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ORIGINAL ARTICLE
Perfusion

Dobutamine Induced Myocardial Perfusion Reserve Index with Cardiovascular MR in Patients with Coronary Artery Disease

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ABSTRACT

Currently, adenosine or dipyridamole is commonly used for the assessment of perfusion reserve. With intolerance to these agents, dobutamine can be used alternatively or it can be used for a combined examination of wall motion and perfusion. The aim of the study was to analyze the feasibility of cardiovascular magnetic resonance (CMR) to assess perfusion reserve with dobutamine.

Alterations of myocardial perfusion were noninvasively assessed in 23 patients with and 4 without significant coronary artery disease by calculation of a myocardial perfusion reserve index from the upslope of the signal intensity curves of a first pass gadolinium bolus before and during dobutamine infusion (20 μg/min/kg). An ischemic threshold value of perfusion reserve index was determined from patients without significant coronary artery disease.

Significant differences were found between ischemic and remote to ischemic segments in patients with single vessel disease (0.90 ± 0.18 vs. 1.73 ± 0.32, $p < 0.0001$*). Differences between nonischemic segments in patients without and ischemic segments in patients with coronary artery disease were significant*

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(2.0 ± 0.39 vs. 0.97 ± 0.20, $p < 0.001$). A cut-off value for myocardial perfusion reserve index of 1.22 for the detection of significant coronary artery stenosis yielded a sensitivity, specificity, and diagnostic accuracy of 81, 73, and 77%, respectively.

Dobutamine MR is feasible in the evaluation of myocardial perfusion and can be used for the detection of myocardial ischemia alternatively to adenosine or dipyridamole in patients with coronary artery disease.

Key Words: *Magnetic resonance; Perfusion reserve; Dobutamine; Coronary artery disease*

INTRODUCTION

One of the major advantages of cardiovascular magnetic resonance (CMR) in comparison with other techniques is the combination of different functional studies during one examination, such as the evaluation of wall motion abnormalities, perfusion defects, and viability. It was recently shown that the assessment of stress induced wall motion abnormalities with CMR is superior to echocardiography for the detection of significant coronary artery stenoses.[1] There is growing evidence that CMR can be used for the assessment of myocardial perfusion from the kinetics of a T1-shortening agent.[2–10] To circumvent the problems of absolute quantification of myocardial perfusion, several authors have determined myocardial perfusion at rest and stress to assess coronary artery disease in a semiquantitative approach.[2–8] In these studies, dipyridamole or adenosine was used for vasodilation, which has been shown to be feasible for the detection of coronary artery stenosis or evaluating the success of angioplasty or stenting.[2,3] Vasodilators, such as dipyridamole or adenosine, are very useful for perfusion studies as their primary effect is the induction of vasodilation with mild influence of hemodynamics.[11] However, some patients cannot be examined with these agents due to intolerance or contraindications such as asthma because they can provoke bronchospasm. In contrast, dobutamine has mainly positive inotropic and chronotropic effects with additional direct and indirect vasodilatory effects.[12,13] Through the stimulation of beta receptors, dobutamine increases cardiac work and, thus, oxygen demand. In the presence of a significant coronary stenosis, oxygen demand can exceed availability and induce myocardial ischemia with consequent wall motion impairment at higher doses. Through the vasodilatory effect of dobutamine, perfusion pressure decreases downstream of coronary stenosis and provokes additional ischemia.[12] It has been shown that myocardial blood flow responses to dobutamine and adenosine are linearly correlated over a wide range and that dobutamine induces a coronary steal effect with a frequency approaching that of adenosine.[14,15] Therefore, dobutamine may be valuable for the assessment of alterations of myocardial perfusion with CMR. Dobutamine has been extensively studied for the diagnosis of coronary artery disease and has been shown to be superior to other stress agents for the induction of wall motion abnormalities.[16–18] It has also been shown to be feasible for the evaluation of myocardial perfusion using PET and SPECT imaging.[19–25] These characteristics in the induction of myocardial ischemia make dobutamine a stress agent that can be used for an integrative CMR examination, which may allow the assessment of wall motion abnormalities and perfusion within a single stress test.

The aim of the current study was to evaluate the value of magnetic resonance imaging for the detection of significant coronary artery stenosis from the alterations of myocardial perfusion using dobutamine stress.

METHODS

Patients

Twenty-seven patients (20 males, 7 females, age 56 ± 9 years) with suspected or proven single or double coronary artery disease admitted to our institution for invasive coronary angiography were prospectively included in the study after written informed consent.

Patients were excluded if they had a history of prior myocardial infarction, unstable angina, triple vessel disease, hemodynamic relevant valvular disease, ventricular extrasystole ≥ Lown III, atrial fibrillation, ejection fraction < 40%, blood pressure > 160/95 or < 100/70 mmHg, known claustrophobia, or a contraindication for an MR examination such as incompatible metallic implants. Anti-angina medication and beta

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blockers were stopped at least 12 hr before the examination.

Coronary Angiography

All patients underwent cardiac catheterization and bi-plane selective coronary angiography. Coronary stenoses were filmed in the center of the field from multiple projections and, as much as possible, overlap of side branches and foreshortening of relevant coronary stenoses were avoided. Coronary angiograms were quantitatively assessed with the QANSAD® QCA system (ARRI, Munich, Germany), for high-grade stenosis ($\geq 75\%$ area stenosis). The examiner was blinded to the MR examination.

