Dobutamine Stress MRI

Th. J. A. Kuijpers

DOBUTAMINE STRESS MAGNETIC RESONANCE IMAGING OF THE HEART

The work presented in this thesis was conducted at the Department of Radiology, Bronovo Hospital, The Hague, in close collaboration with the Department of Cardiology, Bronovo Hospital, The Hague and the Department of Radiology, University Hospital Groningen, Groningen, The Netherlands.

The printing of this thesis was kindly supported by the Bronovo Research Fonds, and Delft Diagnostic Imaging.

Layout and printing: DRUKKERIJ DE KEMPENAER Oegstgeest, 2004.

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Th.J.A. Kuijpers
Thesis
ISBN 90-9018973-4

Stellingen

1. Het gebruik van "Grid-Tagging", als afbeeldingstechniek tijdens dobutamine stress MRI onderzoek van het myocard verhoogt de kans op het aantonen van wandbewegingsstoornissen als gevolg van ischemie (dit proefschrift).

2. Dobutamine stress MRI is een veilig, betrouwbaar en klinisch goed toepasbaar radiologisch onderzoek voor het aantonen van myocard ischemie (dit proefschrift).

3. Bij patiënten met een negatieve dobutamine stress MRI studie kan een betrouwbare schatting worden gemaakt van de kans op het krijgen van myocard infarct en cardiaal overlijden. (dit proefschrift).

4. Indien de gebruikelijke "Target Heart Rate Rule" wordt toegepast tijdens de dobutamine stress test, betekent dit een aanzienlijke beperking van de diagnostische waarde van het onderzoek (dit proefschrift).

5. De geringe interobserver variabiliteit van de beoordeling van de dobutamine stress MR beelden maakt deze cardiale stress techniek ook toegankelijk voor minder ervaren artsen.

6. Het verfijnde regelsysteem van de perfusie van het myocard, veroorzaakt voortdurende veranderingen in de perfusie, die een noodzakelijke voorwaarde vormen voor het optimaal functioneren van de hartspier.

7. Het aantal negatieve cardiale stress onderzoeken bij patiënten met pijn op de borst (stabiele angina) kan aanzienlijk worden verkleind door aan het onderzoek een Calcium-Score bepaling met multislice-CT vooraf te laten gaan.

8. De grootste uitdaging van cardiale diagnostiek met MR en CT is de integratie van de verschillende diagnostische onderzoeken.

9. Ter versterking van het nieuwe Europese zelfbewustzijn zouden Europese wetenschappelijke manuscripten als eerste ingestuurd moeten worden naar een Europees wetenschappelijk tijdschrift.

10. De aanwezigheid van een stafmaatschap in een ziekenhuis bevordert de onderlinge samenwerking tussen de verschillende specialismen en stimuleert substitutie van diagnostische onderzoeken.

11. Pes planus (platvoeten) is voor het maken van een stabiele golfswing eerder een voordeel dan een nadeel.

Groningen, 9 februari 2005
Th.J.A. Kuijpers

RIJKSUNIVERSITEIT GRONINGEN

Dobutamine Stress MRI

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 februari 2005
om 16.15 uur

door

Theodorus Johannes Andreas Kuijpers

geboren op 9 september 1955

te Schiedam

Promotor

Prof. Dr. M. Oudkerk

Beoordelingscommissie

Prof. Dr. W.P.T.M. Mali

Prof. Dr. M. Rees

Prof. Dr. F. Zijlstra

Aan Dieke, Sanne, Erik
Aan mijn ouders

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Dobutamine Stress MRI

Chapter 1

Introduction

CHAPTER I

Introduction

In 1908, Einthoven published a paper showing S-T segment depression after exercise, but he could not explain this finding at that time (1). This empirical discovery has been the cornerstone of exercise stress testing and is still used in bicycle stress testing today. Professor Willem Einthoven, a Dutch physiologist, was awarded the 1924 Nobel Prize for his discovery and development of the electrocardiogram.

The first paper on an exercise tolerance test was published by Master and Oppenheimer in 1929 (2). However, it would take another 12 years before Master and Jaffe proposed that an ECG should be taken before and after the "exercise tolerance test" (3). Conventional physical exercise stress testing has been the most frequently used noninvasive technique for the diagnosis of coronary artery disease since the introduction of the exercise test in 1941. The correlation between angina pectoris and ECG changes was the first step in the recognition of the ischemic cascade, as known today.

In 1987, Nesto reported the temporal sequence of hemodynamical, electrocardiographical and symptomatical expressions of ischemia (4). The development of an ischemic event, whether silent or painful, represents the cumulative impact of a sequence of pathophysiological events. Each ischemic episode is initiated by an imbalance between myocardial oxygen supply and oxygen demand, which may ultimately be manifested as angina pectoris. This sequence of events is called the ischemic cascade (figure 1). The significance of this concept resides in the fact that it re-directs the focus from the end result--angina--to the more fundamental, underlying pathophysiological factors that

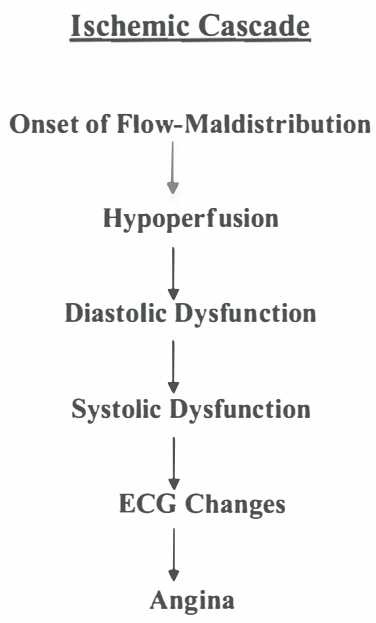

Figure 1. Ischemic Cascade

precede it. Specifically, these events include perfusion abnormalities, diastolic and systolic wall motion abnormalities, ST-segment changes and angina pectoris. Modern evaluation techniques have advanced considerably since the development of the electrocardiogram. The most frequently used modality, which interferes early in the ischemic cascade at perfusion level, is myocardial

scintigraphy. Stress echocardiography and dobutamine stress magnetic resonance imaging (MRI) are mainly focused on the analysis of wall motion abnormalities which occur half-way in the ischemic cascade. Multislice computed tomography and electron beam computed tomography are involved in the analysis of the vessel wall of the coronary arteries and are less frequently used in the assessment of perfsusion and wall motion abnormalities.

The first studies reporting the application of low dose (20 ug) dobutamine stress MR were those of Pennell et al. in 1992 (5), van Rugge et al. (6, 7) and Baer et al. (8, 9) in 1993 and 1994. Since 1999, high dose (40 ug) dobutamine stress MRI studies have been reported by Nagel et al. (10) and Hundley et al. (11).

In 1999, Nagel et al. (10) were the first to directly compare high-dose dobutamine MRI, using a segmental k-space turbo-gradient echo sequence, with a dobutamine echocardiography protocol with optional second harmonic imaging studies in 172 patients. The overall detection of coronary artery disease, as defined by coronary angiography (diameter reduction >50%), proved to be significantly better by dobutamine MRI in terms of sensitivity (88,7 % vs 74,3 %; $p<0.05$) and specificity (85,7 % vs 69,8 %; $p<0.05$) as compared to dobutamine stress echocardiography.

In the past five years, MR has emerged as a new noninvasive imaging modality, providing high-resolution images in any desired plane of the heart, combined with the potential to assess and monitor regional left and right ventricular function (10, 11). The improved temporal resolution of new-fast gradient echo MR sequences such as True Fisp, FFE or FIESTA makes it possible to capture cine loops displaying the beating heart, allowing a qualitative and quantitative analysis of wall motion with well defined endocardial and epicardial borders of

the myocardium. The excellent quality of the MR images explains the development of a number of MR stress techniques, which compete against stress echocardiography for the evaluation of myocardial ischemia and myocardial viability in the clinical work up. Furthermore, new MR methods assessing ischemia by perfusion and viability by late contrast enhancement have recently been established. These new techniques not only use the setting of a stress test but also compete with stress echocardiography and nuclear scintigraphy.

Dobutamine stress MRI can be an accurate choice in the initial assessment of patients suspected with myocardial ischemia. It is operator independent, digital and quantitative just as scintigraphy, and nonionizing and versatile just as echocardiography (12).

The studies described in this thesis are based on MRI with the use of high dose dobutamine for the assessment of myocardial ischemia, performed in a single center during a period of 4 years. This thesis focuses on the detection of myocardial ischemia with high-dose dobutamine using grid-tagging MR techniques for the detection of wall motion abnormalities.

Pharmacological cardiac stress imaging is reviewed in Chapter 2, especially the effects of catecholamines. In Chapter 3, a modified dobutamine stress MR protocol is presented. Chapter 4 discusses the MR imaging procedure, pathophysiology and review of literature. A pilot series of 100 patients is presented in Chapter 5 using this dobutamine stress MRI protocol for the detection of myocardial viability and myocardial ischemia. The assessment of the clinical applicability is discussed, including advantages and disadvantages of the used technique.

Chapter 6 describes the myocardial grid-tagging technique with cine gradient MR which improves the detection of wall motion abnormalities, indicative of myocardial ischemia. The safety and feasibility of dobutamine MR in a series of 400 patients is presented in Chapter 7. Reasons for test termination, safety- and side-effects are discussed. In Chapter 8, a follow-up analysis is presented in patients suspected for myocardial ischemia with a negative (no inducible myocardial ischemia) dobutamine MRI study. Follow-up data were analyzed in categories of risk levels defined by history of coronary artery disease and presence of rest wall motion abnormalities.

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Chapter 2

Pharmacological Cardiac Stress Imaging

CHAPTER 2

Pharmacological Cardiac Stress Imaging

Pharmacological agents can be used to increase cardiac work instead of exercise or to induce coronary arterial vasodilation to increase myocardial blood flow. The use of these agents is well documented in the cardiological literature. They are particularly valuable for the one third of the patients, who are not capable of performing physical exercise (1). Pharmacological stress can be an appropriate substitute for bicycle exercise. Basically, two groups of agents can be distinguished including the beta-agonists (dobutamine) and the vasodilators (dipyridamole and adenosine).

Dobutamine

Dobutamine stress magnetic resonance (MR) is gaining popularity as a noninvasive diagnostic test for detection of obstructive coronary artery disease, and has correlated well with angiographic findings (2-5). Dobutamine, a synthetic catecholamine, has a combined positive inotropic- and chronotropic effect, both increasing myocardial oxygen demand. The most commonly used agents for short term inotropic support are the catecholamines. They can be divided into the natural endogenously occurring catecholamines (dopamine and norepinephrine) and the exogenously (synthetic) administered catecholamines, like isoproterenol and dobutamine. According to their chemical structure, they may activate cardiac beta-1 adrenegic receptors, beta-2 adrenergic receptors or alfa-adrenergic receptors. The type of receptor(s) stimulated by the drug will determine the resultant mechanism of action (Table 1 and 2).

Table 1.

Adrenergic receptor localization and effects of catecholamines

Adrenergic receptor	Localization	Action
Alfa	Arterioles Myocardium	Vasoconstriction >>> contractility

Beta-1	Myocardium
	SA node
	AV node
		>>> contractility
		>>> heart rate
		>>> conduction

Beta-2	Arterioles Lungs	vasoconstriction bronchodilation

Dobutamine is a sympathomimetic drug with ß-1, ß-2, and slight α-1 receptor stimulation properties (6). Continuous intravenous infusion of the drug stimulates cardiac contractility, increases heart rate, and reduces systemic vascular resistance to various degrees, depending primarily on infusion rate (6). Low-dose infusion (≤ 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is generally characterized by increased cardiac contractility, leading to increased stroke volume, whereas blood pressure is maintained through a reduction in systemic vascular resistance (7). During high-dose infusion, stimulation of cardiac contractility persists and heart rate is increased further, whereas the reduction in systemic vascular resistance is less pronounced, resulting in a rise in systemic blood pressure (7).

These properties produce hemodynamic effects similar to those of exercise. Dobutamine has a good tolerance to peripheral vein infusion and has a low arrhythmogenicity. Like dipyridamole, dobutamine can be be used for both perfusion (8) and wall motion imaging (9). Dobutamine exerts its effects by increasing myocardial oxygen demand above availability in the setting of acute ischemia (10). Both dipyridamole and dobutamine have been used for stress wall motion analysis by magnetic resonance (MR). Dobutamine has a number of advantages in the magnet, including operator controlled level of stress, short half-life time of two minutes, and physiological effects mimicking exercise more closely than dipyridamole. The stress induced tachycardia shortens the stress imaging period when gradient-echo MR sequences are used.

Table 2.

Adrenergic receptor activity of Catecholamines

Catecholamine	Alfa peripheral	Beta -1 cardiac	Beta -2 peripheral
Norepinephrine	+++	+++	0
Epinephrine	+++	+++	++
Dopamine	+++	+++	++
Isoproterenol	0	+++	+++
Dobutamine	+	0	++

Pharmagological Stressor

Dobutamine is infused intravenously starting at 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and, if tolerated, increased every 3-6 minutes thereafter by 5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until a maximal dose of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is reached or an end point is achieved. Cine MR images are then displayed to allow side-by-side comparison of baseline wall motion, and motion after the different dose levels of dobutamine. A new or worsening wall-motion abnormality constitutes a positive test for ischemia.

Indications for termination of dobutamine stress MRI are:
Development of new wall motion abnormalities indicative for myocardial ischemia; fall of systolic blood-pressure of > 40 mm Hg; marked hypertension > 240/120 mm Hg; severe chest pain; ventricular arrhythmias, and intolerable side effects of dobutamine (nausea, vomiting).

Complications during dobutamine infusion include nausea, headache, tremor, and anxiety; angina and atypical chest pain; and atrial and ventricular arrhythmias.
Intravenous ß-adrenergic blockers can be administered for prolonged ischemic responses and/or tachyarrhythmias persisting after discontinuation of dobutamine.

Vasodilators such as dipyridamole and adenosine can also be used as stress agents to assess coronary perfusion. These agents cause maximal coronary arteriolar vasodilation, resulting in increases in flow to the territory supplied by the normal epicardial coronary arteries. If this increase in flow is insufficient, because the obstructed artery does not allow an increase in flow, blood is directed away from

the territory supplied by the obstructed artery, causing the "steal phenomenon". Side effects are similar with adenosine and dipyridamole but are reported more frequently with adenosine. Symptoms include flushing, chest pain, headache, dyspnea, and atrioventricular block and can be reversed with aminophylline. Dipyridamole is simple to administer in a 4 minute infusion of 0.56 mg/kg and causes an increase in coronary flow velocity of up to six times baseline (11). The main clinical problem with dipyridamole is its long half-life time of 30 minutes, which results in prolonged side effects.

Adenosine is a strong vasodilatator (4-5 times increase in blood flow). It acts very rapid (seconds) and short, with a half-life of about 10 seconds. Adenosine is given directly at a dose of 140 mcg/kg/minute (3-6 minuts), and causes similar changes in coronary blood flow as dipyridamole (12). It causes an increase in heart rate and a decrease in blood pressure. The side effects are associated with the generalized vasodilatation and include headache, dizziness, flushing, abdominal discomfort and also bronchospasm. These effects van be antagonized by intravenous administration of aminophylline. Adenosine is mainly used in perfsusion imaging (myocardial perfusion scintigraphy and stress perfusion MRI) and is less effective at provoking wall motion abnormalities.

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Chapter 3

Dobutamine Stress MRI protocol

Dobutamine Stress MRI

Dobutamine Stress Protocol for the Detection of Myocardial Ischemia with MRI

Department of Radiology and Cardiology
Bronovo Hospital

Bernadette Blom
Wouter Stam
Truus den Besten
Paul van Dijkman
Dirkjan Kuijpers

Den Haag, October 1999; revision: September 2003

Contents

1. Purpose

Coronary artery disease can result in two different pathophysiological conditions of the myocardium, which can occur at the same time:

(1) myocardial infarction

(2) inducible ischemia

Whereas the first can be detected at rest, the second state can only be detected under stress conditions. One of the earliest signs of myocardial ischemia is wall motion abnormalities during increasing stress, which occur much earlier than ECG changes or anginal pain.

Stress conditions can be induced by physical exercise or standardized stress protocols with pharmacological agents such as dobutamine. These pharmacological agents have been shown to be safe, well tolerated, and to reproducible induce myocardial ischemia.

The current document is a guide to pharmacological stress examinations of the heart with a standard dobutamine scheme for the diagnosis of inducible myocardial ischemia using MR.

2. Stress Agent

Pharmacon: Dobutamine-HCl

Concentration: preferably 2.5 mg/ml

I.v. administration in ml/hr.

3. Mode of action

Dobutamine is a sympathomimetic drug with beta-1, beta-2, and slight alpha-1 receptor stimulation properties. The drug exerts its pharmacological effects in a dose dependent manner. Intravenous infusion of the drug increases cardiac contractility and heart rate, and decreases systolic vascular resistance: During low-dose infusion the major effect is an increase in contractility; at higher doses (up to max. 40 mcg/kg/min) the increase in heart rate and the concomitant increase in myocardial oxygen consumption cause contraction abnormalities in myocardial segments supplied by stenotic coronary arteries, as oxygen demand exceeds availability and induces myocardial ischemia. To fully exert the effects of dobutamine, patients should refrain from ß-blockers and nitrates 4 days prior to the examination, since these drugs counteract the dobutamine action (Table 1).

4. Safety

Monitoring of the patient within the magnet is mandatory during stress examinations with low or high dose dobutamine. In general, monitoring during a MR examination requires the same precautions and emergency equipment as any other stress examination. Specific recommendations are listed in Table 2. Apart from the known specific contraindications for MR, contraindications are identical to those for stress echocardiography and are listed in (Table 3). Whereas only minimal side effects are to be expected during low dose dobutamine, high dose dobutamine may cause severe complications in 0.25% of patients, including infarction (0.07%), ventricular fibrillation (0.07%) and sustained ventricular

tachycardia (0.1%). Thus, although adverse events are rare, preparation and practice for rapid removal of the patient from the magnet is needed in addition to a stringent adherence to the termination criteria (Table 4). The monitoring of blood pressure, cardiac rhythm and patients' symptoms can be done in two ways: Either by connecting the patient to standard equipment with special extensions through a waveguide in the radiofrequency cage which is placed outside the scanner room, or by using special MR compatible equipment, which exists at many MR sites. A defibrillator and all drugs for emergency treatment must be available at the MR site. A specific problem for monitoring within the magnet is that of assessing the changes of ST-segments from the ECG. However, since wall motion abnormalities precede ST changes and can readily be detected with MR imaging, monitoring is effective without a diagnostic ECG. This requires an on-line assessment of the wall motion during image reconstruction performed immediately after image acquisition. In previous guidelines pulse oximetry has been recommended as an additional means for rhythm control mainly in case of ECG failure.

Table 1: **Preparation for dobutamine stress examination and antidote**

Patient instructions:

No anti-anginal medication 4 days prior to the examination

Antidote:

ß-blocker (esmolol) 0.5 mg/kg as slowly injected bolus;

Additional bolus of 0.2 mg/kg as needed.

Sublingual nitroglycerine

Table 2: **Monitoring requirements for stress MR imaging**

Heart rate and rhythm	Continuously
Blood pressure	Eevery 3 minutes
Symptoms	Continuously
Wall motion abnormalities	Every dose increment

Table 3: **Contraindications for dobutamine**

- Severe arterial hypertension (>220/120 mmHg)
- Patients with an Acute Coronary Syndrome
- Complex cardiac arrhythmias
- Atrial Fibrillation
- MRI incompatible metallic implants
- Claustrophobia

Table 4: **Termination criteria**

- Blood pressure decrease > 40 mmHg systolic
- Blood pressure increase > 240/120 mmHg
- New or worsening wall motion abnormalities in at least 2 segments at different consecutive planes of the left ventricle
- Complex cardiac arrhythmias
- Intolerable side effects (nausea, vomiting)
- Severe chest pain

CHAPTER 3

Image interpretation

5. Wall motion abnormalities

Multiple cine loop display is recommended for image interpretation in which at least three different stress levels for each slice are displayed simultaneously. This can be performed by using the cardiac analysis tool implemented on the scanner or an external workstation. The ventricle is analyzed by 17 segments per stress level. Analysis is carried out visually according to the standards suggested by the American Society of Echocardiography.

Image quality is graded as 'good', 'acceptable' or 'bad', and the number of diagnostic segments is reported. Segmental wall motion is classified as normokinetic, hypokinetic, akinetic or dyskinetic and assigned one to four points, respectively.

The sum of points is divided by the number of analyzed segments and yields the Wall Motion Score Index (WMSI). Normal contraction results in a wall motion score of one, a higher score is indicative of wall motion abnormalities.

During dobutamine stress with increasing doses, a lack of increase in either wall motion or systolic wall thickening is indicative of pathological findings.

6. Protocol overview

All 17 segments of the heart can be covered by a combination of 3 short axis and 1 or 2 long axis views (4-chamber and 2-chamber).

The study includes the following scans, which are all breathhold; multiphase scans at end-expiratory level (scan duration ranging from 8 to 18 sec.).

(1) Survey

(2) Single-angulated survey

(3) Double-angulated survey

(4) Short axis view: 3 slices

(5) Long-axis 2-chamber view

Scan (4) will be performed at rest and will be repeated during all dobutamine levels.

7. Patient preparation

It is of special importance to explain to the patient not only the course of the examination but also the breathhold procedure. In general, the breathhold should be performed during end expiration to ensure reproducible slice geometry and to rule out fold-over artifacts.

Patient's written informed consent must be obtained in advance.

Venous line is put into cubital vein (18 gauge).

Saline (low-flow) is injected to avoid local thrombosis.

Blood pressure and heart rate is monitored on contralateral arm.

Gadolinium 0.1mmol/kg i.v. (detection of nonviable myocardium and T1 enhancement to optimize myocardial tagging).

8. MR Imaging technique

MRI can be performed using a 1 or 1.5-Tesla MRI system (Siemens Medical Systems, Erlangen, Germany) with a standard phased array body coil. After scout views in three orthogonal directions to determine the exact heart axis, three short axis planes are acquired. The following pulse-sequences can be used (1 Tesla MR): Standard ECG-triggered segmented k-space gradient-echo imaging pulse sequence (FLASH/ TR 90 msec/ TE 6.1 msec/ α 25° / FOV 325-350 mm/ slice thickness 8 mm, / matrix 256* 256).

