parameter bepalingen. Waarbij de hypothese dat de analyse (intekenen van epicardiale en endocardiale contouren met hiervoor ontwikkelde software) van iedere tweede korte as serie net zo accuraat is als analyse van opeenvolgende korte as series. Bland-Altman analyses laten in dit verband smalle "limits of agreement" zien, waarmee bevestigd wordt dat de analyse van iedere tweede korte as serie net zo betrouwbaar is als de analyse van opeenvolgende korte as series in een normaal gevormd hart. Hiermee wordt de post-processing tijd met circa 50% verminderd.

Vitalitietsbepaling en ischemie detectie kan, naast met een uitgebreid adenosine perfusie CMR protocol, worden gedaan met een dobutamine stress CMR onderzoek (waarbij wordt gekeken naar regionale wandbewegingsstoornissen). Contra-indicatie voor adenosine of dobutamine en locale expertise kunnen een reden zijn om voor een bepaald onderzoek te kiezen. Vanwege het eerder optreden van perfusie afwijkingen voor wandbewegingsstoornissen, kan perfusie imaging verricht worden op piek dosis dobutamine in het geval van een atypische wandbewegingsstoornis om te bevestigen dat het daadwerkelijk om myocardischemie gaat of niet. **Hoofdstuk 6** richt zich op dit thema, waarbij een perfusie serie wordt verricht bij 115 patienten op piek dosis dobutamine gedurende een dobutamine stress

CMR protocol. Het bleek technisch mogelijk en daarnaast bleek dat de toevoeging van perfusie imaging op piek dosis dobutamine een fout-positieve wandbewegingsanalyse kan voorkomen. Bij het uitvoeren van perfusie imaging met MRI bij zeer hoge hartslagen, zoals onder dobutamine infusie, kunnen de perfusie beelden beperkt zijn in hun spatiële coverage. De single shot acquisitie techniek van een perfusie sequentie maakt het mogelijk om een bepaalde slice positie in een bepaald deel van het R-R interval te verkrijgen, met de acquisitie van andere slice posities in een ander deel van het R-R interval. Verkorting van het R-R interval (hetgeen optreedt bij hogere hartslagen) vermindert in potentie het aantal te verkrijgen slice posities met "single heart beat" temporele resolutie binnen een R-R interval. Verkorting van de data acquisitietijd per slice positie daarentegen, zoals bij parallel imaging technieken, kan dit probleem opvangen.

Hoofdstuk 7 vergelijkt een nieuwe parallele imaging techniek (TSENSE), welke data acquisitie met een hogere temporele resolutie en potentieel meer spatiele coverage mogelijk maakt, met een "conventionele" parallele imaging sequentie (GRAPPA). Bij 12 patiënten werden beide sequenties uitgevoerd (rust perfusie) in omgekeerde volgorde bij iedere andere patient. Deze perfusie series werden vervolgens geanalyseerd in termen van signaal-ruis verhouding (SNR) en contrast-ruis verhouding (CNR). Hogere SNR,CNR en beeldkwaliteit werden verkregen met de GRAPPA techniek, maar meer consistente SNR en CNR met de TSENSE techniek. Deze resultaten gecombineerd met de mogelijkheid van meer spatiele coverage geven de TSENSE techniek een rol in het uitvoeren van perfusie imaging bij zeer hoge hartslagen.