Cine images are acquired in the basal, mid-ventricular and apical short-axis planes. The image for the basal plane is acquired about 1.5 cm below the mitral valves.

Tagging: standard FLASH grid sequence (TR96 msec/ TE 4.4 msec/ α 15°/ FOV 325-350 mm/ Slice thickness 8 mm, continuous/ matrix 256*256). Nonselective RF-pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients were used to to achieve tag spacing of 8 mm. Cine tagging images are made of the basal and mid-ventricular segments only.

For cine imaging on a 1.5 Tesla MR, a steady-state free precession sequence with retrospective gating (True Fisp) can be used (25 phases per cardiac cycle, TR < 3 ms; TE 1.5 ms; flip angle, 60°), during breathhold of 4-8 seconds. The inplane spatial resolution is a 1.8 x 1.8 mm, with a slice thickness of 8 mm.

9. MRI Scan procedure

Look at the scout images and check if the coil is positioned well.

Scan 1

Define the plane on transversal slices parallel to the septum through the apex of the left ventricle and the coaptation point of the mitral valve.

Scan 2

Adjust the plane on the single-angulated image through the apex and the middle of the mitral valve to get an angulated long axis view. This slice orientation helps to prevent any angulation errors while planning the short axis views.

Scan 3 (short-axis views):

Make use of the double-angulated image to define 3 slices perpendicular to the long axis of the heart representing the short axis geometry.

Note: Under stress conditions even the normal heart experiences a change in its basal-to-apex dimensions due to rotational deformation.

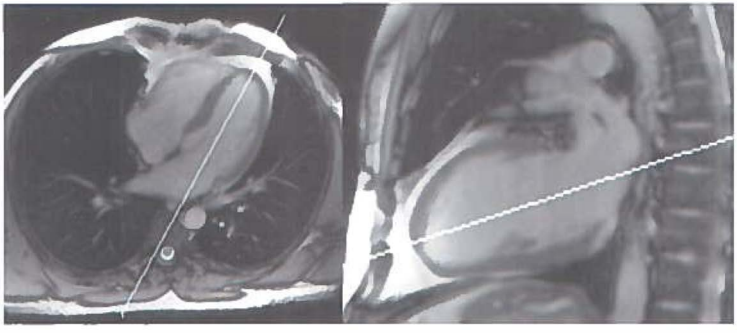
To avoid visualization of the left ventricular outflow tract at higher dobutamine levels as well as to ensure sufficient imaging of the left ventricular cavity (especially critical is the apical slice), the planning on the endsystolic images is recommended: divide the distance from the apical epicardial border to the mitral valve plane in 5 equal parts. Then, distribute the 3 short axes equally within the inner three-fifth of the distance with adaptation of slice gap.

Scan 4 (long-axis):

Plan the 4-chamber view on the equatorial short axis view; the stack should be aligned through the apex of the right ventricle and the papillary muscles. Plan the 2-chamber view on the previously acquired 4-chamber view by just switching the slice orientation and adjust the angulation (through the left ventricular apex and the coaptation point of the mitral valve).

Click through the single phases to ensure sufficient visualization of LV cavity.

Repeat scan 5 on all dobutamine levels for wall motion imaging.

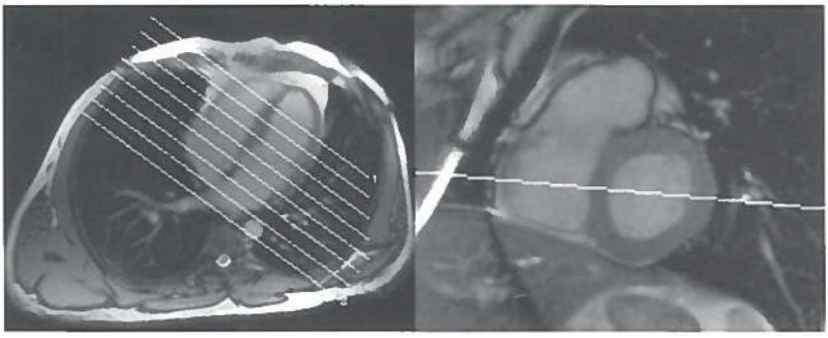


Scan 1

Transversal scout view

Scan 2

Long-axis 2 chamber view

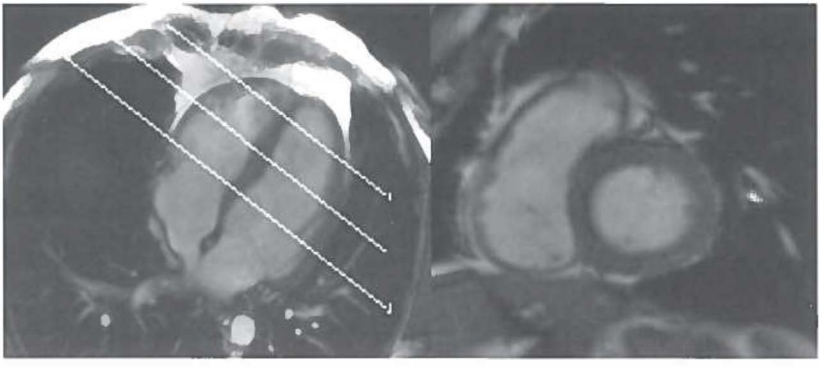


Scan 3

Angulated 4 chamber view

Scan 4

Short-axis view



Scan 5

Double angulated 4 chamber view

Scan 6

Real short-axis view

Flow chart: Dobutamine Stress MRI

SURVEY

REST CINE IMAGES

Rest Wall Motion Abnormalities?
Yes: start with 5 μg; No: start with 10 μg

Gd-IMAGES

Scans: 15-20 minutes after injection

5 or 10 μg/kg/min.

Repeat cine scans after 6 minutes infusion

20 μg/kg/min.

Repeat cine scans after 6 minutes infusion

30 μg/kg/min.

Repeat cine scans after 6 minutes infusion

40 μg/kg/min.

Repeat cine scans after 6 minutes infusion

RECOVERY

Infusion Protocol
Dobutamine Stress MRI

Dobutamine **125** mg in 50 ml NaCL

Tabel bodyweight versus dosis µg/kg/min. in ml/hr.

Dosis (µg)	Bodyweight (kg)											
	50	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**
5	6	6,6	7,2	7,8	8,4	9	9,6	10,2	10,8	11,4	12	12,6
10	12	13,2	14,4	15,6	16,8	18	19,2	20,4	21,6	22,8	24	25,2
20	24	26,4	28,8	31,2	33,6	36	38,4	40,8	43,2	45,6	48	50,4
30	36	39,6	43,2	46,8	50,4	54	57,6	61,2	64,8	68,4	72	75,6
40	48	52,8	57,6	62,4	67,2	72	76,8	81,6	86,4	91,2	96	100,8

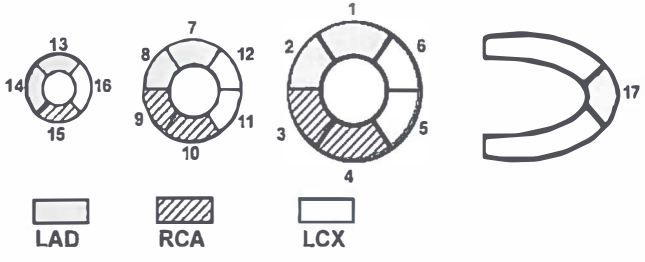
Dobutamine Stress MRI, Bronovo Hospital

Weight: **Patient ID:**
Medication: **Technician:**
MI: **Radiologist:**
PCI /CABG: **Cardiologist:**

Dosis	Time	RR	HR	Complaints / Side effects	MR series
0					
Gado					
5					
10					
20					
30					
40					

WMSI Baseline: **Viability:**

WMSI Peak Dose:
Ischemia



Chapter 4

Dobutamine Cardiovascular Magnetic Resonance.
MR Imaging Procedure, Pathophysiology and Review of Literature.

Chapter 4

Dobutamine Cardiovascular Magnetic Resonance. MR Imaging Procedure, Pathophysiology and Review of Literature.

Dirkjan Kuijpers, Caroline H.C. Janssen, Matthijs Oudkerk

Departments of Radiology, Bronovo Hospital, The Hague and University Hospital Groningen, Groningen, the Netherlands.

Published in

Imaging Decisions 2003; 7: 23-28

Abstract

Dobutamine-stress cardiovascular magnetic resonance (CMR) is a new diagnostic tool for the non-invasive detection of coronary artery disease. With technological advances, CMR has evolved to become an adequate alternative to standard cardiac stress tests such as ECG exercise stress testing, stress echocardiography and perfusion scintigraphy. Magnetic resonance imaging technology is widely available, possible in nearly every patient, and not associated with exposure to ionizing radiation. Its high reproducibility and high image quality of the anatomical features of the left ventricle and left ventricular function at rest and during stress make it an ideal technique for the comprehensive evaluation of patients with suspected coronary artery disease. Besides its ability to detect myocardial ischemia, CMR has proved to be diagnostic for myocardial viability as well. A recent technical refinement in CMR using myocardial tagging has improved the diagnostic accuracy for myocardial ischemia even further. This article reviews the pathophysiology and methodology of dobutamine stress CMR. The recent literature is discussed.

Introduction

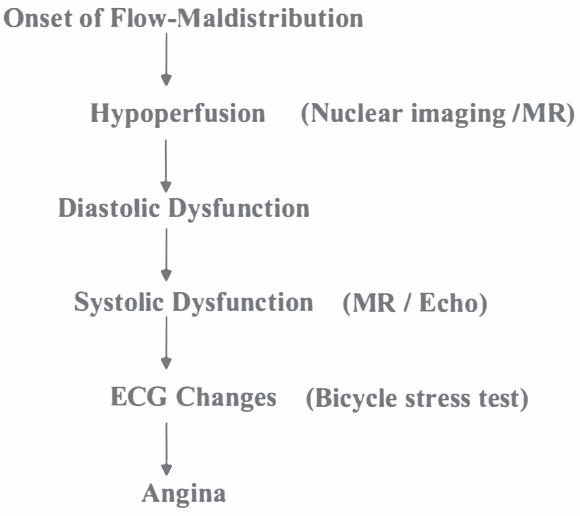
Dobutamine-stress CMR is used to identify wall motion abnormalities of the left ventricle in patients with proven or suspected coronary artery disease (1-4). The ability of CMR to visualize wall motion, especially changes in systolic wall thickening of the left ventricle, enables the detection of wall motion abnormalities, indicative for myocardial ischemia (1-4). Dobutamine-stress CMR has emerged as a highly accurate and safe diagnostic modality not only fot the assessment of myocardial ischemia, but also for the assessment of myocardial viability (5). Although exercise ECG is the most widely used noninvasive test for patients with chest pain syndromes, its sensitivity and specificity are limited (especially in women and patients with left ventricular hypertrophy), and it does not provide direct information about the localization and the extent of coronary artery disease (6,7). Dobutamine stress echocardiography is currently the preferred method for ascertaining left ventricular wall motion abnormalities (8,9). However, dobutamine stress echocardiography has several limitations. Reproducibility is poor and the examination yields no diagnostic information in up to 15% of patients because of an inadequate acoustic window in obese patients (10,11). The weakness of stress echocardiography is also that its use by the occasional user may be attended with loss of accuracy (12). The first study to report the application of dobutamine stress CMR was that of Pennell and coworkers (1). Subsequently, additional low-dose (13-15) and high dose (2-4) dobutamine stress CMR studies have been reported. Recently, the use of high-dose dobutamine CMR in combination with the myocardial tagging technique has been reported, with excellent diagnostic results.

The use of this new technique and the clinical applications are discussed.

Pathophysiology

Pharmacological exercise normally provokes an increase of regional wall motion and thickening, with an increment of ejection faction of the left ventricle caused by a reduction of systolic dimensions. Regional systolic dysfunction is usually caused by coronary artery disease, however cardiomyopathies may show regional wall motion abnormalities as well. The presence of resting wall motion abnormalities is mostly the result of prior myocardial infarction, which could be viable or non-viable myocardial tissue. Residual viable tissue is more common in hypokinetic than akinetic myocardial segments. In the ischemic cascade (Figure 1), regional systolic changes generally precede ECG changes and chest pain but follow the onset of malperfusion and changes in diastolic function. Myocardial ischemia can be defined as a new or worsening wall motion abnormality in at least two segments at consecutive planes of the left ventricle. The presence of inducible wall motion abnormalities implies a significant limitation of blood flow at peak stress, and corresponds to a coronary artery stenosis of >50% diameter. In case of a relatively mild coronary artery stenosis the provocation of ischemia depends on the performance of maximal stress. Inducible wall motion abnormalities recover rapidly after peak stress, but may be persistent if ischemia is severe and stunning is induced (12).

Figure 1. **Ischemic cascade**



Methodology

Cardiac Stress Testing

The primary indication for pharmacological stress is the inability to exercise or to identify viable myocardium. Dobutamine is a beta-agonist and the most commonly used pharmacological stressor up to a peak dose of 40 μg/kg/min. Dobutamine increases myocardial oxygen consumption through increments in inotropic state, heart rate and blood pressure. Dobutamine is competitively antagonized by beta blockers and well suited to analyze wall motion and global ventricular studies, where myocardial ischemia is more reliable provoked by increased myocardial

oxygen demand. In our institution dobutamine-stress CMR is performed in patients with an inconclusive diagnosis of myocardial ischemia by means of history, ECG-recording at rest or during bicycle exercise test. Currently, in our hospital 50% of the patients with an exercise ECG stress test have an inconclusive result. We do not perform stress echocardiography or perfusion scintigraphy in these patients, but examine them directly with dobutamine-stress CMR. Contra-indications for dobutamine stress CMR are: patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120 mmHg), complex cardiac arrhythmias, MRI-incompatible metallic implants or known claustrophobia.

Anti-Anginal Medication, Atropine and Infusion Time

To ensure cardial response to dobutamine, anti-anginal medication is stopped one to four days prior to the dobutamine-stress CMR examination (2-4). In many cardiac stress centers, atropine is given to increase heart rate in patients who fail to reach the target-rate. In the study of Kuijpers et al. (4) all anti-anginal medication was stopped four days prior to the stress test, infusion time of dobutamine was prolonged from three to six minutes and no atropine was given. The target-heart-rate rule, which forms the basis of applying this drug (target rate 85% of maximum; men 220 minus age / women 200 minus age), was not applied in that study. It is known that the addition of atropine can enhance sensitivity to detect coronary artery disease (16). However, the target-rate rule has been questioned in several reports (17-19). The peak rate-pressure product in the study of Kuijpers et al. (4) was similar to that reported by others (2),

which indicated that in that study the same stress level was reached at the end of the test. Because of the side effects of atropine, patients are unable to drive a car after the study, which is a disadvantage for an outpatient procedure. So, to obviate the need for atropine and to obtain an adequate response to dobutamine, the infusion time of each dose of dobutamine was prolonged, from three to six minutes (4).

Both approaches have their advocates and until now there is no clear consensus, which probably indicates that both approaches will function in daily practice.

CMR Imaging Protocol

Before the patient enters the MR suite, the presence of an acute coronary syndrome is ruled out by a physician. After the patient is positioned on the MR scanning table, intravenous access is established via an antecubital vein. At present, in our institution we start with a 0.05 mmol/kg intravenous injection of gadolinium to detect nonviable myocardium and to optimize imaging contrast for myocardial tagging. Imaging of the contrast-enhanced myocardium of the left ventricle takes place about 20 minutes after the injection of gadolinium. ECG monitoring leads, a phased-array surface coil covering the heart and a brachial blood pressure cuff is applied. The entire procedure, including positioning and ECG monitoring takes 10-15 minutes per patient. A single-lead ECG is continuously monitored on the MRI console. Systolic and diastolic blood pressures are recorded, using an automatic device (Welch-Allyn, Emro-medical), at baseline and every three minutes throughout the procedure. Blood pressure and heart frequency are recorded throughout the study by technicians.

After acquisitions at rest, dobutamine is infused intravenously using a digital pump injector situated outside the scanner room. In case an evident wall motion abnormality is detected at rest, infusion is started at 5 μg/kg/min, after which the dobutamine dose is increased to 10, 20, 30, and 40 μg/kg/min. If no wall motion abnormality is detected at baseline (rest) the study is started at 10 μg/kg/min. In the study of Kuijpers et al. (4) imaging began six minutes after each dose increase, and required three minutes per dose increase. Imaging consisted of acquiring three short-axis cine images (basal, mid-ventricular and apical) without and two short-axis cine images (basal and mid-ventricular) with myocardial tagging. Long-axis images were acquired when additional information was needed about a regional wall motion abnormality at the apex of the left ventricle. Other studies (2,3) use three minutes per dose increase, which limits the length of the study significantly.
During the infusion of dobutamine the radiologist and cardiologist are present in the MR suite, to monitor the condition of the patient and to evaluate the images directly. A physician trained in cardiovascular emergencies (ventricular fibrillation) and resuscitation needs to be at the scanner. In our experience, it is advisable to test safety and emergency procedures regularly, together with the MR technicians.

Dobutamine Termination Criteria

Criteria for ending the dobutamine-CMR examinations are:

1. Development of new wall motion abnormalities indicative for myocardial ischemia,

2. Fall of systolic blood-pressure of > 40 mm Hg,

3. Marked hypertension > 240/120 mm Hg,
4. Severe chest pain,
5. Ventricular arrhythmias, and
6. Intolerable side effects of dobutamine (nausea, vomiting).

CMR Imaging Technique

For the assessment of wall motion, cine-imaging of the heart is required with gradient-echo or segmented *k*-space turbo-gradient-echo sequences. Faster image acquisition is possible by the use of echo planner imaging, which allows either reduced scan time or improved temporal resolution. Most of the studies reported use 1.5 T magnetic resonance systems, but other field strengths are used as well. In the tagging study (4), CMR was performed using a standard 1-T MR system. An ECG-triggered segmented gradient-echo pulse sequence was used: FLASH/TR: 90msec; TE: 6.1msec; α: 25°; FOV: 325-350mm; Slice-thickness 8mm; and Matrix 256x256. Tagging was performed using a standard FLASH grid-sequence: TR: 96msec; TE: 4.4msec; α: 15°; FOV 325-350 mm; Slice-thickness 8mm and Matrix 256x256. 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. Each cine breath-hold acquisition took 15-19 heartbeats, and was made in maximum inspiration. If the heart rate reached 100 beats per minute, the number of phases per acquisition was decreased to optimize temporal resolution. The lack of temporal resolution is a disadvantage of 1 T MR systems. The use of a higher field strength increases temporal resolution, and

even a further reduction of acquisition time is possible with real-time imaging (20). However, until now only limited data on real-time imaging are available.

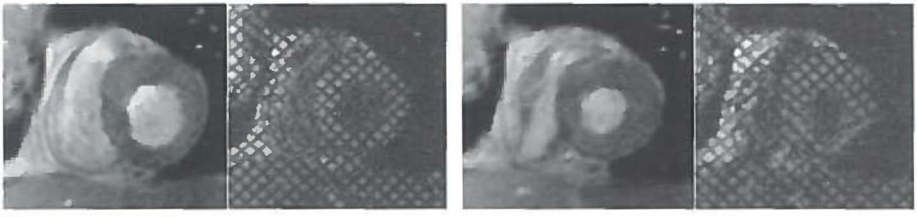
Myocardial Tagging

Myocardial tagging is an imaging method that uses a sequence of radio-frequency pulses to presaturate thin planes of the myocardium just prior to imaging. These 'tags' persist in the myocardial wall during the heart cycle and can be used to analyze the wall motion of the left ventricle by acquiring images perpendicular to the tagging planes. In the study of Kuijpers et al. (4) tagging was performed with a standard FLASH grid sequence. Nonselective radiofrequency pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients were used to achieve tag spacing of 8 mm. This technique is the most frequently used tagging sequence for CMR, which generates two orthogonal sets of parallel planes of magnetic saturation (grid-tagging) by a sequence of nonselective radiofrequency pulses (21). The quantitative harmonic-phase tagged image processing method is based on the use of isolated spectral peaks in SPAMM-tagged MR images (22). Until now, quantitative assessment of myocardial strains in a single slice has taken a few minutes, which makes it almost applicable for wall motion analysis during the stress study. The additional value of quantitative analysis in the diagnosis of myocardial ischemia is probably limited, because the semiquantitative method has already shown excellent results (2-4). In the future, quantitative tagging analysis may be an important adjunct of the standard semiqualitative breath-hold technique, perhaps in combination with real-time imaging as well.

Interpretation of CMR Cine-Images

Gradient-echo MR images provide high natural contrast between flowing blood and the myocardium, as well as between the myocardium and the surrounding structures. These signals allow a reliable delineation of the endo- and epicardial border. Until now, interpretation of the cine-images has occurred qualitatively, according to the (new) guidelines of the American Heart Association (23). Short-axis images are divided into multiple segments, with six segments in the basal and midventricular and four segments in the apical image. According to the new guidelines 17 instead of 16 segments can be assigned to the left ventricle. An additional segment is added at the apex of the vertical long axis of the left ventricle, to optimize analysis of wall motion abnormalities in this area. All the images can be scored using a four-point scale, in accordance with these guidelines: Per segment, wall motion is graded as 1 (normal or hyperkinesia), 2 (hypokinesia), 3 (akinesia), and 4 (dyskinesia). The wall motion score index (WMSI) is derived from the mean score of all segments (n=17) of all images. If wall motion abnormalities are already observed at rest and improve during low-dose dobutamine stress but worsen during peak-stress, then these wall motion abnormality are considered diagnostic of inducible myocardial ischemia. All dobutamine-CMR images are magnified (2x) and displayed as continuous cine loops on high-resolution grey-scale monitors. The cine-images are analyzed directly after each series of images during the examination to rule out new or worsening wall motion abnormalities, indicative of myocardial ischemia.

Figure 2 and 3 shows two patients with chronic airway disease and inability to perform a bicycle exercise stress test. Figure 2d shows preservation of tagging lines at the anterial wall of the left ventricle. There is akinesia of three segments: septal, anterior-septal, and anterior; which indicate myocardial ischemia. Coronary angiography shows a significant stenosis in the left anterior descending coronary artery. The tagging images clearly depict the wall motion abnormality at the anterior wall. Figure 3 shows a matching ischemia at 20 and 30 μg between non-tagged and tagged images of the septal wall on the basal and midventricular short-axis planes of the left ventricle.



A B C D

Figure 2.

Short-axis basal views at baseline (rest) and peak dose dobutamine (40 μg), before and after tagging. Figure 2a (without tagging) and Figure 2b (with tagging) shows a diastolic-phase of a normal left ventricle at rest. Figure 2c shows an early systolic-phase of the same left ventricle at peak-dose dobutamine. The wall contraction pattern (wall-thickening) appears to be normal.

Figure 2d same phase as figure 2c. Preservation of tagging lines at the anterial wall of the left ventricle. There is an akinesia of three segments: septal; anterior-septal; anterior; which indicate myocardial ischemia. Coronary angiography showed a significant stenosis in the left anterior descending coronary artery.

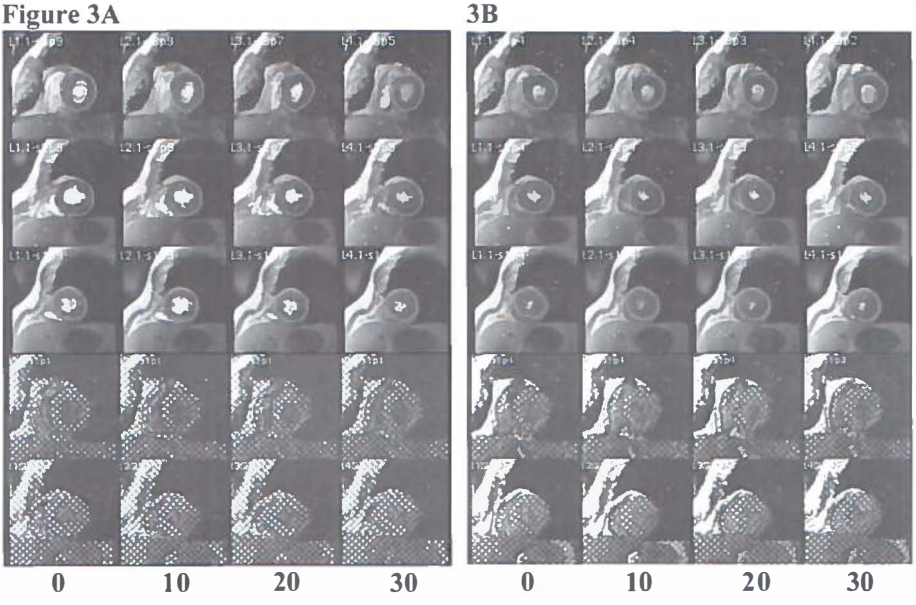


Figure 3.

Overview of dobutamine-CMR images during diastole (figure 3a) and systole (figure 3b). On the x-as the dobutamine levels: 0 (baseline), 10, 20 and 30 μg dobutamine.

On the y-ax the short-axis planes of grid-tagged images (basal and midventricular plane) and non-tagged images (basal, midventricular and apical plane). At 20 and 30 μg dobutamine there is matching ischemia between non-tagged and tagged images of the inferior and septal wall on the basal and midventricular short-axis planes of the left ventricle.

Dobutamine CMR in the literature

Several reports have described the use of high-dose dobutamine CMR for the detection of coronary artery disease (2-4). In a recent study, 211 consecutive patients with chest pain and an inconclusive diagnosis of myocardial ischemia underwent high-dose dobutamine CMR with the use of myocardial tagging, which was successfully performed in 194 patients (4). In this study, dobutamine CMR without tagging detected new wall motion abnormalities in 58 patients, while with myocardial tagging 10 additional patients were detected. Coronary angiography showed coronary artery disease in 65 (96%) of these 68 patients. This study demonstrates that the use of myocardial tagging with high-dose dobutamine CMR is a specific diagnostic technique in the analysis of ischemic heart disease. These data show that 96% of the patients with inducible new wall motion abnormalities had significant coronary artery disease. Two other studies have reported results of dobutamine-CMR (6,7), but no myocardial tagging was used. Nagel et al. (6) compared dobutamine CMR and dobutamine stress echocardiography in 172 patients referred for coronary angiography. Dobutamine CMR provided better sensitivity (86% vs. 74%) and specificity figures (86% vs. 70%) for the detection of new wall motion abnormalities compared to stress echo cardiography.

For both tests, 18 patients could not be examined. For echo, the main reason was poor image quality, and for CMR, claustrophobia and obesity were the main problems. The image quality of CMR was demonstrated to be a major issue in the confidence of interpretation of stress testing in general. This issue was further validated by Hundley et al. (7) who reported the use of dobutamine CMR in patients who failed dobutamine stress echocardiography, and showed a sensitivity and specificity of 83% each.

These data can be compared with the data of the traditional stress tests, such as stress echocardiography and myocardial perfusion scintigraphy. Recently, a pooled analysis was reported of 17 direct comparison studies (stress echocardiography vs. perfusion imaging) with different stressors (nine studies with dobutamine) (24). Pooling of the data of 1405 patients showed an overall sensitivity of 80% for stress echocardiography and 84% for perfusion imaging; the specificity was 86% and 77%, respectively. Perfusion imaging showed a lower accuracy, especially in women and patients with hypertension. These data are comparable with the reported data of standard high-dose dobutamine stress CMR tests. However, the additional use of myocardial tagging increased the number of positive dobutamine CMR studies with 17% in the study of Kuijpers et al. (4). The addition of myocardial tagging to high dose dobutamine stress CMR increases diagnostic accuracy, as it simplifies interpretation of the images. Technical refinements in myocardial tagging and further improvements in spatial and temporal resolution will determine future development of this new diagnostic tool.

Conclusions

Dobutamine CMR using myocardial tagging is a promising new diagnostic tool in the initial assessment of patients suspected of myocardial ischemia. Follow-up studies are needed to evaluate the prognostic value and safety of this imaging technique.

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Chapter 5

Dobutamine Stress Magnetic Resonance Imaging (DS-MRI): A valuable method in the noninvasive diagnosis of ischemic heart disease. Pilot study of the first 100 patients, including a Multi Case Report

Chapter 5

Dobutamine Stress Magnetic Resonance Imaging (DS-MRI): A valuable method in the noninvasive diagnosis of ischemic heart disease.
Pilot study of the first 100 patients, including a Multi Case Report

Co-authors

P.R.M. van Dijkman, B.M. Blom, G. van Herpen.

Departments of Cardiology and Radiology, Bronovo Hospital, The Hague
Department of Medical Informatics, Erasmus University,
Rotterdam, the Netherlands.

Partly published in

J Electrocardiol 2002; 35: 57-59

Abstract

We assessed the clinical applicability of dobutamine stress magnetic resonance imaging (DS-MRI) for the detection of myocardial ischemia and myocardial viability. One hundred patients with suspected coronary artery disease and inconclusive exercise electrocardiography or significant repolarization abnormalities on the resting ECG underwent breath hold DS-MRI (1 Tesla), 4 days after cessation of anti-ischemic medication. Three left ventricular short axis planes were imaged at increasing doses of dobutamine. Recovery of wall thickening in a previously diminished or non contracting segment at low dose dobutamine was considered proof of viability. Development of hypo-, a- or dyskinesia at higher doses of dobutamine was taken to indicate ischemia. If the DS-MRI test was positive for ischemia, coronary angiography was performed. If indicated, this was followed by revascularization. If DS-MRI did not demonstrate ischemia, neither angiography nor revascularization was carried out. Ninety five DS-MRI investigations were available for diagnosis. Forty two patients had DS-MRI scans positive for ischemia and subsequently coronary angiography assessment of the clinical applicability of DS-MRI for the detection of myocardial ischemia was performed. One patient was false-positive. All 53 patients with non-ischemic DS-MRI scans had follow-up for 11-23 months (mean 17 months). One patient died suddenly 2 weeks after the MRI-test. The other 52 patients did not experience any coronary event nor sudden cardiac death. The predictive value of a positive (for ischemia) DS-MRI test is 98% and the predictive value of a negative DS-MRI test is also 98%.

CHAPTER 5

Introduction

It is part of a cardiologist's daily work to determine whether a patient complaining of discomfort to the chest suffers from coronary artery disease. In addition, coronary insufficiency may have to be identified as the cause of e.g. heart failure or rhythm disturbances in patients without chest complaints.

Good history taking and thorough physical examination will always be the fundamental tools of the medical craft and the standard electrocardiogram (ECG) still remains the most indispensable technique of cardiology, a century after Einthoven's epochal publication of a high quality ECG obtained with his string galvanometer in 1902 (1,2). In the words of Elena B. Sgarbossa and Galen Wagner (3) in their excellent chapter on Electrocardiography in Topol's Textbook of Cardiovascular Medicine: "Although technological advancement will continue to provide more sophisticated noninvasive diagnostic techniques, the ECG will remain one of the most important tests for evaluating cardiac patients. Continuing research to improve resolution will enhance analysis techniques. Medical education needs to continue to emphasize the value of the ECG and provide adequate practice in ECG diagnosis".

Functional testing is often necessary for the evaluation of myocardial ischemia. Exercise ECG on bicycle or treadmill is the most widely applied test for this purpose. In the USA the yearly consumption of this test is in the range of six to eight million. The method has its limitations and imperfections. Its sensitivity is reported to be 68% at a specificity of 77% on the average (4) with a tendency to overdiagnosis in women. The test fails or is unreliable if the repolarization in the

resting ECG is abnormal, such as in bundle branch block, left ventricular hypertrophy or previous infarct. In a certain proportion of cases the target load cannot be achieved because of respiratory, neurological, orthopedic or peripheral arterial limitations, or simply from lack of physical skill of the patient. Also, the test hardly allows one to assess the distribution and severity of coronary lesions and, finally, it does not inform about the viability of ischemically compromised myocardial tissue.

Electrocardiographic changes may be brought about by ischemia provoking procedures but they are not the first effects to appear. In the so-called ischemic cascade, failure of contractile power precedes the electrocardiographic events and the occurrence of angina pectoris. Loss of contraction is the earliest and most sensitive indicator of myocardial ischemia and can be observed by echocardiography or magnetic resonance imaging (MRI) under stress. Physical exercise is possible with echocardiography but mostly pharmacological stimulation is applied, using dipyridamole, adenosine or dobutamine. We report here on our results with dobutamine stress MRI (DS-MRI).

Technique

MRI was performed using a 1 Tesla MR system (Impact/Expert Siemens Erlangen, Germany) with a standard phased array body coil. Echo time (TE) was 6.1 ms, repetition time (TR) 90-110 ms, flip angle 20°-25°, matrix 256 and field of view 350. Slice thickness is 8 mm. The so-called breath holding technique was applied. Three ECG gated short axis cross sections were made through the left ventricle

(LV) at the basal, midventricular and apical levels. In these cross sections the drainage areas of the 3 main coronary arteries were visualized. Anti-ischemic medication must have been discontinued 4 days prior to the investigation. Patients with serious hypertension (>220/120 mmHg) were excluded. Also, with the presently available technique, atrial fibrillation makes the examination impracticable and patients with ferromagnetic implants must be refused. After base line images have been obtained dobutamine is administered in increasing doses, starting at 10 μg/kg/min and raised every 6 min by 10 μg to 20, 30 and ultimately 40 μg/kg/min. If wall motion abnormalities were present in the baseline recordings, the initial dosage was 5 μg/kg/min. The ECG was continuously monitored and blood pressure taken every 3 min. The total duration of the procedure was a maximum of 50 minutes. Systolic thickening of the wall of the LV is observed in 16 segments during the whole procedure. Contractility was graded as normal or hyperkinetic, hypokinetic, akinetic or dyskinetic by two independent observers. In the images normal contractility was characterized by uniform, concentric inward movement of the myocardial wall. Improved contractility in an area with wall motion abnormality in the base line recording was taken to indicate viability of the compromised myocardium involved. A test was considered positive for myocardial ischemia if wall motion was seen to decrease or stop in at least 2 cross sectional segments of the same coronary drainage area. In patients with abnormal DS-MRI, suspected of viability and/or ischemia, coronary angiography (CAG) was performed within 3 weeks after the MRI study. A significant coronary lesion was defined as a narrowing of >50%. The decision for balloon angioplasty (PTCA) or coronary bypass surgery (CABG) was made in the regular consultations with the cardiac surgeons and interventional cardiologists.

Patients with a non-ischemic DS-MRI were not catheterized and were only followed up. It should be noted that "nonischemic" does not at all have to mean "normal". If there is loss of wall motion in the base line MRI without signs of viability and without further loss of contractility during the investigation there is no inducible ischemia.

Material and Methods

The number of patients presented for the study was 100, of whom 62 male and 38 female, age 62 ±12 years. The reason for presentation was suspicion of coronary ischemia while the ECG exercise test was inconclusive or the resting ECG showed significant repolarization abnormalities precluding correct interpretation of the exercise ECG. The examination was unsuccessful in 5 cases for reasons of insufficient breath-hold technique in 2 patients, nausea in 1, hypotension > 40 mmHg in 1 and medication not stopped in 1 patient.

Results

Of the 95 cases available for evaluation 42 were classified as suspect for myocardial ischemia. In 7 patients with resting wall motion abnormalities myocardial viability could be identified during low dose dobutamine. Significant coronary artery disease was demonstrated by CAG in 41, followed by revascularization in 38 (22 PTCA, 16 CABG, in 3 revascularization proved not feasible). In 1 case, therefore, MRI misdiagnosed (LBBB with abnormal septal motion). The positive predictive value (PPV) was thus 41/42 = 98%. The 53

non-ischemic cases were followed up for a period of between 11 and 25 months, 17 months on average. During the observation period, only 1 person encountered cardiac problems (asystoly in hospital in one patient with ischemic myopathy). This yields a negative predictive value (NPV) of 52/53 = 98%.

Discussion

Exercise ECG as a simple and inexpensive non-invasive method of investigation will retain its well-deserved place in diagnostic cardiology. Its limitations have been described above. Both stress echocardiography and DS-MRI give more insight in the functional condition of the myocardium. Echocardiography has some drawbacks: it demands high professional quality of the investigator and acceptable echogenic quality of the patient. DS-MRI, in contrast, does not require high manual skill of the investigator and is not dependent on the physical properties of the patient. Nevertheless, DS-MRI also cannot always be carried out, as pointed out before. In a comparison between stress echocardiography and DS-MRI by Nagel et al. (5) on 172 patients DS-MRI had both a sensitivity and specificity of 86% with respect to CAG and scored better than echocardiography. In a study by Hundly et al. (6) in 153 patients who were entirely inaccessible for echocardiography excellent MRI images could be produced. Sensitivity and specificity were both 83% with respect to CAG. Alternative methods of functional investigation of the myocardium make use of isotope preparations, SPECT-perfusion scintigraphy employing thallium-201 or technetium-99m and PET-perfusion scintigraphy using rubidium. Stress can be physical exercise or administration of the same pharmacological agents as in DS-MRI. By neither

method is information obtained about viability of myocardial tissue although this shortcoming might be removed by the advent of F18-fluorodeoxyglucose, a marker of glucose metabolism.

Among these various non-invasive methods for the detection of coronary insufficiency DS-MRI seems to be of much promise. In our study, still limited in size, it was proven to have high diagnostic accuracy, so that the next, invasive step of coronary angiography can be more deliberately made, or avoided. Grid-tagging is a feature that when addd to to DS-MRI is likely to further improve its diagnostic power (7). Stronger magnetic fields may take for prettier pictures but are not necessary for acceptable diagnosis.The number of examined cases, also using the grid-tagging technique, is expanding steadily, but before reporting a reasonable (although admittedly arbitrary) observation, more time and study are necessary; whereas sensitivity can be assessed by coronary angiography, such intervention was not deemed justified in our DS-MRI negative patients. Specificity is, therefore gauged against the non-occurrence of a cardiac event during follow-up.

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Multi Case Report

(Published in: Neth Heart J 2003; 11:84-8).

ABSTRACT

We report 3 patients in whom dobutamine stress magnetic imaging (DS-MRI) was essential in assessing myocardial ischemia. Two patients were referred to the cardiologist because of chest pain. Patient A had typical exertional angina and a normal resting electrocardiogram (ECG). Patient B had typical exercise induced angina and had recently experienced an attack of severe chest pain at rest for 15 minutes. The ECG showed a complete left bundle branch block (LBBB). Patient C was referred for heart failure of unknown origin. There were no complaints of chest pain during rest or exercise. Echocardiography in this patient demonstrated global left ventricular (LV) dilatation, systolic dysfunction and a small dyskinetic segment in the inferior wall. In all those patients exercise stress testing had failed to demonstrate myocardial ischemia. Patient A and C produced normal findings whereas in patient B the abnormal repolarisation due to pre-existent LBBB precluded a diagnosis of ischemia.

Breath-hold DS-MRI was performed to study LV wall motion and wall thickening at rest through increasing doses of dobutamine. A test was considered positive for myocardial ischemia if wall motion abnormalities developed at high dose levels of the drug (20 μg/kg/min or more with a maximum of 40 μg/kg/min) in previously normal vascular territories or worsened in a segment that was normal at baseline. Recovery of wall thickening in a previously hypo- or akinetic segment at a low

dose level of dobutamine (5-10 μg/kg/min) was taken as proof of viability.

Patients A and B developed hypokinesia progressing into akinesia at high dose dobutamine in the anteroseptal area of the LV indicative of ischemia. These findings were corroborated by coronary angiography demonstrating severe coronary artery disease which led to coronary artery bypass grafting (CABG) in patient A and balloon angioplasty in patient B. In patient C global recovery of LV contractions during low dose dobutamine was followed by hypokinesia in the inferoseptal area during high dose dobutamine. This biphasic response indicates myocardial viability as well as ischemia. CABG was carried out because of multiple stenoses in the left coronary artery. Postoperatively LV function normalised.

DS-MRI is a valuable method for detecting myocardial ischemia and viability in patients with suspected coronary artery, and can be applied in every hospital which has MRI equipment at its disposal.

Patients

In this multiple case report we present 3 patients in whom DS-MRI served to elucidate different ischemic cardiac problems without the need to use other approved imaging techniques.

Patient A is a 68-year old man who was referred by his family doctor because he had been experiencing chest pain over the past 3 months, occurring during physical exercise but not at rest. This limited his daily activities, notwithstanding

treatment with atenolol and amlodipin. Hypertension had been found previously, and some years before he had undergone a cardiological examination because of atypical precordial symptoms. No abnormalities were found at the time and the symptoms soon disappeared. Physical examination revealed nothing remarkable and the blood pressure was 150/90 mmHg. The resting ECG was normal. Bicycle ergometry test showed normal (100%) validity with adequate rise in blood pressure and heart rate. Neither angina pectoris nor ST-segment depression occurred during exercise. In view of the discrepancy between the typical symptoms and the normal findings at bicycle ergometry, we proceeded to DS-MRI. At a dose of 20 μg/kg/min retrosternal pressure appeared. After 30 μg/kg/min dobutamine the examination was terminated. Before dobutamine wall movements were normal in all segments. At 20 μg/kg/min hypokinesia set in, followed by akinesia of the anteroseptal and midseptal regions of the LV wall, characteristic of ischemia of the RDA supply area. Coronary angiography (CAG) thereupon demonstrated a 90 % stenosis in the RCA, a 70 % stenosis of the left main stem, i.e. proximal to its branching into RDA and RCx, and a 70 % stenosis in the RCx. Emergency coronary artery bypass grafting (CABG) was performed in which the left internal mammary artery was anastomosed to the RDA and a venous jump graft connected to the RCx and the posterior descending branch of the RCA.

Patient B is a 62-year old woman with no previous cardiac history. She was referred to the cardiologist because of symptoms of retrosternal pressure for 4 months, increasing in duration and frequency over the last few weeks.

The symptoms were typical of exercise induced angina pectoris. Two months before her visit she had had a single severe attack of pressure on the chest at rest accompanied by perspiration, which disappeared spontaneously after 15 minutes. The family history was positive for cardiovascular disease at a relatively young age. Physical examination did not reveal significant abnormalities and the blood pressure was 160/80 mmHg. The ECG showed regular sinus rhythm with a complete left bundle branch block (LBBB). Because of the repolarisation disturbances already present at rest in this condition an exercise ECG is not useful. Therefore DS-MRI was carried out. On the initial images, without dobutamine, the inferior wall appeared thin <5½ mm with akinesia, indicative of an old infarct in the supply area of the RCA (fig. 1a). The other wall segments showed good contractions. During dobutamine administration the heart rate rose from 77/min to 131/min, the blood pressure to 190/85 mmHg. From a level of 30 μg/kg/min onwards she experienced the familiar retrosternal pressure. On the MR images, hypokinesia became visible at a dose of 20 μg/kg/min, followed by akinesia, in the midanteroseptal segment, the drainage region of the RDA (fig. 1b and 1c). The inferior wall did not change its movement pattern.

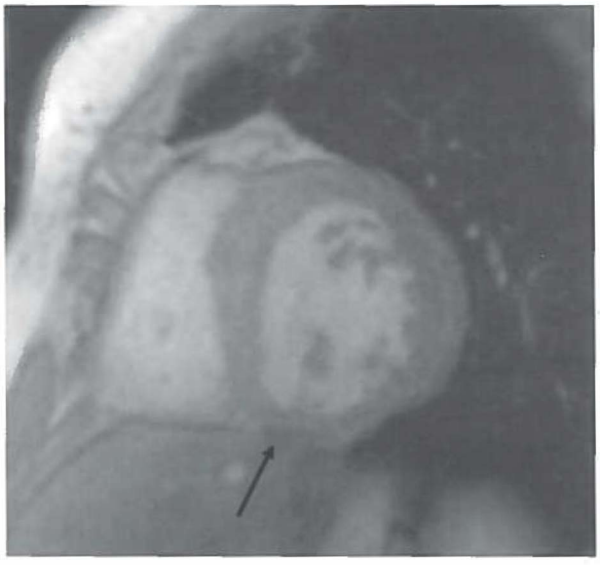

Figure 1

Enddiastolic basal short axis MR image (a) of patient B; thinning of the inferior wall (arrow) is visible because of a myocardial infarction in the past.