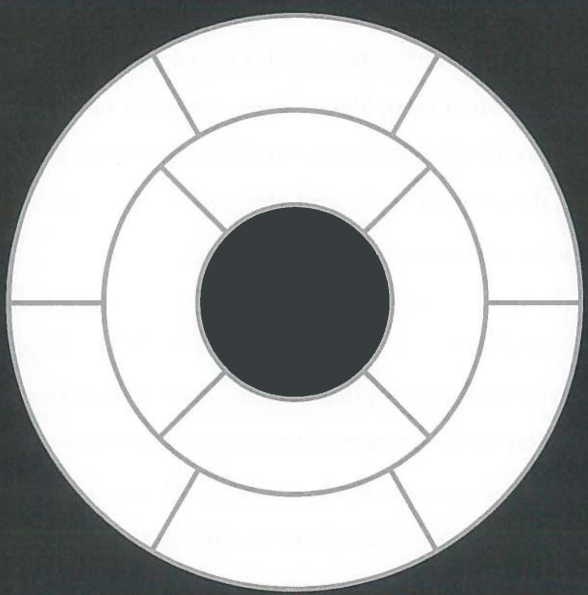
Concluderend, dit proefschrift richt zich op MR perfusie in de detectie van myocardischemie en gebruikte protocollen. In een patiëntengroep zonder voorgeschiedenis van een myocardinfarct kan een snel adenosine "stress-only" onderzoek betrouwbaar in een protocoltijd van circa 15-20 minuten significante ischemie uitsluiten. Het systematisch gebruik van beoordelingscriteria in het geval van een visuele analyse van perfusie beelden verbetert aanzienlijk de mate van overeenkomst van beoordelaars met een expert.

In een post-infarct setting (in geval van een uitgebreid adenosine perfusie CMR protocol dan wel dobutamine stress CMR) kan de analyse van elke tweede korte as cine serie een aanzienlijke tijdsbesparing opleveren in de bepaling van globale linker ventrikel functionele parameters. In dezelfde setting kan de specificiteit van een dobutamine stress CMR onderzoek worden vergroot door perfusie imaging uit te voeren op piek dosis dobutamine. Bij beeldvorming onder hoge hartslagen kan een TSENSE perfusie sequentie een rol spelen om voldoende spatiële coverage te behouden.

Al deze factoren tesamen, met de voordelen van MR (verbeterde diagnostische accuraatheid, spatiële resolutie en zonder toepassing van ioniserende stralen) ten opzichte van huidige stress-testen voor de detectie van ischemie rechtvaardigen en indiceren een meer wijdverspreide routinematige implementatie van deze techniek in de toekomst.

chapter 10

Dankwoord
About the author
List of publications



DANKWOORD

De enkele naam op de voorkant van een proefschrift verhult vaak de nodige mensen achter deze persoon. In mijn geval is dat niet anders. Bij uitstek is dit dan ook het gedeelte van een promotietraject om een aantal mensen een hart onder de riem te steken en ze die eer te geven die ze toekomt. Allereerst wil ik mijn promotor Prof. Dr. M. Oudkerk bedanken voor de geboden kans. Tevens bedankt voor alle inzichten, discussies en begeleiding gedurende het gehele promotietraject. Samen met dr. Kuijpers heeft u de basis gelegd voor het MR stress onderzoek.

Mijn volgende dankbetuiging gaat dan ook uit naar dr. Kuijpers, beste Dirkjan. Direct vanaf mijn eerste contact met de MRI stress testen in het Bronovo was ik enthousiast, maar hoe kan het dan ook anders met een zodanig uitbundige, positieve leermeester. Wie wil daar nu niet vijf uur op een dag voor in de trein zitten. Ook in een latere fase van dit promotietraject hebben wij middels mail, telefoon en congressen de nodige zaken kunnen bespreken, bedankt hiervoor.

Roelof Bodewes, Paul van Dijkman, Marco Götte, Roy Irwan, Caroline Janssen, Peter Kappert, Marjan Kerkhof, Peter van Ooijen, Jelle Overbosch, Dorine Rijlaarsdam-Hermsen, Paul Sijens, Dirkjan van Veldhuisen, Pieter van der Vleuten en Tineke Willems, van harte bedankt voor de assistentie, als co-auteur, bij de verschillende artikelen en vooral ook veel succes bij een eventuele promotie en toekomstige publicaties.

De leden van de beoordelingscommissie wil ik hartelijk danken voor de beoordeling en goedkeuring van dit proefschrift. Alle collega arts-assistenten en radiologen en een ieder in het UMCG dan wel het Bronovo ziekenhuis die op welke wijze dan ook betrokken is geweest bij dit eindresultaat van harte bedankt, eveneens voor de leuke sfeer. Bernadette Blom en collega laboranten in het Bronovo ziekenhuis van harte bedankt voor alle inspanningen. Iedereen op het secretariaat en het planbureau van de afdelingen radiologie en cardiologie bedankt voor de medewerking.