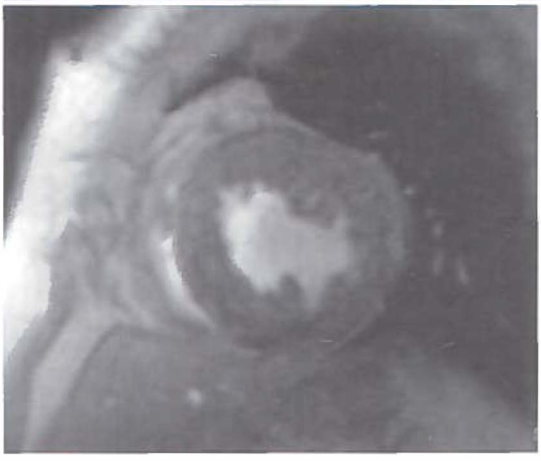

Figure 1B

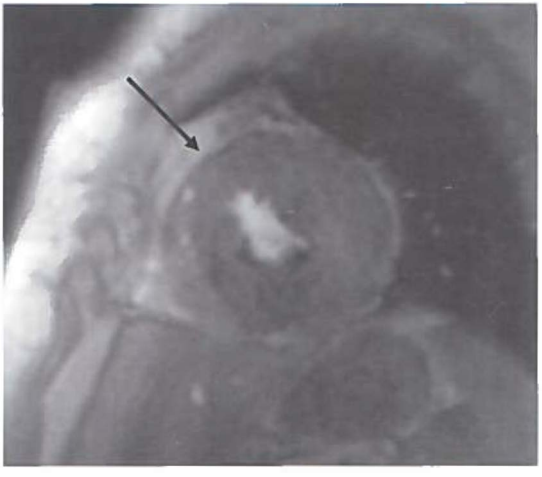

Figure 1C

Endsystolic midventricular MR images of patient B before (b) and during (c) infusion of dobutamine (40 μg/kg/min). Akinesia of the anteroseptal wall (arrow) develops during high dose dobutamine because of ischemia in the territory of the ramus descendens anterior.

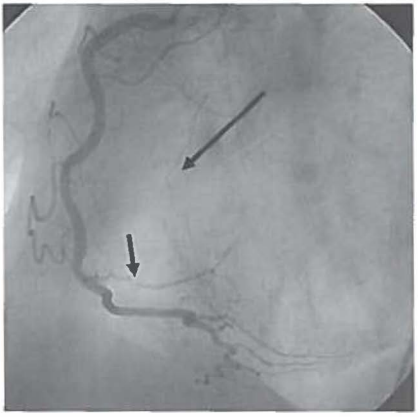

Figure 2A

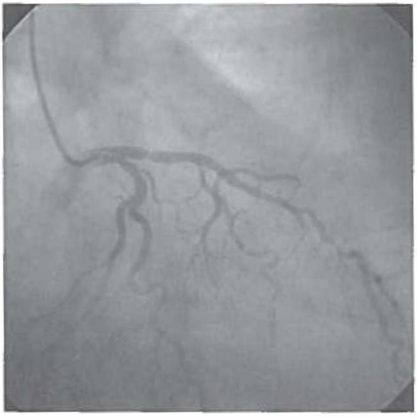

Figure 2B

During visualisation of the right coronary artery (A) an occlusion of the posterolateral branch (short arrow) was seen, responsible for the inferior wall infarction, in combination with retrograde filling of the ramus descendens anterior of the left coronary artery (long arrow).

In the left coronary artery (B) 2 severe stenoses are visible in the ramus descendens anterior.

These findings were reason for performing CAG. The posterolateral branch of the RCA was found occluded in addition to 2 serious stenoses in the RDA (fig.2). The LV angiogram showed the inferior wall to be akinetic. Percutaneous transluminal coronary angioplasty of the 2 stenoses in the RDA, with stent implantation in the proximal one was successfully performed. The patient was then free of symptoms. The RCA had been left untreated because of the lack of viability in the myocardium supplied by this vessel.

Patient C is a 74-year old man, who lives in Australia for the greater part of the year. He was referred because of cardiac decompensation. His previous history was uneventful. Symptoms of exertional dyspnoea began in connection to a cold and a long air trip from Australia. He did not experience retrosternal pressure. The chest X-ray revealed an enlarged heart and pulmonary congestion with Kerley-B lines. After treatment by the family doctor with furosemide and enalapril his shortness of breath had disappeared and he felt his usual self again. On physical examination in our outpatient clinic his blood pressure was 145/100 mmHg. There were no signs of overfilling and normal heart sounds without murmurs were heard. The resting ECG was normal. Bicycle ergometry resulted in normal exercise validity (100%) with adequately rising blood pressure and heart rate. Anginal complaints and ST-segment depression remained absent. The echocardiographic examination showed a somewhat diminished LV function with a small dyskinetic region proximally in the inferior wall. The end-diastolic internal diameter of the LV measured 64 mm, the end-systolic diameter 48 mm, exceeding the normal limits of 60 and 35 mm, respectively, as measured on the two-dimensional scan.

Considering his satisfying reaction to treatment and his impending return to Australia the examination was not extended. A year later he was again sent in to the outpatient clinic because of recurrence of pulmonary congestion, again following a long flight from Australia. Like the first time, he did not experience retrosternal pressure. On the echocardiogram the same small dyskinetic segment was visible in the proximal inferior wall. The end-diastolic internal diameter of the LV, however, now measured 67 mm, the systolic diameter 58 mm, constituting a further dilatation of the left ventricle with marked deterioration of its systolic function. The analysis was thereupon expanded by DS-MRI. Before dobutamine the overall LV function was seen to be diminished, with dyskinesia of the inferior wall. At dose levels of 5 and 10 μg/kg/min improvement of LV contractions was evident in all segments. Even at the highest dobutamine dosage of 40 μg/kg/min the patient did not report any chest discomfort. At 30 μg/kg/min hypokinesia of the inferoseptal wall set in. Thus, we are dealing here with a biphasic reaction indicative of both viability and ischemia. CAG demonstrated severe two-vessel coronary artery disease, including a 70 % stenosis of the RDA, an 80 % stenosis of the first diagonal branch and two 90 % stenoses of the dominant RCx. These lesions were held responsible for the episodes of cardiac decompensation. Subsequently CABG was carried out in which a single venous graft was connected to the RDA and a venous jump graft to the first diagonal branch of the RDA and the obtuse marginal branch of the RCx. Implantation of an internal mammary artery proved technically infeasible. A short time afterwards the patiënt again left for Australia. A year later when back in the Netherlands he was again seen in our outpatient clinic.

He was doing well and functioning normally. Air travel this time had not resulted in decompensation. On the echocardiogram the LV function appeared improved. The small dyskinetic area in the inferior wall was still present but the LV dimension had normalised to end-diastolic 59 mm and end-systolic 41 mm.

Discussion

The 3 patients described demonstrate the varying manifestation patterns of ischemic heart disease and the diagnostic problems with which the cardiologist is faced. Before deciding to perform invasive treatment convincing proof must be obtained that the symptoms are of ischemic nature (2).

Patient A presented the problem of a normal ergometric examination while his history was that of typical angina. A diagnosis of angina pectoris is made in the presence of 3 symptoms: 1. symptoms of chest pain provoked by exertion, cold, wind or emotion; 2. disappearance of the symptoms at rest; and 3. their disappearance within minutes after taking sublingual nitroglycerin. On the basis of history, age and sex the prior probability of coronary artery disease can be assessed. The indication for exercise ECG must be related to this prior probability (3). In addition the ECG at rest should preferably be normal for a reliable analysis of the ST-segments during exercise. The test will not yield useful information if the prior probability is low (<20 %), because its less than perfect specificity will produce a high proportion of false positive predictions, whereas in the case of high prior probability there is little extra information to be gained by the test. Notwithstanding these considerations, the cardiac surgeon and interventional

cardiologist generally like to have hard confirmation of the presence of ischemia. In the case of patient A the prior probability of coronary disease amounted to 94 %. The absence of exercise induced ST-segment depression was not entirely expected, but at a sensitivity level of 65 % (for a 0.1-0.15.mV horizontal depression) at a specificity of 89 %, a normal test result is not so surprising and should not lead one astray from a diagnosis of cardiac ischemia. Supplementary investigations are then called for, such as myocardial perfusion scintigraphy under physical exertion or pharmacological stress. The appearance of reversible perfusion defects is regarded as proof of ischemia. Unfortunately, the method has its pitfalls in the form of patiënt-linked artefacts and of technical artefacts (4). The figures reported for sensitivity and specificity of thallium scintigraphy are higher than those for exercise ECG, viz. 89 % and 81-91 %, respectively (5).

Patient B also had a typical history of angina pectoris. The presence of a LBBB, however, made exercise ECG practically useless. Scintigraphy could be an alternative, but, again, LBBB is not the most suitable condition for the test because of the frequent occurrence of spurious septal perfusion defects. A possible explanation is that coronary flow mainly takes place during diastole. The relaxation of the septum in LBBB gets out of phase and precedes that of the rest of the LV. Coronary inflow in the septum is thus impeded by the intracavitary pressure still present in the LV, and increasingly so at higher heart rates and higher pressures. Adenosine stress testing could perhaps circumvent the problem of asynchrony since that technique essentially does not increase heart rate (4).

In **patient C** it was most important to establish whether viability was still present in the affected myocardial segments, in combination with ischemia (6). Viability can be visualised by means of proton emission tomography (PET). The isotope fluor-18-deoxyglucose (FDG) is a glucose analogon and uptake of FDG in myocardial tissue signifies intact glucose metabolism, i.e. viability. When FDG-PET is applied in combination with perfusion isotope, information can be obtained about viability as well as ischemia. Unfortunately, PET is available in only a few hospitals in the Netherlands. FDG-SPECT offers an alternative but requires adaptation of existing SPECT installations with high energy collimators. A recent improvement of perfusion scintigraphy appears to be gated-SPECT imaging, which allows the simultaneous assessment of both perfusion and function through one single study. This method must still find its way in clinical practice (7).

Echocardiography on the other hand is ubiquitous and DS-echo is an attractive solution providing information on both viability and ischemia in one examination (8). DS-echo has been proven capable of reliable identifying high- and low-risk patients. The technique, however, requires considerable experience on the part of the investigator and is moreover dependent on the 'echogenic' qualities of the patiënt. DS-MRI does not have the aforementioned draw-backs. It is neither dependent on the manual skill of the investigator nor on the suitability of the patient. It is a tomographic technique that does not make use of radioactivity and carries a low risk. Nevertheless DS-MRI is not entirely without failure. Patients with ferromagnetic implants and patients suffering from claustrophobia cannnot be investigated. An irregular heart rate (e.g. atrial fibrillation) is a relative

contra-indication, as is poor breathing control. Total failure rate is around 5% (9). The value of DS-MRI for the study of viability and ischemia and its higher success rate than DS-echo has been established in preceding investigations (1, 10, 11). In our 3 patients, three different isotope imaging techniques would have been necessary to clarify all ischemic problems. In patient A exercise- or pharmacological stress myocardial perfusion scintigraphy, in patient B adenosine perfusion scintigraphy and in patient C FDG-PET or FDG-SPECT in combination with perfusion scintigraphy (or perhaps gated SPECT). In experienced hands and under favourable imaging conditions DS-echo could have furnished equivalent information. Because DS-MRI is also applicable in less echogenic patients we advocate a wider use of this technique, in preference to the other methods mentioned, for the investigation of cardiac ischemia and viability, the correct assessment of which is of prime importance for selecting the best treatment.

Acknowledgement

We thank Prof. Dr. E.E. van der Wall (Professor of Cardiology, LUMC) for his valuable comments.

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Chapter 6

Dobutamine Cardiovascular Magnetic Resonance for the Detection of myocardial Ischemia with the use of Myocardial Tagging

Chapter 6

Dobutamine Cardiovascular Magnetic Resonance for the Detection of Myocardial Ischemia With the Use of Myocardial Tagging

Dirkjan Kuijpers, Kai Yiu J.A.M. Ho, Paul R.M.van Dijkman,
Rozemarijn Vliegenthart, Matthijs Oudkerk

Departments of Radiology and Cardiology, University Hospital Groningen and,
Bronovo Hospital, The Hague, the Netherlands

Published in
Circulation 2003; 107: 1592-1597

Presented in part at the:
ESCR/CIRSE, September 22-26, 2001, Gothenburg
(Selected as one of the best cardiac papers, ESCR/CIRSE, Gothenburg)
ECR March 1-5, 2002, Vienna
CIRSE October 6-7, 2002, Luzern
NVVR September 19-20, 2002, Noordwijk
RSNA December 1-6, 2002, Chicago
NVVR Februari 17-20, 2004, Utrecht
Cardiovascular Workshop October 1-2, 2004, Seville

Abstract

Background- The purpose of this study was to assess the value of high dose dobutamine cardiovascular magnetic resonance (CMR) with myocardial tagging for the detection of wall motion abnormalities as a measure of myocardial ischemia in patients with known or suspected coronary artery disease.

Methods and Results- Two hundred eleven consecutive patients with chest pain underwent dobutamine-CMR, 4 days after antianginal medication was stopped. Dobutamine-CMR was performed at rest and during increasing doses of dobutamine. Cine-images were acquired during breath-hold with and without myocardial tagging at 3 short-axis levels. Regional wall motion was assessed in a 16-segment short-axis model. Patients with new wall motion abnormalities (NWMA) were examined by coronary angiography. Dobutamine-CMR was successfully performed in 194 patients. Dobutamine-CMR without tagging detected NWMA in 58 patients, whereas NWMA were detected in 68 patients with tagging (P=0.002 McNemar). Coronary angiography showed coronary artery disease in 65 (96%) of these 68 patients. All but 3 of the 65 patients needed revascularization. In the 112 patients with a negative dobutamine-CMR study, without baseline wall motion abnormalities, the cardiovascular occurrence-free survival rate was 98.2% during the mean follow-up period of 17.3 months (range, 7 to 31).

Conclusions- Dobutamine-CMR with myocardial tagging detected more NWMA compared to dobutamine-CMR without tagging, and reliably separated patients with a normal life expectancy from those at increased risk of major adverse cardiac events.

(*Circulation.* 2003; 107:1592-1597.)

CHAPTER 6

Introduction

Myocardial tagging allows determination and quantification of left ventricular wall thickening of specific myocardial segments (1-3). Myocardial tagging was first used in combination with low-dose dobutamine cardiovascular magnetic resonance (CMR) for the assessment of myocardial viability (4,5). High-dose dobutamine-CMR (up to 40 μg/kg per minute) has been useful for the detection of myocardial ischemia (6,7). The cine-CMR technique allows accurate delineation of the endocardium and epicardium, and offers a reproducible assessment of left ventricular wall thickening (8). Reduction of myocardial circumferential shortening and systolic wall thickening are sensitive parameters for the detection of myocardial ischemia (3,9). The addition of myocardial tagging to dobutamine-CMR may further enhance diagnostic accuracy (1). Without tagging, ventricular contraction is evaluated by the movement of the endocardium and epicardial boundaries. With tagging, extra visual markers are created within the myocardium, which move with the movements of the myocardial wall. This facilitates the assessment of its contractile behavior.

The purpose of the present study was to assess the value of high-dose dobutamine-CMR with myocardial tagging for the determination and evaluation of myocardial ischemia in patients presenting with chest pain.

Methods

Study Population

The study population consisted of 211 consecutive patients with chest pain referred for diagnosis of myocardial ischemia regardless of known coronary artery disease (CAD). The patients were recruited from the outpatient clinic of the Department of Cardiology. All patients had an inconclusive diagnosis of myocardial ischemia by means of history, ECG-recording at rest and if performed during bicycle exercise test. Dobutamine stress echocardiography (DSE) or perfusion scintigraphy was not performed. The outcome of the dobutamine-CMR study was used as an arbiter to decide about coronary angiography (CAG). Patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120 mmHg), CMR-incompatible metallic implants or known claustrophobia were excluded.

Eighty-three patients had a previous myocardial infarction, and 49 patients had undergone revascularization procedures (25, PTCA); 19, (CABG); 5 patients, both procedures). To ensure myocardial response to dobutamine, all anti-anginal medication was stopped 4 days before the CMR examination. The Medical Ethics Committee approved the study protocol. All subjects gave informed consent.

MR Study

After the patient was positioned on the MR scanning table, an intravenous access was established through an antecubital 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. Systolic and diastolic blood pressures were recorded, using an automatic device (Welch-Allyn, Emro-medical), at baseline and every 3 minutes throughout the procedure. After baseline acquisitions, dobutamine was infused intravenously using a digital pump injector situated outside the scanner room. In case a wall motion abnormality (WMA) was detected at baseline, infusion was started with 5 μg/kg per minute, after which dose of dobutamine was increased to 10, 20, 30, and 40 μg/kg per minute. If no WMA was detected at baseline, we started with 10 μg/kg per minute. Imaging began 6 minutes after each dose increase, and required 3 minutes per dose increase. Imaging consisted of acquiring 3 short-axis cine images (basal, mid-ventricular and apical) without and 2 short-axis cine images (basal and mid-ventricular) with myocardial tagging. During the infusion of dobutamine the radiologist and cardiologist were present in the MR suite, to monitor the condition of the patient and to evaluate the images directly.

Criteria for ending the dobutamine-CMR examinations were (1) development of new WMA (NWMA), (2) fall of systolic blood-pressure of> 40 mm Hg, (3) marked hypertension> 240/120 mmHg, (4) severe chest pain, (5) ventricular arrhythmias, and (6) intolerable side effects of dobutamine. The total duration of

the CMR study, including preparation of the patient and scan time, averaged 50 minutes (SD, 12).

MR Imaging technique

CMR was performed with the use of a standard 1-T MRI system (Impact-Expert, Siemens Medical Systems, Erlangen). We used an ECG-triggered segmented gradient-echo pulse sequence (FLASH/TR:90msec/TE:6.1msec/α:25°/FOV:325 to 350 mm/slice-thickness 8mm/matrix 256x256). 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.

Tagging was performed with a standard FLASH grid-sequence (TR:96msec/TE:4.4msec/ α:15°/FOV 325 to 350 mm/slice-thickness 8mm, continuous/matrix 256x256). Nonselective radiofrequency pulses separated by spatial modulation of magnetization (SPAMM) encoding gradients were used to achieve tag spacing of 8mm. Each cine breath-hold acquisition took 15 to 19 heartbeats, and was made in maximum inspiration. If the heart rate reached 100 beats per minute, the number of phases per acquisition was decreased to optimize temporal resolution.

MR Image Analysis

Myocardial ischemia was defined as an induced WMA in at least two segments at different consecutive planes of the left ventricle. Short-axis images were divided into multiple segments with 6 segments in the basal and midventricular and 4

segments in the apical image. All the images were scored using a 4-point scale, according to the guidelines of the American Society of Echocardiography (10). Per segment the wall motion was graded as 1=normal or hyperkinesia, 2=hypokinesia, 3=akinesia, and 4=dyskinesia. Baseline (at rest) WMA was defined as WMA in 1 or more segments.

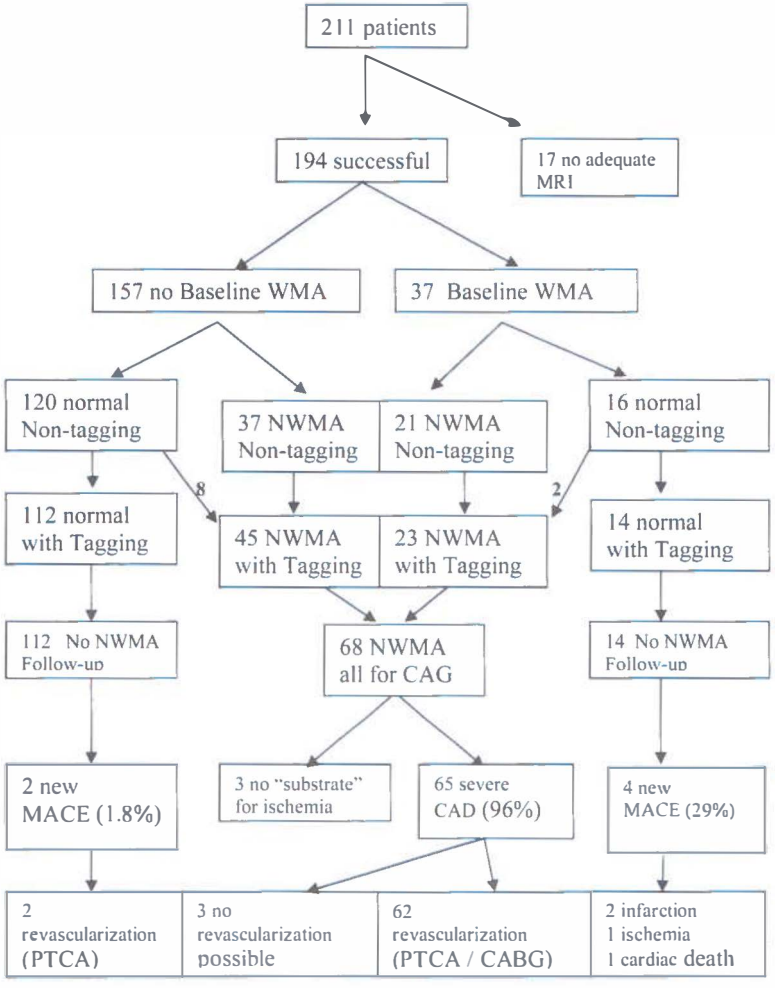
Wall motion score index (WMSI) was derived as the mean score of all segments (n=16) of all short-axis images. WMSI data of the cine images with and without tagging were determined from baseline and peak-stress images. The WMSI data with tagging included 12 segments of basal and mid-ventricular level with tagging and 4 segments of the apical plane without tagging.

If WMA's were already observed at rest and improved during low-dose dobutamine stress but worsened during peak-stress, then these WMAs were considered diagnostic of inducible myocardial ischemia. If segments that were akinetic at rest became dyskinetic during stress, without improvement with low-dose dobutamine, this was not considered diagnostic of inducible ischemia (11).

All dobutamine-CMR images were magnified (2x), and displayed as continuous cine loops on high-resolution grey-scale monitors. The short-axis images were analyzed during and directly after the examination by two experienced investigators who interpreted the images independently. Differences in classifications were settled in a consensus review. All data were expressed as mean value +/- SD; a *P*-value of <0.05 was considered statistically significant. WMSI values were compared using a paired-t test. The numbers of patients defined as having NWMA were compared between dobutamine-CMR with and without tagging by use of the McNemar test.