Tussen al deze geweldige mensen is er een aantal die ik in het bijzonder wil bedanken. Mother Goose, Stella. De steun en toeverlaat van de AGNIO's

op de werkvloer en tijdens congressen. Ook ik persoonlijk heb dit zeer gewaardeerd. Ondanks dat je het nodige hebt meegemaakt de laatste tijd, heb je je opgeruimde karakter behouden en je werk met verve gedaan. Een opgeruimde positieve instelling zit ook bij Peter Kappert wel goed. Peter, zonder jou flexibele instelling was het vrijwel onmogelijk geweest om delen van dit onderzoek uit te voeren. Wat dit aan gaat sta je dan ook symbool voor een aantal van je collega's. Twee hiervan wil ik het bijzonder noemen. Sonja van Lieshout en Jan Grozema bedankt voor alle hulp.
Daarnaast waren er op de G2 en op R&D van de afdeling radioloog veel leuke mensen die hebben meegewerkt aan dit proefschrift en in ieder geval ook voor een hoop gezelligheid hebben gezorgd. Riksta, Ying, Dong-ming, Monique, Ying-ru, Tineke, Hester, Martine, Wisnu, Jaap, Hildebrand, Marion, Jolanda, Alain, Marjolein, Marcel, Peter en Paul allen van harte bedankt. Mister Green, beste Jaap ook ontzettend bedankt voor alle lay-out inspanningen.
Oprecht hoop ik dat ik niet iemand ben vergeten die mij wel op een belangrijke manier heeft gesteund, bij voorbaat vergeef me. In ieder geval zal ik mijn secondanten niet vergeten. Wie had ik nu beter kunnen kiezen als mijn paranimfen dan Gonda en Anne, De swedish cook en het geheim van MnDpDp en vele andere interessante "discussies" zullen me altijd bij blijven. Bedankt ook voor het spelen van klankbord bij tijd en wijle. Het is mij een eer dat jullie mijn paranimfen willen zijn.
Vrienden, familie bedankt voor alle interesse en steun en vooral eigenlijk alles buiten dit proefschrift om. In het bijzonder wil ik mijn moeder bedanken, uiteraard voor alle zorg en liefde, maar vooral ook voor alle stimulans altijd.

Degene die dit dankwoord en mijzelf compleet maakt is mijn lieve vrouw, Dorien. "There are many things in life that will catch your eye, but only one will catch your heart". Lieve Doortje, eigenlijk hebben we maar één dilemma in ons leven, die we doorgaans afsluiten met... evenveel dan?

ABOUT THE AUTHOR

Daniël Lubbers was born on the 24th of December 1974 in Groningen, the Netherlands. He grew up in Groningen and attended high school at the Röling college. Before being enrolled in Medical School in 1998, he studied clinical psychology, with a specialty in neuropsychology at the University of Groningen. This led to a Masters Degree in 2000, with a thesis on visual attention: learning, training and generalization-effects. His clinical rotations for Medical School were done at the Martini hospital in Groningen. In December 2003, he graduated from Medical School at the University of Groningen. Hereafter, he worked for a year and a half as a resident at the Emergency Department of St. Lucas hospital in Winschoten, The Netherlands. In August 2005, he started at the department of Radiology performing research leading to this PhD thesis. At the annual conference of the Radiological Society of North America (RSNA) 2007 he received a Cum Laude award for his educational exhibit on "Dobutamine and adenosine stress Cardiovascular MRI (CMR) in the detection of myocardial ischemia: Current status and clinical implementations." Furthermore on this topic and related topics he had several invited lectures from the European Society of Cardiac Radiology and the Netherland Heart days. He started his residency in Radiology in July 2007.

LIST OF PUBLICATIONS

(1) Lubbers DD, Kuijpers D, Oudkerk M. Myocardial wall motion imaging with cardiac magnetic resonance imaging. Imaging decisions 2006 autumn; 10(3): 8-15.

(2) Irwan R, Lubbers DD, van der Vleuten PA, Kappert P, Gotte MJ, Sijens PE. Parallel imaging for first-pass myocardial perfusion. Magn Reson Imaging 2007 June;25(5):678-83.