Patients with a negative dobutamine-CMR study were followed by an outpatient clinic three months after the examination. After this period the patients were called every 3 to 6 months to assess their clinical status of major adverse cardiac events (MACE), which was defined as myocardial ischemia, myocardial infarction, heart failure or cardiac death. The survival-free of MACE was calculated by the Kaplan-Meier method, and compared between groups using the log-rank test.

Figure 1. Flow chart illustrating course of dobutamine-CMR study.



Angiography

When NWMAs were detected the dobutamine-CMR study was followed by CAG within 3 weeks. The CAGs were documented at 12.5 images (matrix: 512x512) per second in multiple (standard) projections. Hemodynamically significant CAD was defined as a diameter reduction of >50% in one or more major epicardial coronary arteries. Immediately after the procedure, a trained observer interpreted all angiographic studies blindly and independently. Patients were classified as having 1-, 2-, or 3-vessel disease.

Results

Of the original 211 patients (Figure 1), dobutamine-CMR was successfully performed in 194 (92%). Seventeen (8%) patients could not be investigated adequately because of nausea (n=3), severe drop in systolic blood pressure (> 40mmHg) (n=2), arrhythmia (n=1), breathing artifacts (n=5), claustrophobia (n=5) or because anti-anginal medication was not stopped in time (n=1).

Besides minor complications, one patient had ventricular fibrillation, which was successfully treated by resuscitation.

The demographic and hemodynamic data are listed in Table 1. The association between dobutamine-CMR findings and WMSI values are listed in Table 2.

TABLE 1. Demographic and Hemodynamic data (n=194)

Variable	Mean or %
Age, y	62±12
Male, %	66.8
Previous myocardial infarction, %	42.7
PTCA, %	15.5
CABG, %	12.4
Body weight, kg	79±13
Rest diastolic blood pressure, mm Hg	85±11
Peak diastolic blood pressure, mm Hg	90±14
Rest systolic blood pressure, mm Hg	153±28
Peak systolic blood pressure, mm Hg	174±25
Rest heart rate, bpm	80±16
Peak heart rate, bpm	127±19
Rate-pressure product* at rest	12345±3711
Rate-pressure product* at peak stress	22036±4464
Maximum dose dobutamine, µg/kg/minute	37±6

Values are expressed as mean ± SD or percentages.
* Rate-pressure product = (heart rate) x (systolic blood pressure).

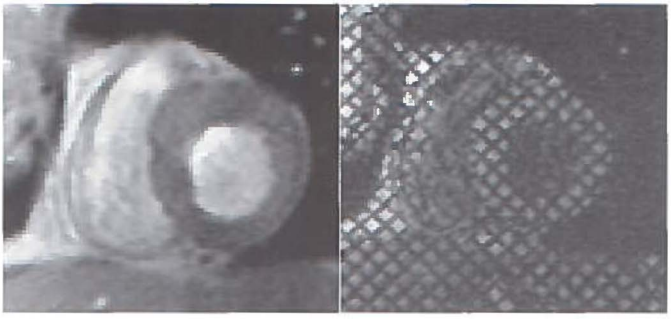
TABLE 2. Wall Motion Score Index Before and After High-Dose Dobutamine by Status of New Wall Motion Abnormalities

	Baseline-WMSI	Peak-WMSI
NWMA present		
Non-tagged Studies (n=58)		
No baseline WMA (n=37)	1.0	1.35±0.23*
Baseline WMA (n=21)	1.29±0.24	1.71±0.37*
Tagged Studies (n=68)		
No baseline WMA (n=45)	1.0	1.35±0.16*
Baseline WMA (n=23)	1.29±0.23	1.71±0.38*
NWMA absent		
Non-tagged Studies (n=136)		
No baseline WMA (n=120)	1.0	1.0
Baseline WMA (n=16)	1.19±0.16	1.19±0.16
Tagged Studies (n=126)		
No baseline WMA (n=112)	1.0	1.0
Baseline WMA (n=14)	1.18±0.17	1.18±0.17

WMSI is expressed as mean ± SD. *$P<0.001$ vs baseline WMSI.

No Baseline WMA

On the baseline images, no WMA was detected in 157 (81%) of 194 patients. Forty-six patients had a history of non-Q-wave myocardial infarction. When stressed with dobutamine, non-tagged images showed NWMA in 37 patients (24%) (Mean-WMSI=1.0 at rest, and 1.35 (SD:0.23) with dobutamine, $P<0.001$). Eight (5%) additional patients with NWMA were detected through the use of the tagged images (Figure 2). In 112 patients (71%), no NWMA was found.



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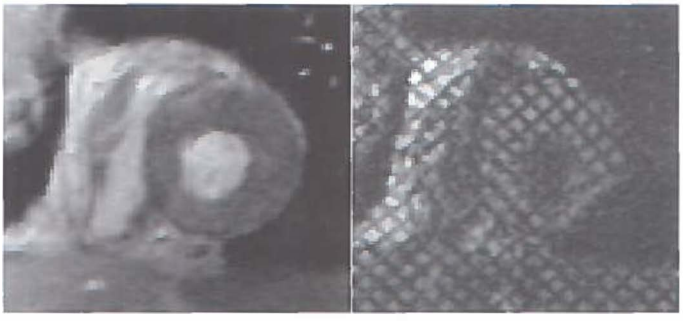

C D

Figure 2.

Short-axis basal views at baseline (rest) and peak dose dobutamine (40 μg), before and after tagging. A (without tagging) and B (with tagging) show diastolic phase of a normal left ventricle at rest. C, Early systolic phase of the same left ventricle at peak dobutamine dose. Wall contraction pattern (wall-thickening) appears to be normal. D, same phase as C. Preservation of tagging lines at the anterial wall of the left ventricle. There is akinesia of 3 segments: septal, anterior-septal, and anterior, which indicate myocardial ischemia.

CAG showed significant stenosis in the left anterior descending coronary artery.

Baseline WMA

On the baseline images, WMA was already present in 37 (19%) of 194 patients. All these patients had a history of myocardial infarction. Without tagging, 21 patients (57%) had NWMA when stressed with dobutamine (mean WMSI=1.29 (SD: 0.24) at rest, and 1.71 (SD: 0.37) with dobutamine; $P< 0.001$). The tagging technique detected 2 (5%) additional patients with NWMA. Twenty-three patients (62%) were found positive with tagging (mean-WMSI=1.29 (SD: 0.23) at rest, and 1.71 (SD: 0.38) with dobutamine, $P<0.001$), whereas no NWMAs were found in 14 patients (38%).

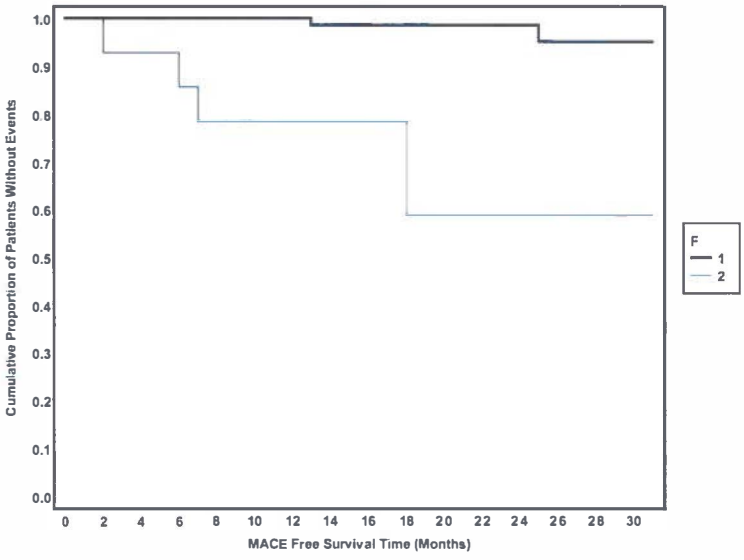

Figure 3.

Kaplan-Meier curves showing survival free from MACE during follow-up for negative dobutamine-CMR studies, with (dotted line) and without (black line) baseline WMA (log-rank: $p<0.0001$).

No NWMA and no Baseline WMA

Of the 112 patients who had no inducible myocardial ischemia and without baseline WMA, 110 (98,2 %) patients were free of MACE during the follow-up period of 7 to 31 months (average, 17.3 months). Two patients (1.8%) had myocardial ischemia, which occurred more than 12 months after the examination. Both patients underwent PTCA. The Kaplan-Meier curve is presented in Figure 3. The annual MACE rate of patients without NWMA and without baseline WMA was 0.7%.

No NWMA and Baseline WMA

Fourteen patients showed baseline WMA, which did not change when stressed with dobutamine (mean-WMSI=1.18, (SD: 0.17)). Of these 14 patients 4 (29%) showed a new MACE during follow-up. One patient suffered sudden death 2 months after the examination. He had sustained an extensive inferior wall infarction in the past and suffered from heart failure. Two patients had a non-fatal myocardial infarction, which occurred more than 6 months after the study. The fourth patient had myocardial ischemia, necessitating revascularization (CABG), which occurred 18 months after the study.

New Wall Motion Abnormalities

Of the 194 patients, 58 (30%) patients were found positive for NWMA with matching ischemia between non-tagged and tagged images (Figure 4). Of the remaining 136 patients 10 (5%) additional positive studies were detected only with the use of tagging, which is an increase of 17% (P=0.002 McNemar).

Sixty-five (96%) of 68 patients with NWMA showed significant CAD at CAG. One-vessel disease was found in 25 patients, and 2- or 3-vessel disease in 40 patients. Of the 10 patients only detected by the tagging technique 3 had 1-vessel disease, 4 had 2-vessel disease and 3 had 3-vessel disease. Revascularization was deemed necessary and possible in 62 (95%) patients. In 3 patients, revascularization was technically not feasible. Three (4%) of the 68 patients showed no significant CAD at angiography, whereas both the non-tagged and tagged CMR images were found positive. Two patients had a left bundle branch block with an abnormal septal wall motion at the baseline images. In the other

patient, CAG showed diffuse coronary artery irregularities without significant stenoses.

The mean maximum dose of dobutamine for detecting ischemia was 33 μg/kg/minute (SD, 8.3). The majority of the NWMA (75%) were detected at high-dose dobutamine (30 and 40 μg), whereas only 25% were detected at low-dose dobutamine (20 μg).

During the examinations, 116 of 194 (60%) of the patients had chest discomfort, but in only 60 them (52%) myocardial ischemia was shown to be present.

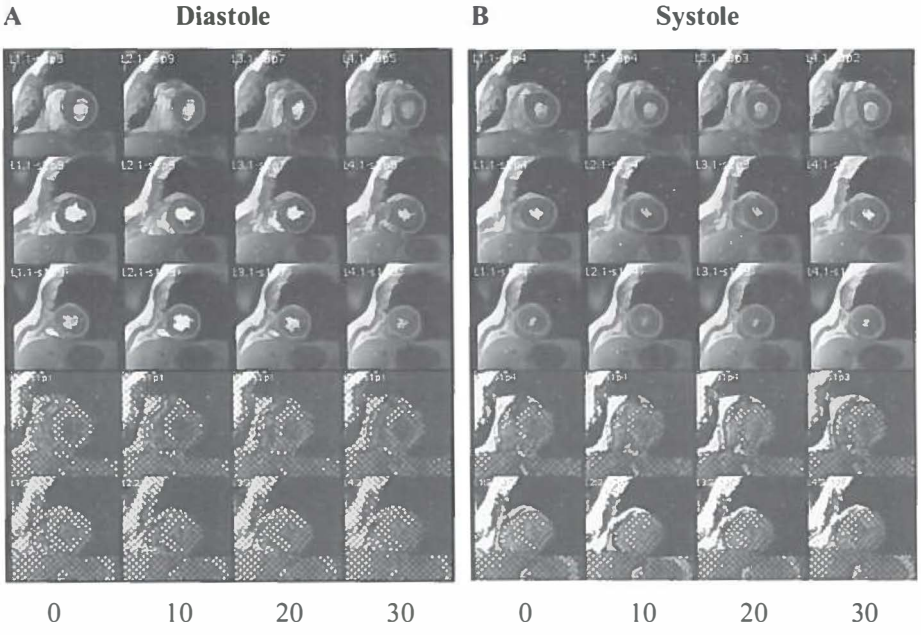

Figure 4.

Overview of dobutamine-CMR images during diastole (A) and systole (B). *x*-Axis, dobutamine levels: 0 (baseline), 10, 20 and 30 μg dobutamine; *y*-axis, short-axis planes of grid-tagged images (basal and midventricular plane) and non-tagged images (basal, midventricular and apical plane).

At 20 and 30 μg dobutamine there is matching ischemia between non-tagged and tagged images of the inferior and septal wall on the basal and midventricular short-axis planes of the left ventricle.

CHAPTER 6

Discussion

This is the first study that demonstrates that the use of myocardial tagging with high-dose dobutamine-CMR detects more NWMA than dobutamine-CMR studies without tagging. The results suggest that dobutamine-CMR is a specific diagnostic technique in the analysis of ischemic heart disease.

Our data demonstrate that 96% of the patients with NWMA, detected by dobutamine-CMR, had significant CAD. Two other studies have reported results of dobutamine-CMR (6,7); however, no myocardial tagging was used. Nagel et al. (6) compared dobutamine-CMR and DSE in 172 patients referred for CAG. Dobutamine-CMR provided better sensitivity (89% vs. 74%) and specificity figures (86% vs. 70%) for the detection of NWMA compared to DSE. However, all patients with a history of myocardial infarction had been excluded from the study.

Hundley et al. (7) reported the use of dobutamine-CMR in 139 patients who failed DSE, and came up with findings similar to those of Nagel et al. (6). In our study 3 (4%) of 68 patients showed false-positive dobutamine-CMR findings. Two of these false judgments occurred in the beginning of our dobutamine-CMR series, because of abnormal septal wall motion in left bundle branch block. Although they can be regarded as a "learning error", both patients were counted as having false-positive results.

The WMSI of the patients with a positive dobutamine-CMR study were mainly determined by WMAs in the basal and mid-ventricular planes. Isolated apical

WMAs were not encountered. If the apical plane was excluded from the analyses, the number of positive dobutamine-CMR studies would drop by 3%.

Target Heart Rate Rule

In many cardiac stress studies with echocardiography, atropine is given to increase heart rate in patients who fail to reach the target-rate. In our study no atropine was given and the target-rate rule (target rate 85% of maximum; men 220 minus age / women 200 minus age) was not applied. It is known that the addition of atropine can enhance sensitivity to detect CAD (12). However, the target-rate rule, which forms the basis of applying this drug, has been questioned (13-15). The peak rate-pressure product in our study was similar to that reported by Nagel et al. (6). Only peak heart-rate was higher in their study, most likely due to atropine. However, the mean diastolic and systolic blood-pressure at rest, and peak-stress and the heart-rate at rest were higher in our series. Maybe this was due to the fact that all anti-anginal medication was stopped over a longer period of time. Because of the side effects of atropine, patients are unable to drive a car after the study. To obviate the need for atropine and to obtain an adequate response to dobutamine we prolonged infusion time of each dose from 3 to 6 minutes.

Myocardial Tagging

SPAMM is the most frequently used tagging sequence for CMR, which generates two orthogonal sets of parallel planes of magnetic saturation (grid-tagging) by a

sequence of nonselective radiofrequency pulses (1). In the present study, grid-tagging was used at the basal and mid-ventricular short-axis images only, because the tags were too broad in relation to the small apex of the left ventricle, giving rise to blurring and unacceptable image quality.

Other forms of tagging can give narrower tags, such as the DANTE-tagging sequence (16). In addition, an image processing technique such as HARP (harmonic-phase) does not rely on the tags facing the same direction (17). These techniques were not available on our MR system. The quantitative HARP-image processing method is based on the use of isolated spectral peaks in SPAMM-tagged MR images. Until now, quantitative assessment of myocardial strains in a single slice will take about three minutes, and analysis of a complete data set about 60 minutes (17). In our opinion these quantitative image-processing times are still too long to perform a safe high dose dobutamine-CMR study. Second, the additional value of quantitative analysis in the diagnosis of myocardial ischemia is probably limited, because the semi-quantitative methods, including our method, has shown excellent results (6,7).

Recently, online analysis of WMA of the left ventricle was performed successfully with real-time CMR (18). In the future real-time imaging may be an important additional tool to the standard breath-hold technique, perhaps in combination with quantitative analysis as well.

Complications

The major reasons for study failure were minor complications (n=7), and inability to sustain breath-hold (n=5), which is comparable to other studies (6,7).

One patient (0.5%) had ventricular fibrillation at the end of the study after 40 μg of dobutamine. After review of the images it was obvious that NWMAs were already present at 20 μg, which was not noted during the study. This patient was ischemic at a level of 20 μg and we 'overstressed' the patient over 2 levels of dobutamine.

In a previous study, severe complications occurred in 0.25% of the patients, including ventricular fibrillation (0.07%) and sustained ventricular tachycardia (0.1%) (19).

Follow-up

We demonstrate that patients with a normal dobutamine-CMR study without baseline WMA had a MACE rate of 1.8%, during the mean follow-up of 17.3 months. In a series of patients with a normal DSE, the annual MACE rate was 1.2% over a 5-year period (20). These results seem to be comparable; however long-term follow-up studies are needed to determine the negative predictive value of dobutamine CMR.

In the group of patients with a normal dobutamine-CMR study and baseline WMA, 4 of 14 (29%) patients showed a MACE within a mean follow-up of 17.3 months. The value of this complication rate, however, is uncertain because the number of patients in this group was limited. It is known that the presence of baseline WMA

is a risk factor for the development of MACE (20). This group of patients with baseline WMA should be monitored closely during follow-up.

Study limitations

First, because CAG was not performed in the patients with a negative dobutamine-CMR study, our data could be influenced by referral bias. The outcome of the dobutamine-CMR in this study was used as a direct arbiter for subsequent clinical follow-up. Initially, the additional value of the tagging data were unknown; however, the possibility of any adverse clinical effect of this strategy was regarded as minimal, since tagging was performed as an additional imaging test besides the standard non-tagging images. The sensitivity and specificity of the test could not be determined directly, since not all patients were studied by CAG.

Second, images were analyzed semi-quantitatively. Possible improvements could be acquired using quantitative wall motion analysis; however, until now, it is a time-consuming procedure, and no decisions can be made during the study. We believe that it is crucial to stop a dobutamine-CMR study immediately when a patient becomes ischemic, since overstressing can lead to ventricular fibrillation. A quantitative analysis has clinical potential when the results are available within a few seconds after each cine-acquisition.

Third, we used a 1 Tesla-MR system. The more standard 1.5 Tesla systems can reduce cine acquisition substantially, which improves patient acceptance and image quality. Also, the entire procedure time can be shortened if 3-minutes infusion time is used, as is a standard protocol in many centers.

Fourth, we used only 3 short-axis planes, whereas the apical short-axis was performed without tagging. This could produce sampling errors so that small areas of WMA may have been missed, especially in the apical plane.

Conclusions

In conclusion, we demonstrate that high-dose dobutamine-CMR using myocardial tagging improves the detection of NWMAs, which are indicative of myocardial ischemia. Dobutamine-CMR with tagging is not only a reliable but also a safe diagnostic technique in the analysis of myocardial ischemia. It reliably separates patients with a normal life expectancy from those at increased risk of major adverse cardiac events.

Acknowledgment

We thank Bernadette Blom, Wouter Stam, Marielle Broeders and Truus den Besten for assistance in performing the CMR studies.

The authors thank Dr J.C. de Groot for assistance in preparing the manuscript.

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Chapter 7

Safety and Feasibility of Dobutamine Cardiovascular Magnetic Resonance in Patients Suspected of Myocardial Ischemia.

Chapter 7

Dobutamine Stress MRI. Part I. Safety and Feasibility of Dobutamine Cardiovascular Magnetic Resonance in Patients Suspected of Myocardial Ischemia.

Dirkjan Kuijpers, Caroline HC Janssen, Paul RM van Dijkman, Matthijs Oudkerk

Department of Radiology and Cardiology, Bronovo Hospital, The Hague, Netherlands. Department of Radiology, State University and Academic Hospital Groningen, Groningen, the Netherlands

Published in

Eur Radiol 2004; 14 (10): 1823-1828

Presented in part at the:

NVVR October 2-3, 2003, Noordwijk

ESCR October 31- November 1, 2003, Berlin

RSNA November 30 - December 5, 2003, Chicago

ESCR Januari 30 - Februari 2, 2004, Curacao

NVVR Februari 17-20, 2004, Utrecht

ECR March 5-9, 2004, Vienna

and

Awarded as best poster presentation at the ESCR November 1, 2003, Berlin.

Abstract

Objective: The aim of the study was to evaluate safety and feasibility of dobutamine cardiovascular magnetic resonance (CMR) in patients with proven or suspected coronary artery disease.

Materials and Methods: Dobutamine CMR was evaluated retrospectively in 400 consecutive patients with suspicion of myocardial ischemia. Dobutamine was infused using an incremental protocol up to 40 μg/kg body weight per minute. All anti-anginal medication was stopped 4 days before the CMR study and infusion time of dobutamine was 6 minutes per stage. Hemodynamic data, CMR findings and side effects were reported. Patients with contraindications to CMR (metallic implants and claustrophobia) were excluded from analysis.

Results: Dobutamine CMR was successfully performed in 355 (89%) patients. Forty-five (11%) patients could not be investigated adequately because of non-cardiac side effects in 29 (7%), and cardiac side effects in 16 (4%) patients. Hypotension (1.5%) and arrhythmias (1%) were the most frequent cardiac side effects. One patient developed a severe complication (ventricular fibrillation) at the end of the study. There were no myocardial infarctions or fatal complications of the stress test. The most frequent non-cardiac side effects were nausea, vomiting and claustrophobia. Age >70 years, prior myocardial infarction and rest wall motion abnormalities showed no significant differences with side effects (p>0.05).

Conclusion: Dobutamine CMR is safe and feasible in patients with suspicion of myocardial ischemia.

Key Words: magnetic resonance imaging; myocardium; stress; ischemia, dobutamine.

Introduction

Dobutamine cardiovascular magnetic resonance imaging (CMR) is used to identify wall motion abnormalities of the left ventricle, indicative of myocardial ischemia in patients with proven or suspected coronary artery disease [1-4]. According to international guidelines, dobutamine is used to analyze wall motion abnormalities, while adenosine is mainly used to analyze perfusion abnormalities of the myocardium [5,6]. Recent studies show that CMR is gaining an important role in diagnosing patients suspected of coronary artery disease [7-9]. With the use of myocardial tagging, dobutamine CMR has emerged as a reliable modality to detect myocardial ischemia and provide prognostic information as well [4, 10]. The presence of resting wall motion abnormalities (RWMA), in the absence of myocardial ischemia, has been shown to be a high risk factor for the development of future major cardiac adverse events [4]; however, the relation of RWMA to side effects during the dobutamine CMR study is unknown. No large clinical experience for the evaluation of side effects during dobutamine CMR has been reported so far. The purpose of the present study was to assess the safety and feasibility of dobutamine CMR over a period of 4 years at a single center.

Materials and Methods

Study Population

Between August 1999 and July 2003, 400 consecutive dobutamine CMR studies were acquired in our institution. Demographic and hemodynamic data were collected retrospectively. The patients were recruited from the outpatient clinic of the Department of Cardiology. All patients had chest pain and an inconclusive diagnosis of myocardial ischemia by means of history, ECG-recording at rest and if performed during bicycle exercise test. Patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (>220/120 mmHg), CMR-incompatible metallic implants or known claustrophobia were excluded from analysis. Many patients had known coronary artery disease, including previous myocardial infarction (37 %), previous coronary revascularization (19 %) or were receiving beta blockers (58 %). Diabetes mellitus was present in 16 % of the patients (Table 1). The local Ethical Committee approved the study protocol.

Dobutamine CMR protocol

To ensure cardiac response to dobutamine, all anti-anginal medication was stopped 4 days before the dobutamine-stress CMR examination. Before the patient entered the CMR suite, the presence of an acute coronary syndrome was ruled out by a physician. After the patient was positioned on the scanning table, intravenous access was established via an antecubital 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 three minutes throughout the procedure. Blood pressure and heart rate were recorded by the technicians throughout the study. The imaging methodology of dobutamine CMR has been described in detail previously [4]. In brief, MRI was performed using a standard 1-Tesla system (Impact-Expert, Siemens Medical Systems, Erlangen). Three short axis cine breath-hold CMR images of the left ventricle were taken at rest and during incremental dosage of dobutamine up to 40 μg/kg/minute. An ECG-triggered segmented gradient-echo pulse sequence was used: FLASH/TR: 90msec; TE: 6.1msec; α: 25°; FOV: 325-350mm; Slice-thickness 8mm; and Matrix 256x256. Tagging was performed with a standard FLASH grid-sequence: TR: 96msec; TE: 4.4msec; α: 15°; FOV 325-350 mm; Slice-thickness 8mm and Matrix 256x256. Each cine breath-hold acquisition (one slice) took 15-19 heartbeats, and was made in maximum inspiration. If the heart rate reached 100 beats per minute, the number of phases per acquisition was decreased to compensate for shortening of RR interval at higher heart rates. 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. In case a wall motion abnormality (WMA) was detected at baseline, infusion was started with 5 μg/kg/min, after which dose of dobutamine was increased to 10, 20, 30, and 40 μg/kg/min. If no WMA was detected at baseline we started with 10 μg/kg/min. Imaging began six minutes after each dose increase, and required three minutes per dose increase. Imaging consisted of acquiring three short-axis cine images,

(basal, mid-ventricular and apical) without and two short-axis cine images (basal and mid-ventricular) with myocardial tagging. The images were scored, according to the guidelines of the American Heart Association [11]. Short-axis images were divided into multiple segments with six segments in the basal and midventricular and four segments in the apical image. 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 wall motion abnormality in at least two segments at consecutive planes of the left ventricle during infusion of dobutamine. The absence of new or worsening wall motion abnormalities was defined as a negative dobutamine CMR study. A RWMA was defined as hypokinesia, akinesia or dyskinesia in one or more short-axis segments at rest. When new wall motion abnormalities were detected the dobutamine CMR study was followed by coronary angiography.

During the infusion of dobutamine the radiologist and cardiologist were present in the CMR suite, to monitor the condition of the patient and to evaluate all the images directly. Via a microphone direct contact with the patient was maintained between the scanning of the images and throughout the examination. A defibrillator (not MR compatible) and medication for emergency treatment were present in the preparation room besides the scanner. A physician (cardiologist) trained in cardiovascular emergencies and resuscitation was present in the CMR suite. The condition of the patients was controlled clinically up to 30 minutes after the end of the dobutamine infusion.

Criteria for ending the dobutamine-CMR examinations were development of new wall motion abnormalities indicative for myocardial ischemia; fall of systolic blood-pressure of > 40 mm Hg; marked hypertension > 240/120 mm Hg; severe chest pain; arrhythmias and intolerable side effects of dobutamine (nausea, vomiting).

Baseline clinical and dobutamine CMR characteristics are given as mean value ± standard deviation for continuous variables and as number (percent) for categorical variables. Patients were classified according to cardiac and non-cardiac side effects. Differences in categorical variables were assessed by chi-square analysis. Hemodynamic values were compared using a paired *t* test. A *p* value of 0.05 or less was considered to indicate statistical significance. The target heart-rate (THR) rule was defined as 85% of the maximum exercise heart rate predicted for age and sex (220 minus age in men; 200 minus age in women) [12]. The THR rule was not used during the stress studies. Retrospectively, the data of the acquired heart rates were evaluated in relation to the target heart rate rule and compared with dobutamine CMR findings.

Results

Hemodynamic data and the Target Heart-rate Rule

Dobutamine CMR was successfully performed in 355 (89%) of the patients. The demographic and hemodynamic data are shown in Table 1. The rate-pressure product during dobutamine CMR increased from 11.902±3.506 to 21.169±4.444 ($p<0.05$), heart rate increased from 79 ± 16 to 125 ± 18 beats per minute ($p<0.05$)

TABLE 1. Demographic and Hemodynamic data (n=355)

Variable	Mean or %
Age, y	63±12
Male, %	71
Prior myocardial infarction, %	37
Prior Revascularization, %	19
Use of Beta Blocker, %	58
Diabetes Mellitus	16
Body weight, kg	77 ± 13
Rest systolic blood-pressure, mm Hg	149 ± 26
Peak systolic blood-pressure, mm Hg	169 ± 27
Rest heart-rate, bpm	79 ± 16
Peak heart-rate, bpm	125 ± 18
Rate-pressure product* at rest	11902 ± 3506
Rate-pressure product* at peak stress	21169 ± 4444
Maximum dose dobutamine, μg/kg per minute	37.8 ± 5

Values are expressed as mean ± SD or percentages.
*Rate-pressure product = (heart rate) x (systolic blood pressure).

TABLE 2. Dobutamine CMR results if the Target Heart Rate Rule (THR) was applied: 85% x (200 minus age for women; 220 minus age for men). Retrospective analysis of 355 dobutamine CMR studies.

Peak Heart Rate	Neg. CMR study	Pos. CMR study	Total
>10 beats of THR	67 (26 %)	38 (40 %)	105 (30 %)
THR ± 10 beats	101 (39 %)	30 (32 %)	131 (37 %)
<10 beats of THR	93 (35 %)	26 (28 %)	119 (33 %)
Total	261 (100 %)	94 (100 %)	355 (100 %)

and systolic blood pressure from 149 ± 26 to 169 ± 27 mm Hg ($p<0.05$). The total duration of the CMR study, including preparation of the patient and scan time, averaged 48 minutes (SD, 11).

Retrospectively, the peak heart rates were evaluated according to the THR rule, which is used frequently in dobutamine stress studies. The values are presented in Table 2. Differentiation was made in three groups: THR ± 10 beats, > 10 beats and < 10 beats. The THR was not reached in 93 (35%) of 261 patients with a negative dobutamine CMR study. A major part of the positive dobutamine CMR studies (40%) were found at higher peak heart rates then calculated by the target heart-rate rule.

End points of dobutamine CMR studies

Side effects led to premature termination of the procedure in 45 (11%) dobutamine CMR studies (Table 3). Out of 355 patients who completed the infusion protocol without side effects, 94 (26%) had inducible myocardial ischemia. The mean maximum dose of dobutamine for detecting ischemia was 33 μg/kg/minute (SD, 8.3). The majority of the new wall motion abnormalities (76%) were detected at high-dose dobutamine (30 and 40 μg), whereas only 24% were detected at low-dose dobutamine (20 μg). The mean maximum dose of dobutamine of all the patients was 37.8 ± 5 μg/kg per minute. Coronary angiography showed significant coronary artery disease in 89 (95%) of these 94 patients. One- vessel disease was found in 32 (36%), and 2- or 3-vessel disease in 57 (64%) of the patients. During the examinations, 211 (59%) of the patients had chest discomfort, but in only 84 of them (24%) myocardial ischemia was shown to be present.

TABLE 3. Side Effects and Reasons for test termination

	Numbers and %	Dobutamine Level (mean)
Non-Cardiac Side Effects during study	29 (7.3)	27
Nausea and or vomiting	11 (2.8)	31
Claustrophobia	9 (2.3)	5
Breath-hold imaging artifacts	6 (1.5)	23
Anti-anginal medication not stopped	3 (0.8)	23
Cardiac Side Effects during study	16 (4.0)	22
Hypotension	6 (1.5)	30
Arrhythmias	4 (1.0)	20
Severe chest pain or shortness of breath	3 (0.8)	20
Hypertension	1 (0.3)	20
Aortic Dissection type A at start study	1 (0.3)	0
Ventricular Fibrillation	1 (0.3)	40

RWMA, rest wall motion abnormalities; Dobutamine level at μg/kg per minute.

TABLE 4. Characteristics in 400 dobutamine CMR studies

	Side Effects (n=45)	**No Side Effects (n=355)**	***p* values**
RWMA	7 (16 %)	56 (16 %)	$p = 0.970$
Age > 70 years	16 (36 %)	109 (31 %)	$p = 0.624$
Prior myocardial infarction	11 (24 %)	134 (38 %)	$p = 0.113$
Use of Beta-blockers	21 (47 %)	207 (58 %)	$p = 0.185$

RWMA, rest wall motion abnormalities. *P* values according to the chi square analysis.

During the examinations, 84 of 94 (89%) of the patients with ischemia developed angina; however, 10 (11%) patients did not reveal any pain sensation. Five of them were known to have diabetes mellitus.

The end of the protocol was reached in 261 (74%) of 355 CMR studies after the maximum dose of dobutamine (40 μg/kg/min.) and a negative dobutamine CMR test.

RWMA were detected in 57 (22%) of the 261 patients with a negative dobutamine CMR study. The patients with and without side effects were correlated with RWMA, age > 70 years. myocardial infarction and use of beta blockers, 4 days prior to the study (Table 4). No significant differences were found between these characteristics and the appearance of side effects (p>0.05). Nitroglycerin during or at the end of the study was required for 4 (1%) patients.

Cardiac side effects and test termination

Cardiac side effects and reasons for test termination are shown in Table 3. One (0.25%; 95 % Confidence Interval 0.000016 - 0.014) major complication (i.e., Death, myocardial infarction, or ventricular fibrillation) occurred in 400 patients. This patient developed ventricular fibrillation during infusion of dobutamine (40 μg/kg/minute). The patient was successful resuscitated and recovered well after coronary bypass grafting.

The most frequent minor complication was symptomatic and severe hypotension, which occurred in 6 (1.4%) patients. All patients completely recovered, usually after discontinuation of dobutamine. Two patients required short-term inpatient observation because of hypotension, bradycardia and severe chest pain. Treatment consisted of sublingual nitroglycerine, fluids and observation.

Hypertension (systolic blood pressure >220 mm Hg) occurred in one patient. Blood pressure normalized spontaneously after termination of dobutamine infusion.

Arrhythmias developed in 4 patients (1%): 2 patients with persistent premature ventricular contractions and 2 patients with atrial fibrillation. Premature ventricular contractions were seen in 6 (1.5%) patients which disappeared in 4 of them at a higher dose of dobutamine. One patient showed shortness of breath at the onset of the stress study. It was concluded that he had unstable angina, probably the result of stopping his anti-anginal medication. The dobutamine CMR study was not performed and he was admitted to the emergency unit. He recovered well and no myocardial infarction was found. No other side effects were seen in the other 399 patients due to stopping of the medication.

Noncardiac side effects and test termination

Noncardiac side effects occurred in 27 (7%) patients (Table 3). The most common were nausea and or vomiting (2.8%). In 9 of 10 patients (mean age 66 year) nausea started at a dobutamine dose of 30 μg. Claustrophobia and breath-hold artifacts are typically CMR related side-effects (3.8%). In 3 patients there was no heart rate increase during the study due to the fact that the beta blocker medication was not stopped before the study.

CHAPTER 7

Discussion

The present study of 400 consecutive examinations shows that dobutamine CMR is a safe test and well tolerated in the majority of the patients. Feasibility of dobutamine CMR is hampered by claustrophobia and breath-hold imaging artifacts, which are typical CMR side effects. In spite of the pretest screening for claustrophobia, the dobutamine CMR test failed in 2.3% of the patients because of anxiety. The non-cardiac side effects were comparable to those reported by other dobutamine CMR studies [2-4, 10]. If we exclude the typical CMR side effects, including the patients who did not stop their anti-anginal medication, the number of noncardiac side effects was 2.7%, which is comparable to dobutamine stress echocardiography (DSE) (3%) [13-15]. The use of shorter or more open magnets might reduce the number of patients with claustrophobia in the future.

High dose dobutamine stress imaging may cause severe complications in about 3 per 1000, including infarction, ventricular fibrillation and sustained ventricular tachycardia [13-15]. Neither death nor myocardial infarction occurred in this study. Ventricular fibrillation occurred in one patient (0.25%), with good clinical outcome. This 71-year-old man had diabetes mellitus and a history of myocardial infarction 2 years before the study. The cine images at rest showed minor septal wall motion abnormalities of the left ventricle. The myocardium was ischemic at a level of 20 μg and we 'overstressed' the patient with higher dosis of dobutamine. After review of the images it was obvious that myocardial ischemia was already present at 20 and 30 μg, which was not noted during the study. Also,

the patient did not report any chest discomfort or pain during the study, probably the result of the presence of diabetes. According to our experience it is advisable to test safety and emergency procedures regularly, together with the MR technicians.

The most frequent cardiac side effects in this study were hypotension and arrhythmias which were well tolerated and comparable to DSE [13-15]. The cardiac side effects seem to be not the result of stopping all anti anginal medication 4 days before the study. Only one patient had unstable angina prior to the dobutamine CMR study and was admitted for 1 day to the hospital. The dobutamine CMR study which was performed 2 weeks later showed inducible ischemia. Although patients were subjected to a prolonged dobutamine infusion protocol, only one patient developed hypertension necessitating termination of the study. The remaining dobutamine related side effects seem to be comparable to those reported for DSE [13-15], which favors a prolonged infusion protocol like the one used in this study.

Safety of CMR protocol

The most important limitation of current CMR technology is inadequate monitoring and concern over patient safety. Routine clinical performance of dobutamine CMR requires detection of arrhythmias and inducible ischemia [16].

In dobutamine CMR, the ECG is used to monitor heart rate and rhythm and not to analyze ST segments to diagnose ischemia. Myocardial ischemia is detected by analyzing changes in systolic wall motion of the left ventricle, which generally

precede ECG changes and chest pain [17, 18]. Patients must perform repeated breath-holds of about 6-12 seconds throughout the study, which may hinder communication with the patient. The acquired images reflect only a short period of wall motion during the infusion of dobutamine. So the onset of myocardial ischemia can be masked for several minutes. Stress echocardiography overcomes all the above mentioned safety issues. Real time CMR imaging in the new generation CMR scanners will overcome this problem [19, 20]. Continuous evaluation of the left ventricle will create an additional safety margin for the detection of ischemia and arrhythmias.

Feasibility of dobutamine protocol

In this study, a different stress protocol was used compared to the methods in previous reported high dose dobutamine CMR studies [2, 3]. To ensure cardial response to dobutamine, we stopped all anti-anginal medication 4 days before the dobutamine CMR examination. In most imaging protocols, beta blocker medication is withhold only 1 day before the study and atropine is applied to increase heart rate in patients who fail to reach the THR [2, 3, 21]. A recent report showed that the presence and severity of CAD may be underestimated in patients receiving beta-blocker therapy [22]. Most of our patients use beta blockers (metoprolol) with long half-lives (e.g., 20 h) and should be stopped at least 3 to 4 days to minimize their activity. The risk of beta blocker withdrawal, including severe hypertension or an unstable coronary syndrome, is mainly based on literature regarding propranolol [23-25] which is not used in our institution for the treatment of angina pectoris and myocardial ischemia. In our study, only one

patient appeared to have an acute coronary syndrome before the start of the study.

During the stress studies the THR rule was not applied to this group of patients. In cardiac stress testing, this equation provides an approximation of the maximal heart rate to be reached at peak aerobic exercise, whereas dobutamine stress imaging aims to uncover wall motion abnormalities by increasing contractility and heart rate and by creating flow heterogeneity between myocardial regions subtended by normal coronary arteries and those subtended by stenotic coronary arteries. However, the variance of the maximal heart rate for any given age is considerable [26]. The main source of error is that there is a significant reduction and variability in heart rate with increasing age, particularly in patients with coronary artery disease [26, 27]. Peak heart rate by itself is an unreliable index of relative load [12]. The chronotropic and inotropic reserve of the heart defines the myocardial aerobic capacity, which is estimated by the product of the heart rate and the systolic blood pressure. Measurements of the rate-pressure product during exercise make it feasible to determine in the individual patient the threshold of myocardial ischemia [27]. The peak rate-pressure product in this study was similar to that reported by other dobutamine stress studies [2, 21], which indicate that in this study the stress level was at least as high as reported in former studies.

Chronotropic incompetence (patients who reached a submaximal heart rate) according to THR rule was present in 33 % of the patients (Table 2), which is similar to previous reports [28]. Elhendy et al. reported that premature

ventricular contractions occurred more commonly in patients with chronotropic incompetence, with the exception of other forms of arrhythmias [28], which are comparable to our findings.

In this study, 4 patients who revealed a submaximal heart rate response in all 4 studies showed temporary premature ventricular contractions. In this study, infusion time was prolonged from 3 to 6 minutes, mainly because of imaging reasons. The multiple breath hold cine CMR sequences (at least 5 series per infusion level) could not be made within 3 minutes, and especially older patients need a few minutes rest between the infusion levels to avoid breath-hold artifacts. In our experience, even with the use of a 1.5 Tesla MR system a 3 minutes infusion interval is too short to perform all these multiple breath-hold cine images. Real-time CMR imaging with sufficient image quality may overcome this problem in the future [29].

There is also an advantage of this 6 minutes infusion protocol. This prolonged dobutamine infusion protocol induces better steady states of dobutamine. The effect of the additional stress factor of the prolonged infusion time is unknown, but is probably reflected in the high number (40%) of positive studies found at a much higher heart rate as can be calculated by the THR rule. If we had stopped the study at the reached THR, 40 % of positive studies would have been missed.

Conclusions

The results of this single-center study of 400 consecutive studies confirm that the dobutamine CMR protocol is safe and feasible in patients with known or suspected coronary artery disease. Because of potential cardiac side effects, a cardiologist should be present during the studies to monitor potential arrhythmias and complaints of the patients.

Acknowledgements

We are indebted to Dr. W.J. Post for data analysis.

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Chapter 8

Risk Stratification with Dobutamine Cardiovascular Magnetic Resonance in patients Suspected of Myocardial Ischemia.

Chapter 8

Dobutamine Stress MRI. Part II. Risk Stratification with Dobutamine Cardiovascular Magnetic Resonance in patients Suspected of Myocardial Ischemia.

Dirkjan Kuijpers, Paul R M van Dijkman, Caroline H C Janssen, Rozemarijn Vliegenthart, Felix Zijlstra, Matthijs Oudkerk

From the Department of Radiology and the Department of Cardiology, State University and Academic Hospital of Groningen, Groningen; the Department of Radiology and the Department of Cardiology, Bronovo Hospital, The Hague, the Netherlands.

Published in

Eur Radiol 2004; 14 (11): 2046-2052

Presented in part at the:

ESCR October 31 - November 1, 2003, Berlin

ESCR Januari 31 - Februari 2, 2004, Curacao

NVVR Februari 17-20, 2004, Utrecht

and

Awarded as best scientific paper and best oral presentation at the cardiac section ECR March 5-9, 2004, Vienna

Abstract

Objective The aim of this study was to determine the prognostic value of dobutamine cardiovascular magnetic resonance (CMR) in patients suspected of myocardial ischemia.

Materials and Methods Clinical data and dobutamine CMR results were analyzed in 299 consecutive patients. Follow-up data were analyzed in categories of risk levels defined by history of coronary artery disease and presence of rest wall motion abnormalities (RWMA). Major adverse cardiac events (MACE) as evaluated end points included cardiac death, nonfatal myocardial infarction and clinically indicated coronary revascularization.

Results Follow-up was completed in 214 (99%) patients with a negative dobutamine CMR study (no signs of inducible myocardial ischemia) with an average of 24 months. The patients with a negative dobutamine CMR study and RWMA showed a significantly higher annual MACE rate (18%) than the patients without RWMA (0.56%) ($p<0.001$). Patients without RWMA showed an annual MACE rate of 2 % when they had a history of coronary artery disease and < 0.1 %, without a previous coronary event ($p<0.001$). Dobutamine CMR showed a positive and negative predictive value of 95 and 93%, respectively. The cardiovascular occurrence-free survival rate was 96.2%.

Conclusions In patients suspected of myocardial ischemia, dobutamine CMR is able to assess risk levels for coronary events with high accuracy.

Key Words: magnetic resonance imaging • myocardium • stress • ischemia • prognosis

Introduction

The appropriate management of patients with symptoms and signs of myocardial ischemia is primarily based on noninvasive risk assessment of their risk for future major adverse cardiac events (MACE) [1, 2]. The standard exercise ECG test is the most applied noninvasive exercise test in patients with a normal resting ECG who are able to perform exercise [1, 2]. Patients with a low risk exercise ECG have an excellent prognosis and for patients with a high risk it is justified to perform coronary angiography [3, 4]. The patients who are not able to perform exercise and patients with an intermediate-risk based on exercise ECG, who form at least 50 % of the patients undergoing exercise testing, remain a diagnostic problem to the treating physician [4, 5]. To optimize risk stratification in this group of patients additional cardiac stress imaging is necessary, which formed the basis of this study. Dobutamine cardiovascular magnetic resonance imaging (CMR) is used to identify wall motion abnormalities of the left ventricle, indicative for myocardial ischemia in patients with proven or suspected coronary artery disease (CAD) [6-10]. Dobutamine CMR has shown to be an accurate and safe diagnostic modality to assess myocardial ischemia [7-10], however the prognostic value is not well established. The purpose of this study was to determine the prognostic value of dobutamine CMR for MACE in patients suspected of myocardial ischemia.