(3) Lubbers DD, Willems TP, van der Vleuten PA, Overbosch J, Gotte MJ, van Veldhuisen DJ, Oudkerk M. Assessment of global left ventricular functional parameters: analysis of every second short-axis Magnetic Resonance Imaging slices is as accurate as analysis of consecutive slices. Int J Cardiovasc Imaging 2008 February;24(2):185-91.

(4) Lubbers DD, Janssen CH, Kuijpers D, van Dijkman PR, Overbosch J, Willems TP, Oudkerk M. The additional value of first pass myocardial perfusion imaging during peak dose of dobutamine stress cardiac MRI for the detection of myocardial ischemia. Int J Cardiovasc Imaging 2008 January;24(1):69-76.

(5) Lubbers DD. MR (stress) first-pass perfusion imaging of the myocardium. Course syllabus North Netherlands Heart Days 2008.

(6) Lubbers DD. MR (stress) first-pass perfusie imaging van het myocardium. Sandwich Course Dutch Radiological Society June 2008 course syllabus: 39-42.

(7) de Vos AM, Rutten A, van de Zaag-Loonen HJ, Bots ML, Dikkers R, Buiskool RA, Mali WP, Lubbers DD, Mosterd A, Prokop M, Rensing BJ, Cramer MJ, van Es HW, Moll FL, van de Pavoordt ED, Doevendans PA, Velthuis BK, Mackaay AJ, Zijlstra F, Oudkerk M. Non-invasive cardiac assessment in high risk patients (The GROUND study): rationale, objectives and design of a multi-center randomized controlled clinical trial. Trials 2008 August 1;9:49.:49.

(8) Lubbers DD. Dobutamine stress CMR. European Society of Cardiac Radiology 2008 Educational syllabus: 73-4.

(9) Tio RA, Slart RH, deBoer RA, van der Vleuten PA, de Jong RA, van Wijk LM, Willems TP, Lubbers DD, Voors AA, van Veldhuisen DJ.

Reduced regional myocardial perfusion reserve is associated with impaired contractile performance in idiopathic dilated cardiomyopathy. Netherlands Heart Journal 2009. in press

(10) van der Vleuten PA, de Jonge GJ, Lubbers DD, Tio RA, Willems TP, Oudkerk M, Zijlstra F. Evaluation of global left ventricular function assessment by dual-source computed tomography compared with MRI. Eur Radiol 2009 February;19(2):271-7.

(11) A.M de Vos, Oudkerk M, Rutten A, de Jonge GJ, Lubbers DD, Prokop M, van den Dungen JJ, Mali WMThP, Cramer PA, Doevendans PA, Rensing BJ, van der Zaag-loonen HJ, Bots ML, Zijlstra F. High prevalence of treatable severe coronary artery disease: findings in a randomized controlled trial in cardiac asymptomatic peripheral arterial disease patients. 2009 submitted.

(12) de Jonge GJ, van Ooijen PM, van der Vleuten PA, Lubbers DD, Kasemier JH, de Bock GH, Oudkerk M. The reliability of automatic measurement of left ventricular function with dual-source computed tomography datasets. Eur. Radiol 2009. Epub ahead of print.

(13) Lubbers DD, Rijlaarsdam – Hermsen D, Kuijpers D, Kerkhof M, Sijens PE, van Dijkman PRM, Oudkerk M. Performance of adenosine "stress"-only perfusion MRI in patients without a history of myocardial infarction: a clinical outcome study. 2009. Submitted for publication European Heart Journal.

(14) Lubbers DD, Kuijpers D, Oudkerk M. Protocols and indications for MR (stress) first-pass perfusion imaging of the myocardium. Imaging Decisions 2009 Summer; Issue 13.2

(15) Lubbers DD, Kuijpers D, Bodewes R, Kappert P, Kerkhof M, van Ooijen P, Oudkerk M. Inter-observer variability of visual analysis of "stress"- only adenosine first-pass perfusion imaging in relation to clinical experience and reading criteria. 2009. Submitted for publication European Radiology.