Methods

Patients and Study Design

Patients suspected of myocardial ischemia were prospectively enrolled for dobutamine CMR irrespective of a previous coronary event, between August 1999 and July 2002. The patients were recruited from the outpatient clinic of the Department of Cardiology. All patients had an inconclusive diagnosis of myocardial ischemia by means of clinical findings, ECG-recording at rest and an intermediate-risk at bicycle exercise ECG stress-test [1, 2]. Patients who were not able to perform an exercise ECG test were classified as having an unknown exercise risk score. Patients with an acute coronary syndrome, atrial fibrillation, severe arterial hypertension (> 220/120 mmHg), CMR incompatible metallic implants, and contraindications for dobutamine or known claustrophobia were excluded from enrollment. To ensure cardiac response to dobutamine, all anti-anginal medication was stopped 4 days before the dobutamine CMR examination. The Medical Ethics Committee approved the study protocol. All subjects gave informed consent.

Dobutamine CMR

The imaging methodology of dobutamine CMR has been described in detail previously [9]. In brief, CMR was performed using a standard 1 T CMR system (Impact-Expert, Siemens, Erlangen). Short axis cine breath-hold CMR images of the left ventricle with and without myocardial tagging were taken at rest and during incremental dosage of dobutamine (10, 20, 30 and 40 μg/kg per minute) at

6 minutes per stage. We used an ECG-triggered segmented gradient-echo pulse sequence: FLASH; TR: 90msec; TE: 6.1 msec; α: 25°; FOV 325-350 mm; slice-

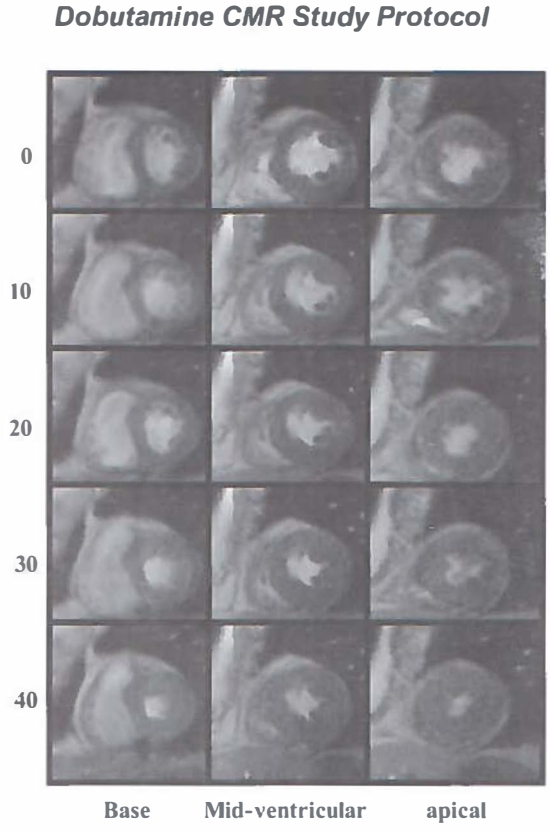

Figure 1.

Dobutamine stress MRI protocol at baseline (0) and during dobutamine infusion at 10, 20, 30 and 40 μg/kg per minute. Short axis views of the left ventricle (base; midventricular; apex) showing increase of systolic wall thickening as a normal reaction at increasing dosis of dobutamine.

thickness 8 mm. 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. Myocardial tagging was performed with a standard FLASH grid-sequence: TR: 96 msec; TE: 4.4 msec; α: 15°; FOV 325-350 mm; slice-thickness 8 mm).

Myocardial ischemia was defined as a new (induced) or worsening wall motion abnormality in at least two segments of consecutive planes of the left ventricle during infusion of dobutamine. The absence of new or worsening wall motion abnormalities was defined as a negative (non ischemic) dobutamine CMR study (Fig. 1). A RWMA was defined as hypokinesia, akinesia or dyskinesia in one or more segments during rest. The wall motion score index was derived as the mean score of 16 segments of all short-axis images [11]. Images were analyzed during and directly after the examination by two experienced investigators who interpreted the images independently. Differences in classifications were settled in a consensus review. Cine images were analyzed directly without post-imaging processing. When new wall motion abnormalities were detected, indicating inducible myocardial ischemia, the dobutamine-CMR study was followed by coronary angiography within 3 weeks. Hemodynamically significant coronary artery disease was defined as a diameter reduction of >50% in one or more major epicardial coronary arteries.

Follow-Up

Follow-up data were obtained in February 2003. Two physicians unaware of the dobutamine CMR testing results assessed the events of the patients. The present

status was determined by review of the hospital medical records and/or by contacting the patient's general physician. The date of the last review or interview was used to calculate follow-up time. A previous coronary event was defined as the presence of a history of myocardial infarction or coronary revascularization. Evaluated end points were nonfatal myocardial infarction (angina of > 30 minutes duration and either ≥ 2 mm ST segment elevation in 2 consecutive ECG leads or a rise in creatine kinase level and its myoglobine fraction 2 times the upper limit of normal) [12], cardiac death (death in the presence of acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure) [13] and coronary revascularization. The decision to perform coronary revascularization was solely based on objective signs of myocardial ischemia (>3 months after the initial negative dobutamine CMR study). Patients who returned with new symptoms with an acute coronary syndrome or were known with RWMA were admitted directly for coronary angiography. In the other patients with new symptoms myocardial ischemia was confirmed by a new dobutamine CMR and if positive coronary angiography. Deaths due to other causes were recorded. In case of two MACE, the worst event was chosen as outcome (cardiac death over myocardial infarction over coronary revascularization). Follow-up of the patients with a negative dobutamine CMR study was completed in 99 % of the patients. The mean follow-up period was 24 months, with a SD of 11 (range from 7 to 43 months). The target heart-rate (THR) rule (defined as 85% of the maximum exercise heart rate predicted for age and sex (220 minus age in men; 200 minus age in women) was used retrospectively in this study to correlate MACE with patients who reached a submaximal heart rate.

Statistical Analysis

Baseline clinical and dobutamine CMR characteristics are given as mean value ± SD for continuous variables and as number (%) for categorical variables. Patients were classified according to the history of coronary events, presence and extent of RWMA and the presence of new wall motion abnormalities. The probability of the absence of MACE as a function of follow-up duration was estimated by the Kaplan-Meier method. The annual (1 year) MACE rates were compared between groups by use of the log-rank test. A p value of 0.05 or less was considered to indicate statistical significance.

Results

Demographic and Dobutamine CMR Results

A total of 327 patients were eligible for enrollment; 24 (7 %) patients could not be investigated adequately because of minor side effects (n=13), breathing artifacts (n=4), claustrophobia (n=5) or because anti-anginal medication was not stopped in time (n=2). The follow-up data of 2 patients were not available and 2 patients refused to undergo angiography. Data of 299 patients were analyzed.

Eighty-five (28 %) patients with a positive dobutamine CMR, indicative of inducible myocardial ischemia were examined by coronary angiography. 81 (95 %) of these 85 patients were found to have significant coronary artery disease. False positive findings were found in 4 patients. Seventy-four of these remaining 81 patients underwent early coronary revascularization (68 within 60 days and 6 within 90 days). Coronary revascularization was technically not feasible in 7 of

81 patients due to the presence of diffuse severe coronary atherosclerosis. The mean maximum dose of dobutamine in this group of patients was 32.29 ± 8.31 μg/kg per minute. From the patients with a positive dobutamine CMR study 4 died, one of them during, and 3 patients more then 2 months after the coronary revascularization procedure. One patient died of malignancy.

Follow up was obtained of the remaining 214 (72 %) patients with a negative dobutamine CMR study. Data from these patients, who were treated medically, are reported in Table 1. The mean rate-pressure product during the test increased from 11.967 ± 3.381 to 22.818 ± 5.088; heart rate increased from 81 ± 17 to 130 ± 21 beats per minute and systolic blood pressure from 148 ± 31 to 175 ± 29 mm Hg. The mean maximum dose of dobutamine of the studies was 36.85 ± 6.08 μg/kg/minute. No myocardial infarctions or fatal complications occurred during the studies. The mean wall motion score index of patients with RWMA and a negative dobutamine CMR study was 1.26 ± 0.19 at both rest and peak dose dobutamine. The total duration of the CMR study, including preparation of the patient and scan time, averaged 48 minutes (SD, 12).

Follow-up results of dobutamine CMR negative patients

During the mean follow up of 24 months (SD, 11 months) the total number of MACE was 15 (7 %) in 214 patients with a negative dobutamine CMR study.

Of the 178 patients, without RWMA with a negative study, 6 suffered an event. All events were coronary revascularizations (3: percutaneous transluminal coronary angioplasty; 3: coronary artery bypass grafting). These 6 events occurred 5-36 months (mean 21.7 months) after the dobutamine CMR study, and

TABLE I.

Demographic data and major adverse cardiac events in patients with a negative dobutamine CMR study, with and without rest wall motion abnormalities.

(N=214)	+RWMA (N=36)	-RWMA (N=178)
Patient characteristics		
Age (year)	63±11	63±12
Women/men (n)	7:29	28:150
Weight (kg)	77±17	78±13
Clinical Data		
Hypertension	9(25)	51(29)
Diabetes Mellitus	6(17)	29(16)
Hypercholesterolemia	12(33)	52(29)
Prior Revascularization	9(25)	31(18)
Prior MI	31(86)	43(24)
Prior MI and or prior revascularisation	31(86)	46(26)
No History of CAD	5(14)	132(74)
Use of beta blocker	10(28)	54(30)
Age > 70 year	11(31)	61(34)
Dobutamine-CMR data		
WMSI: 1.12-1.25	28(78)	0
WMSI: 1.37 or greater	8(22)	0
MACE		
Cardiovascular death	1(3)	0
Nonfatal myocardial infarction	3(8)	0
Clinically indicated revascularisation	5(14)	6(3.4)

Values are expressed as n (%) unless otherwise indicated; RWMA, resting wall motion abnormalities; CAD, coronary artery disease; WMSI, wall motion score index; MACE, major adverse cardiac events.

TABLE 2.

Risk levels of the different patient groups according to the history of coronary artery disease and rest wall motion abnormalities in patients with a negative dobutamine CMR study.

Risk Level	Numbers	History of CAD / MI	Presence of RWMA	One year MACE rate (%)
Low	(n = 132) 44%	No	No	<0.1
Intermediate	(n = 46) 15%	Yes	No	2
High	(n = 36) 12%	Yes/No	Yes	18

CAD, coronary artery disease; RWMA, rest wall motion abnormalities; MACE, major adverse cardiac events; MI, myocardial infarction.

after the onset of new symptoms (4 of the 6 patients with an event present themselves with an acute coronary syndrome) and were confirmed by coronary angiography.

In the 36 patients with RWMA 9 events occurred: documented cardiac death in 1, nonfatal myocardial infarction in 3 and coronary artery bypass grafting in 5 patients. These 9 events occurred 2-32 months (mean 11 months) after the dobutamine CMR study, after the onset of new symptoms and were confirmed by coronary angiography.

During the follow-up period of all the patients with a negative dobutamine CMR study, the 2-year event rate for myocardial infarction, cardiac death and coronary revascularization was 3.1 % for the patients without RWMA and 27.2 % for the patients with RWMA. The positive and negative predictive values of the dobutamine CMR test were 95 % (0.908-0.998) and 93 % (0.896-0.964), respectively. The cardiovascular occurrence-free survival rate was 96.2 % during

the mean follow-up of 24 months. The proportion of patients free of events is shown in Kaplan-Meier curves (Fig. 2). The annual MACE rates were 0.56 % in 178 patients without RWMA and 18 % (highest risk level) in the 36 patients with RWMA (log-rank $p<0.001$). The different risk levels are presented in Table 2. Of the 6 patients without RWMA and a negative dobutamine CMR study who suffered an event, 5 of them were known with a previous myocardial infarction or previous coronary revascularization. This subgroup (1B) of 46 patients with a previous coronary event showed an annual MACE rate of 2 % (intermediate risk level) and the subgroup (1A) without a history of coronary artery disease (132 patients) <0.1 % (lowest risk level). There was a significant difference in MACE free survival of the patients with RWMA (1A versus 1B or group 2: $p<0.001$ and 1B versus group 2: $p<0.05$). The Kaplan-Meier curves of the 3 groups are presented in Fig. 3.

Table 3 summarizes the dobutamine CMR results of all the studies in relation to the history of myocardial infarction and coronary revascularization. In 137 (84 %) of 164 patients without such a history, dobutamine CMR showed no evidence of myocardial ischemia. The annual MACE rate in this group of patients was <0.1 %. If we also exclude diabetes mellitus in this patient group, the annual MACE rate would decrease to 0 %. Of the patients with a negative dobutamine CMR study, 33 % reached a submaximal heart rate (chronotropic incompetence according to THR rule) However, there was no significant difference in MACE between the patients who reached the THR and those who did not ($p>0.05$). Also, the mean rate-pressure product, as a measure of maximum stress testing, of the patients with and without an event did not differ significantly ($p>0.05$).

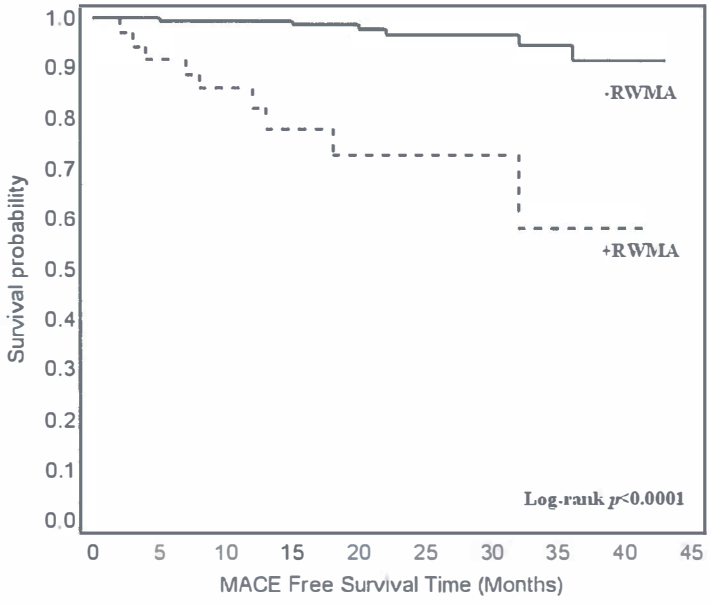

Figure 2.

Kaplan-Meier curves showing survival free from major adverse cardiac events (MACE) during follow-up for negative dobutamine CMR studies with (dotted line, N=36) and without (black line, N=178) rest wall motion abnormalities (log-rank $p<0.001$).

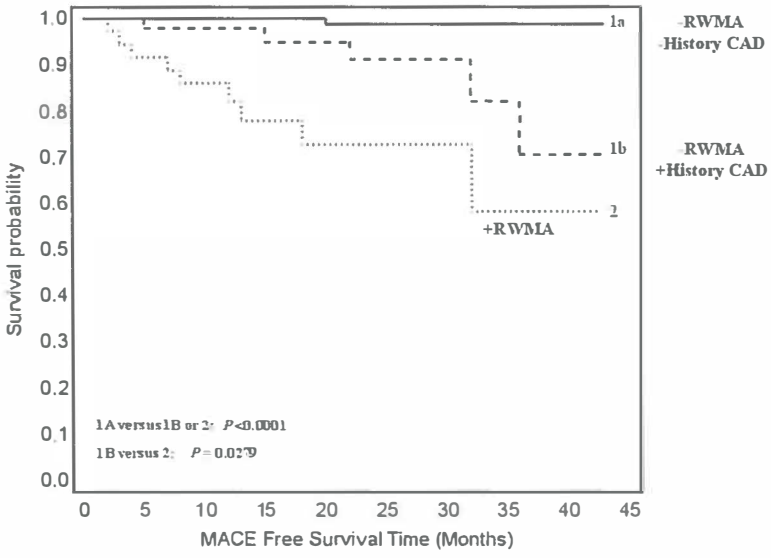

Figure 3.

Kaplan-Meier curves showing survival free from major adverse cardiac events (MACE) during follow-up for negative dobutamine CMR studies without rest wall motion abnormalities (RWMA), group 1A and 1B and with RWMA (group 2, N=36). Group 1A: patients without history of coronary artery disease (N=132). Group 1B: patients with a history of coronary artery disease (N=46). 1A vs. 1B or 2: log-rank $p<0.001$; Group 1B vs. 2: log-rank $p<0.05$.

TABLE 3.

Correlation of history of coronary artery disease [Myocardial Infarction (MI) and coronary revascularisation] with dobutamine CMR.

	+MI +Revascularisation	–MI –Revascularisation	Total number
+ Dobutamine CMR	58 (43 %)	27 (16 %)	85
– Dobutamine CMR	77 (57 %)	137 (84 %)	214
Total numbers	146 (100 %)	164 (100 %)	299

DISCUSSION

This is the first prospective dobutamine CMR study in a well defined patient group which shows that cardiac prognosis can be assessed in patients suspected of myocardial ischemia. Our results show that the overall annual MACE rate, including myocardial infarction and cardiac death as end points of the follow-up, is less then 1 %, which is similar to that shown with DSE [14].

In addition, we performed an analysis by including coronary revascularization as an end point of the study as well. By adding revascularization, the number of events will be reflected particularly in the patients who are at high risk for coronary events. However, the intent to perform a revascularization procedure can be a potential problem in longitudinal follow up studies, because it may be determined on an individual basis. The decision to perform a revascularization in the patients in our study who returned with new symptoms was made on criteria

of objective signs of myocardial ischemia within the same team of medical specialists, leaving no room for individual decision making.

If coronary revascularization is added as an end point, three significant groups of patients can be distinguished with different risk levels for MACE. The lowest risk level includes the patients without RWMA and without a prior history of coronary artery disease with an annual MACE rate of < 0.1 %. These patients have an excellent prognosis and probably do not require clinical follow-up. The highest risk level includes the patients with RWMA, with an annual MACE rate of 18 %. The patients without RWMA and a history of CAD showed an annual MACE rate of 2 %. RWMA are the hallmark of prior myocardial infarctions, and survivors of myocardial infarctions have a MACE rate up to 14 times that of the general population [15], which is reflected in the results of this study.

There is only one report which describes the prognostic value of dobutamine CMR; however, the patient group was ill defined and was therefore not comparable to this study [10]. Of the group of patients with an inconclusive diagnosis of myocardial ischemia, 28 % were found positive at dobutamine CMR. This number is relatively low compared to other studies [7, 8], because the patients with severe angina and a high-risk exercise ECG are not included in our group of patients. Because of the high sensitivity and specificity of dobutamine CMR, it also has the potential to reduce the number of "negative" invasive angiograms, besides its ability to detect myocardial infarctions [16, 17] and ischemia [6-10]. In the United States more than 1 million invasive diagnostic coronary angiography procedures are performed annually and between 20 and 40 % of them reveal no clinically significant coronary artery stenoses [18].

Recently, an approach was suggested for the assessment of coronary risk and selected use of noninvasive tests in asymptomatic patients [19]. It was suggested that in patients with an intermediate coronary risk, noninvasive testing could improve the assessment of risk and alter the categorization of these patients (to a low or high coronary risk profile) in order to affect preventive strategies. A low, intermediate and high coronary risk profile was defined as a 10-year risk of coronary events of <10 %, 10 to 20 % and >20 %, respectively [20]. This approach was applied on asymptomatic patients; however, the patients in our study showed a variety of complaints which are in fact non-specific complaints for coronary artery disease. Following from this observation, the patient population in our study consists basically of two groups. The first group can be placed in the high coronary risk profile, because of established coronary artery disease (i.e., myocardial infarction). The patients with a high coronary risk profile and negative findings of dobutamine CMR will stay at that high level, for the long term, despite the negative findings of dobutamine CMR. Whatever the outcome of dobutamine CMR in these patients will be, this will not modify decisions regarding preventive therapy to reduce their coronary risk factors. Only the detection of myocardial ischemia will be an indication for immediate coronary angiography and if possible invasive coronary intervention to improve their survival [3]. The second group is composed of all the other patients whom have to be regarded as non-classified. The results of clinical findings and exercise ECG classified the patients in our study as having an intermediate or unknown risk. Our study showed that in the assessment of coronary risk, dobutamine CMR is able to differentiate these patients in a lower or higher coronary risk profile. Eighty-four percent of the patients without a prior coronary event were categorized or recategorized to a

lower coronary risk profile. The remaining patients (16 %) were shifted to the high coronary risk profile because of positive findings at dobutamine CMR.

Patients who reached a submaximal heart rate (chronotropic incompetence) according to the THR rule were present in 33 % of the examinations, which is similar to previous reports [21]. In this study, there was no significant difference in MACE between the patients who reached the THR and those who did not. The clinical meaning of chronotropic incompetence in the context of dobutamine stress testing is not clear and this phenomenon may be the result of applying an inappropriate gold standard [21].

Until now, there are only limited reports available of stress perfusion CMR for the detection of myocardial ischemia [22]. It is unknown yet whether function (dobutamine) or perfusion (adenosine) CMR provides the most accurate information in the detection of myocardial ischemia. Perfusion CMR would expect to perform better, since it is at the origin of the ischemic cascade; however, the additional value of perfusion CMR is probably limited because dobutamine CMR alone yields already a high diagnostic accuracy. The CMR perfusion technique [22] requires substantial post processing time, which is in contrast to dobutamine CMR were cine images can be evaluated instantly to decide whether or not myocardial ischemia is present and whether or not the infusion of dobutamine should be stopped to avoid overstressing, which may lead to complications [9]. Both stress CMR modalities compare favorable with stress echocardiography [7] and perfusion scintigraphy [23, 24].

The major advantage of CMR over other stress imaging modalities is its high spatial resolution, which makes it possible to combine dobutamine CMR with contrast enhancement studies of the myocardium [16, 17, 25-28], and particularly the subendocardium [29]. The intermediate risk profile found in this study may represent a group of patients with subendocardial non-Q-wave infarcts, because these small infarcts do not give RWMA. Dobutamine CMR in combination with late contrast enhancement with gadolinium may clarify this hypothesis. Direct comparative studies will be necessary to evaluate the relation between wall motion abnormalities and perfusion defects of the left ventricle in order to optimize CMR stress imaging even further.

This follow-up study shows limitations. Because coronary angiography was not performed in all the patients with a negative dobutamine-CMR study, the sensitivity and specificity of the test could not be determined. The cine images were analyzed semi-quantitatively. Possible improvements could be acquired using quantitative wall motion analysis soft ware; however, currently it is a time-consuming procedure, and no decisions can be made during the study to stop the procedure when a patient becomes ischemic. We used a 1 Tesla-MR system. The more standard 1.5 Tesla systems can reduce cine acquisition substantially, which improves patient acceptance and image quality.

Conclusion

The practical implications from this study can be summarized as follows:

From the patients presenting with chest pain without a history of coronary artery disease and an inconclusive diagnosis of myocardial ischemia, 44 % show no wall motion abnormalities at dobutamine CMR. The results of this study indicate

that in this group of patients, cardiac prognosis is excellent and further clinical follow-up is not needed.

The patients with a positive dobutamine CMR study (28 %) can be examined with coronary angiography and, if possible subsequent coronary revascularization.

In the remaining patients with a negative dobutamine CMR study, especially the patients with RWMA (12 %), no acute invasive evaluation of their coronary arteries is necessary. However, because of the high risk of future MACE, this group of patients needs to be followed closely.

Acknowledgements

We are indebted to Dr. W.J. Post for data analysis.

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Chapter 9

Summary / Samenvatting
Curriculum Vitae
List of Publications

Summary

In the past five years cardiovascular magnetic resonance imaging (MRI) has emerged as a new noninvasive imaging modality providing high-resolution images in any desired plane of the heart, combined with the potential to assess and monitor regional left and right ventricular function. The improved temporal resolution of new-fast gradient echo MR sequences such as True Fisp, FFE or FIESTA, enables one to capture cine loops displaying the beating heart, allowing a qualitative and quantitative analysis of wall motion with well defined endocardial and epicardial borders of the myocardium. The excellent quality of the MR images explains the development of MR stress techniques for the evaluation of myocardial ischemia and myocardial viability in the clinical work up. The studies described in this thesis are based on MRI with the use of high dose dobutamine for the assessment of wall motion abnormalities of the left ventricle. All studies were performed in a single center during a period of 4 years on a 1 Tesla MR system. This thesis focuses on the detection of wall motion abnormalities indicative for myocardial ischemia. Besides the analysis of the standard cine-loops of the left ventricle, a grid-tagging MR technique was used to for the detection of wall motion abnormalities.

In **Chapter 2**, pharmacological cardiac stress imaging is reviewed, especially the effects of catecholamines. Dobutamine, as a synthetic catecholamine, has a combined positive inotropic- and chronotropic effect, which both increase myocardial oxygen demand. During high-dose infusion, stimulation of cardiac contractility persists and heart rate increases further, whereas the reduction in

systemic vascular resistance is less pronounced, resulting in a rise in systemic blood pressure. These properties produce hemodynamic effects similar to exercise. The advantages and disadvantages of dobutamine in relation to other catecholamines are discussed.

A modified dobutamine Stress MRI protocol is presented in **Chapter 3**. In general, three left ventricular short axis planes are examined for the occurrence of disorders in wall movement during infusion of increasing doses of dobutamine (10, 20, 30 and 40 μg/kg/min). In our studies, a different stress protocol was used compared to the methods reported previously in high dose dobutamine MR studies. First, to ensure cardial response to dobutamine, we stopped all anti-anginal medication four days prior to the dobutamine stress MRI examination. In most imaging protocols, beta-blocker medication is withheld only one day prior to the study. Most of our patients use beta-blockers (metoprolol) with long half-lives (e.g., 24 h), which should be stopped at least 3 to 4 days to minimize their activity. The risk of beta-blocker withdrawal, including severe hypertension or an unstable coronary syndrome, is mainly based on literature regarding propranolol, which is not used in our institution for the treatment of angina pectoris and myocardial ischemia.
Second, the dobutamine infusion time was prolonged from 3 to 6 minutes per stage, mainly because of imaging reasons. The additional advantage of this prolonged infusion time is discussed.

Chapter 4 discusses the MR imaging procedure, the pathophysiology of the ischemic cascade and reviews the literature with regard to MR stress imaging.

In **Chapter 5,** a pilot series of 100 patients is presented in whom this modified dobutamine stress MRI protocol for the detection of myocardial viability and myocardial ischemia was used. The assessment of the clinical applicability is discussed, including advantages and disadvantages of the used technique. Of the 100 patients subjected to dobutamine stress MRI, 95 yielded results suitable for diagnosis. Of the 42 patients, who were considered positive for ischemia and in whom coronary angiography was subsequently performed, 41 had such coronary abnormalities that revascularization was indicated. The 53 patients, who were considered negative, were followed for 11-23 months (mean follow up 17 months). The predictive value of a positive dobutamine stress test was 98 % and the predictive value of a negative test was also 98 %. No severe complications were encountered.

Chapter 6 describes a myocardial grid-tagging technique with cine gradient MRI, which improves the detection of wall motion abnormalities, indicative of myocardial ischemia. The purpose of this study was to assess the additional value of myocardial tagging for the detection of wall motion abnormalities as a measure of myocardial ischemia in patients with known or suspected coronary artery disease.

Two hundred eleven consecutive patients with chest pain underwent dobutamine-MRI with this new imaging technique. Cine images were acquired during breath-hold with and without myocardial tagging at three short-axis levels. Regional

wall motion was assessed in a 16-segment short-axis model. Patients with new wall motion abnormalities (NWMA) were examined by coronary angiography. Dobutamine stress MRI was successfully performed in 194 patients. Dobutamine Stress MRI without tagging detected NWMA in 58 patients, whereas NWMA were detected in 68 patients with tagging (P=0.002 McNemar). Coronary angiography showed coronary artery disease in 65 (96%) of these 68 patients. All but three of the 65 patients needed revascularization. The cardiovascular occurrence-free survival rate in the 112 patients with a negative dobutamine-CMR study, with no baseline wall motion abnormalities, was 98.2% during the mean follow-up period of 17.3 months (range 7 to 31). The conclusion of this study was that Dobutamine stress MRI with myocardial tagging detected more NWMA compared to dobutamine stress MRI without tagging. It also reliable separated patients with a normal life expectancy from those with increased risk of major adverse cardiac events.

Chapter 7 presents the safety and feasibility of dobutamine stress MRI in a series of 400 patients with proven or suspected coronary artery disease. Dobutamine was infused using an incremental protocol up to 40 μg/kg body weight per minute. All anti-anginal medication was stopped 4 days prior to the MRI study and infusion time of dobutamine was 6 minutes per stage. Hemodynamic data, MRI findings and side effects were reported. Patients with contraindications to MRI (metallic implants and claustrophobia) were excluded from analysis. Dobutamine MRI was successfully performed in 355 (89%) patients. Forty-five (11%) patients could not adequately be investigated because of non-cardiac side effects in 29 (7%), and cardiac side effects in 16 (4%)

patients. Hypotension (1.5%) and arrhythmias (1%) were the most frequent cardiac side effects. One patient developed a severe complication (ventricular fibrillation) at the end of the study. No myocardial infarctions or fatal complications of the stress test were observed. The most frequent non-cardiac side effects were nausea, vomiting and claustrophobia. Age >70 years, prior myocardial infarction and rest wall motion abnormalities showed no significant differences with side effects (p> 0.05). The conclusion of this study was that dobutamine stress MR is safe and feasible in patients suspected for myocardial ischemia.

In **Chapter 8** a follow-up analysis is presented in patients with a negative (non inducible myocardial ischemia) dobutamine stress MRI study, suspected for myocardial ischemia. Clinical data and dobutamine MRI results were analyzed in 299 consecutive patients. Follow-up data were analyzed in categories of risk levels defined by history of coronary artery disease and presence of rest wall motion abnormalities (RWMA). Major adverse cardiac events (MACE) as evaluated end points included cardiac death, nonfatal myocardial infarction and clinically indicated coronary revascularization. Follow-up was completed in 214 (99%) patients with a negative dobutamine MRI study with an average of 24 months. Patients with a negative dobutamine MRI study and RWMA showed a significantly higher annual MACE rate (18%) than patients without RWMA (0.56%) (p < 0.001). Patients without RWMA showed an annual MACE rate of 2% when they had a history of coronary artery disease and < 0.1 %, without a previous coronary event (p< 0.001). Dobutamine stress MRI showed a positive and negative predictive value of 95% and 93%, respectively. The cardiovascular occurrence-free survival rate was 96.2%.

In conclusion:

The presented studies in this thesis focus on the application of dobutamine stress MRI in patients with stable chest pain, most likely due to obstructive coronary artery disease. In comparison with the standard gradient MR sequences, a significant higher number of patients with wall motion abnormalities, indicative of myocardial ischemia, could be detected with the use of the myocardial grid-tagging MR technique. In addition, dobutamine stress MRI showed to be a safe and feasible stress imaging technique in a series of 400 patients. During a follow-up period of 2 years, dobutamine stress MRI was able to assess risk levels for major adverse coronary events with high accuracy.

Samenvatting

In de afgelopen vijf jaar heeft de magnetische resonantie (MR) zich op het gebied van cardiovasculair onderzoek ontwikkeld tot een betrouwbare, niet-invasieve beeldvormende modaliteit, waarmee beelden met een hoge ruimtelijke resolutie kunnen worden geacquireerd en gereconstrueerd in elk gewenst vlak door het hart. Daarnaast is de tijdsresolutie zo hoog dat een groot aantal beelden per seconde kan worden gegenereerd, waardoor de wandbewegingen van linker- en rechter hartkamer goed in beeld kunnen worden gebracht. De temporele resolutie van de nieuwe snelle gradiënt-echo MR sequenties, zoals True-FISP, FFE of FIESTA, maakt het mogelijk om de hartspier (myocard) kloppend zichtbaar te maken en dit als bewegende beelden in cine-loops weer te geven. De contouren van de linker- en rechter kamer komen hierbij goed in beeld, waardoor het mogelijk is een kwalitatieve en kwantitatieve analyse uit te voeren van de wandbewegingen van het myocard. Onderzoek van de spierfunctie van het hart tijdens lichamelijke of tijdens farmacologisch geïnduceerde inspanning (stress-onderzoek) werd en wordt routinematig verricht onder ECG controle of door middel van echografische visualisatie. Vanwege de superieure kwaliteit van de MR beelden heeft het stress onderzoek onder MR visualisatie, voor de evaluatie van zowel ischemie als vitaliteit van het myocard, zich als belangwekkend alternatief ontwikkeld.

Voor de farmacologische inspanningsinductie werden de studies, beschreven in dit proefschrift, uitgevoerd met behulp van intraveneuze toediening van hoge dosis dobutamine voor het aantonen of uitsluiten van een verminderde doorbloeding van de hartspier (myocard-ischemie). Alle patiëntenonderzoeken werden verricht in

een periode van vier jaar op één en hetzelfde 1 Tesla MR systeem. Dit proefschrift richt zich op het aantonen van stoornissen van wandbewegingen van de linkerkamer, die het gevolg zijn van ischemie. Behalve van de directe beoordeling van de cine-loops van de kloppende hartspier wordt gebruik gemaakt van de zogenaamde grid-tagging techniek om het contractie-patroon van de verschillende spiersegmenten beter in onderlinge samenhang te kunnen beoordelen.

In **hoofdstuk 2** van dit proefschrift wordt een overzicht gegeven van farmacologische stoffen, die bij cardiale stresstechnieken worden gebruikt. In het bijzonder worden de eigenschappen en effecten van de catecholaminen beschreven. Dobutamine is een synthetische catecholamine, met een gecombineerd positief inotroop (contractiekracht) en chronotroop (hartfrequentie) effect, welke beiden de zuurstofbehoefte van het myocard verhogen. Gedurende het inspuiten (infusie) van een hoge dosis dobutamine neemt zowel de hartfrequentie, alsook de mate van contractie van het myocard toe. De toegenomen contractiliteit van het myocard veroorzaakt een stijging van de bloeddruk. Deze eigenschappen van dobutamine leiden tot hemodynamische effecten, die overeenkomen met fysieke inspanning. De halfwaardetijd van dobutamine is ongeveer 2 minuten, waardoor de techniek klinisch praktisch toepasbaar is. De voor- en nadelen van dobutamine in vergelijking met andere catecholaminen worden besproken.

In **hoofdstuk 3** wordt een gemodificeerd dobutamine stress MRI (Magnetic Resonance Imaging) protocol voorgesteld, zoals dat wordt toegepast in de patientenonderzoeken beschreven in dit proefschrift.
Dit dobutamine stress protocol omvat 3 parallelle korte-as opnamen van de linkerkamer gedurende infusie van een oplopend dobutamine dosisschema (10, 20, 30 and 40 µg/kg/minuut). Het protocol wijkt op een aantal punten af van bestaande MR stress protocollen. In de eerste plaats wordt alle anti-angineuze medicatie 4 dagen voor het onderzoek gestopt, om een adequate en gestandaardiseerde respons op de toegediende dobutamine te verkrijgen. De voorgeschreven beta-blokkers bij de onderzochte patiëntengroep hebben een lange halfwaardetijd tot maximaal 24 uur. Om zeker te zijn dat de effecten daarvan zijn uitgewerkt, moet tenminste 3 tot 4 dagen voor het begin van de stress studie met de medicatie gestopt worden. In de tweede plaats wordt de infusieperiode verlengd van 3 naar 6 minuten per dosisniveau om de beeldvorming te optimaliseren. De voordelen van een verlengd infusieprotocol, zoals een hogere stress factor, worden besproken.

In het kader van de pathofysiologie van de ischemische cascade wordt een overzicht van de bestaande literatuur met betrekking tot dobutamine stress MRI gegeven in **hoofdstuk 4.**

Het eerste cohort van 100 patiënten dat met dit dobutamine stress MRI protocol is onderzocht op vitaliteit en ischemie van de hartspier wordt gepresenteerd in **hoofdstuk 5**. De klinische toepasbaarheid en de voor- en nadelen van dit onderzoeksprotocol worden toegelicht. In 95 van de 100 onderzochte patiënten

werd optimale beeldvorming bereikt ter analyse van wandbewegingsstoornissen van de hartspier. Bij 42 patiënten werd ischemie vastgesteld. Met uitzondering van één patient konden door middel van invasief angiografisch diagnostisch onderzoek afwijkingen worden aangetoond in de kransslagaders, die met het stroomgbied van de afwijkende contraherende hartspier correspondeerden. Deze vernauwingen van de kransslagaders worden gezien als oorzaak voor de wandbewegingsstoornissen van de hartspier als gevolg van de verminderde perfusie (doorstroming) van het corresponderende stroomgbied. Bij deze groep patienten was revascularisatie geïndiceerd. De 53 patiënten, die negatief waren, werden 11-23 maanden vervolgd (gemiddeld 17 maanden). De voorspellende waarde voor een positieve dobutamine test was 98% en de negatief voorspellende waarde was eveneens 98%. Er werden geen ernstige complicaties geregistreerd.

Hoofdstuk 6 beschrijft de grid-tagging techniek voor het myocard met cine-gradient MR, die de detectie van wandbewegingsstoornissen, indicatief voor ischemie, verbetert. Het doel van deze deelstudie is om de meerwaarde van deze grid-taggingtechniek voor het aantonen van regionale wandbewegingsstoornissen bij patiënten, verdacht voor ischemisch coronair vaatlijden, vast te stellen. Deze nieuwe afbeeldingstechniek werd bij 211 opeenvolgende patiënten met pijn op de borst (stabiele angina) toegepast, naast de reeds bestaande standaard afbeeldingsmethode. De beelden zonder- en met taggingtechniek werden onafhankelijk van elkaar beoordeeld. Regionale wandbewegingsstoornissen werden geanalyseerd in een 16 segments korte-as model van de linkerkamer. Patiënten met nieuwe, geïnduceerde, wandbewegingsstoornissen werden aangeboden voor coronair angiografie. De stress-studie werd bij 194 patiënten

succesvol uitgevoerd. Zonder gebruik van grid-tagging werden bij 58 patiënten nieuwe wandbewegingsstoornissen ontdekt, met tagging echter bij 68 patiënten. Met angiografisch onderzoek werd dit bij 65 (96 %) van de 68 patiënten bevestigd. Bij 62 patiënten bleek een revascularisatieprocedure noodzakelijk. 98.2% van de 112 patiënten met een negatieve dobutamine stress studie, zonder wandbewegingsstoornissen in rust, bleef ziektevrij gedurende een vervolgperiode van 17 maanden. Uit dit onderzoek blijkt dat met dobutamine stress MRI in combinatie met de grid-tagging techniek significant meer nieuwe wandbewegingsstoornissen worden gedetecteerd dan zonder toepassing van deze techniek. Bovendien kan er een betrouwbaar onderscheid worden gemaakt tussen patiënten met een normale levensverwachting en die met een verhoogd risico op cardiale complicaties.

De toepasbaarheid en de veiligheidsaspecten van dobutamine stress MRI (**hoofdstuk 7**) is onderzocht bij 400 opeenvolgende patiënten. Bij 355 (89%) patiënten werd de stress studie succesvol uitgevoerd. Vijfenveertig (11%) patiënten konden niet onderzocht worden vanwege niet-cardiale complicaties bij 29 (7%) van hen en cardiale complicaties bij 16 (4%)van hen. Bloeddrukdaling (1.5%) en ritmestoornissen (1%) waren de meest frequente cardiale bijwerkingen. Eén patiënt kreeg een ernstige complicatie (ventrikelfibrillatie) aan het einde van het onderzoek en werd succesvol gereanimeerd. Er traden geen myocardinfarcten of andere complicaties bij deze patiëntengroep op. De meest frequente niet-cardiale bijwerkingen waren misselijkheid, braken en claustrofobie. Er werd geen relatie gevonden tussen enerzijds de bijwerkingen en anderzijds: leeftijd boven 70 jaar, doorgemaakt myocard infarct, of wandbewegingsstoornissen in rust. Uit deze

studie blijkt dat dobutamine stress MRI een veilig en goed toepasbaar onderzoek is bij patiënten, die verdacht worden van myocard ischemie.

In **hoofdstuk 8** worden de vervolgresultaten gepresenteerd bij de patiënten met een negatieve dobutamine stress MRI (dat wil zeggen, geen tekenen van ischemie). Bij 299 opeenvolgende patiënten werden klinische vervolggegevens in het licht van de dobutamine stress MRI resultaten geanalyseerd. De vervolggegevens werden ook geëvalueerd bij 2 risico categorieën, namelijk bij patienten met een voorgeschiedenis van coronair vaatlijden en bij patiënten die bij onderzoek in rust wandbewegingsstoornissen hadden. Eindpunten voor deze studie waren: overlijden ten gevolge van een cardiale oorzaak, niet dodelijk myocardinfarct en klinisch geïndiceerde revascularisatie. De vervolggegevens waren bij 214 (99%) van de patiënten met een negatieve stress-studie volledig beschikbaar, met een gemiddelde follow up duur van 24 maanden. Patiënten met een negatieve dobutamine stress-studie, maar wel met wandbewegingsstoornissen in rust, toonden een significant hogere complicatiekans (18%) dan patiënten, die deze wandbewegingsstoornissen niet hadden (0.56%; $p<0.001$). Patiënten met een voorgeschiedenis van coronair vaatlijden (doorgemaakt myocardinfarct) toonden een complicatiekans van 2%, indien zij geen wandbewegingsstoornissen hadden in rust. Zonder een dergelijke voorgeschiedenis was dit percentage <0.1% ($p<0.001$). De positieve- en negatieve voorspellende waarde van dobutamine stress MRI voor een ziektevrije overleving van 2 jaar was respectievelijk 95 en 93%. Indien alleen gekeken werd naar cardiovasculaire oorzaken bedroeg deze overleving zelfs 96.2%.

Samenvattend:

Dit proefschrift richt zich op de toepassing van dobutamine stress MRI ter analyse van patiënten met pijn op de borst, als uiting van mogelijk onderliggend coronairlijden. Hierbij is gebleken dat, door gebruik te maken van "grid-tagging" als afbeeldingstechniek tijdens dobutamine stress MRI onderzoek, de kans op het aantonen van wandbewegingstoornissen van de hartspier, als gevolg van ischemie, wordt verhoogd. Tevens bleek bij 400 onderzochte patiënten dat dobutamine stress MRI een veilig en klinisch goed toepasbaar onderzoek is bij patiënten, die verdacht worden van myocard ischemie. De vervolgstudie gedurende een periode van 2 jaar toonde aan dat bij patienten met een negatieve dobutamine stress MRI studie een betrouwbare schatting kan worden gemaakt van de kans op het krijgen van myocardinfarct en cardiaal overlijden.

Curriculum Vitae

The author of this thesis was born in Schiedam, The Netherlands, on September 9, 1955. In 1972, he graduated from secondary education (HBS-B) at the Rijks Hogere Burgerschool Woerden. He started his medical training at the University of Leiden and obtained the Doctoral degree in medicine in 1978. His medical qualification was obtained in April 1980. In 1981, he started his radiological residency at the Academic Hospital Leiden (former head: Prof. Dr. A.E. van Voorthuisen). From 1982 to 1983, he was assistant-secretary of the Netherlands Society of Bone Tumors. He became a staff member (vascular and intervention section) of the department of Radiology at Leiden University Medical Center in 1985. From 1992 to 1993, he was a part-time staff member (MRI section) at the department of Radiology, Daniel den Hoed Cancer Clinic, Erasmus Medical Center, Rotterdam (former head: Prof. Dr. M. Oudkerk). Since 2002, he is a part-time staff member at the department of Radiology (Cardiac-Radiology), State University and Academic Hospital Groningen, Groningen (head: Prof.dr. M. Oudkerk). Since October 1985, he is working in the department of Radiology (general radiology and cardiac-radiology) at the Bronovo Hospital in The Hague (head of department). His work on Dobutamine stress MRI was awarded (Magna cum Laude) by the European Society of Cardiac Radiology (Berlin, November, 2003) and with the first prize in the cardiac section by the European Congres of Radiology (Vienna, March 2004). In November 2004, he was awarded with the "Haagse Specialisten-prijs" for his scientific work on Dobutamine Stress MRI.

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