Cardiovascular Magnetic Resonance

All patients had a central vein catheter placed in the superior vena cava via the right cubital vein. The position of the catheter was controlled with x-ray and corrected if needed. Patients were examined in the supine position with a 1.5 T whole body MR tomograph (ACS NT, Philips, Best, The Netherlands), using a five-element phased array cardiac surface coil. After two rapid survey scans to determine the exact position and axis of the left ventricle, one short axis view at the height of the origin of the papillary muscles was chosen for perfusion imaging using an ECG triggered T1-weighted inversion recovery single shot turbo-gradient echo sequence (inversion pulse, prepulse delay 360 msec, flip angle 15°, echo time 1.7 msec, repetition time 9 msec). Slice thickness was 8 mm. During a short expiratory breath hold of 10 heartbeats, 10 dynamic images without contrast agent were acquired. During a second expiratory breath hold, a bolus of gadolinium-DTPA 0.025 mmol/kg body weight (Magnevist, Schering AG, Berlin, Germany) was rapidly injected manually and flushed through with 10 mL of 0.9% NaCl. Sixty dynamic images (one image per heart beat) were acquired during the first and second pass of the contrast agent (Fig. 1). Care was taken to achieve breath holding during the first passage of the contrast agent through the myocardium to minimize breathing artifacts. During the acquisition of later images, the patients were allowed to take single deep breaths when needed. Because of semiquantitative evaluation of the signal intensity curves a low dose of gadolinium-DTPA was injected rather than the higher doses usually used for qualitative assessment.

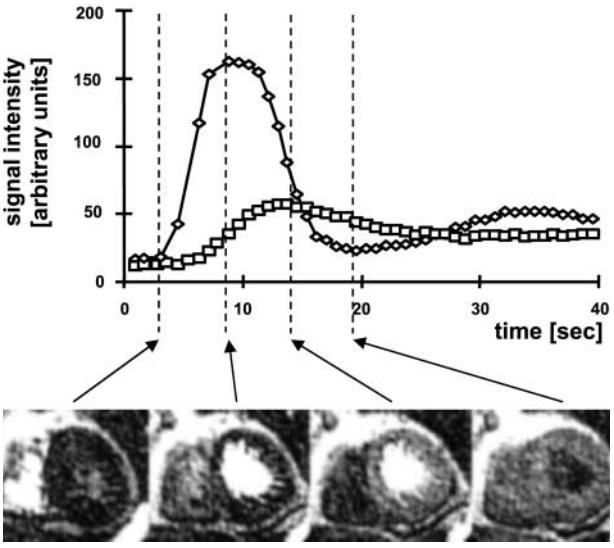

Figure 1. MR images of the transit of the gadolinium bolus through the right ventricle, the left ventricle, and the left ventricular myocardium with an example of a signal intensity time curve of left ventricular cavity (diamonds) and the myocardium (squares).

After 15 min, to allow for the clearance of the first contrast agent injection, dobutamine was administered beginning with 5, then 10, and 20 μg/min/kg body weight for 3 min each. During the last dose of dobutamine infusion, first pass perfusion was repeated identical to the rest protocol. Due to acquisition time, image acquisition had to be performed of every other heart beat at higher heart rates. An ECG rhythm strip was continuously acquired by using a standard MR equipment and blood pressure was measured every minute during the dobutamine infusion. The dobutamine infusion was discontinued upon patient request or when chest discomfort occurred, indicative of progressive or severe angina, or dyspnea, decrease in systolic pressure (>40 mmHg), severe supra-ventricular or ventricular arrhythmias, or other adverse effects occurred. A beta blocker was administered intravenously as clinically required.

Image Analysis

In all images, the endo- and epicardial contours were traced by an examiner, blinded to the angiographic results, and corrected manually for changes of diaphragmatic position due to breathing or diaphragmatic drift. Care was taken to place the contours on the myocardium and to exclude the left ventricular cavity and the pericardium. The myocardium was then divided into six

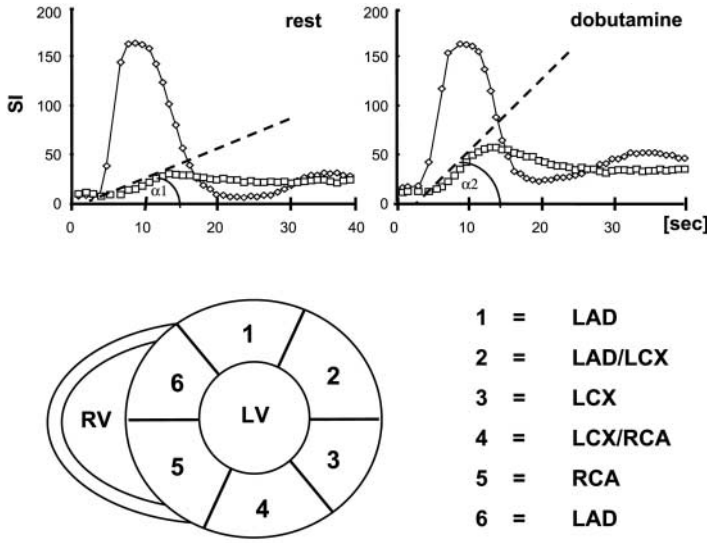

Figure 2. The six evaluated myocardial segments of the left ventricular myocardium with the determination of the coronary artery territories for each segment. Myocardial perfusion reserve index was calculated from the alterations of the upslopes at rest and during dobutamine infusion each after correction for the upslope of the left ventricular cavity. The upslope was determined using a linear fit. SI: signal intensity (arbitrary units); LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; RV: right ventricle; LV: left ventricle.

equiangular segments and numbered clockwise beginning with the anterior septal insertion of the right ventricle (Fig. 2). An additional region of interest was placed within the cavity of the left ventricle, which excluded the myocardial segments and the papillary muscles. Images acquired after premature ventricular beats or insufficient cardiac triggering were excluded from the analysis to guarantee steady-state conditions. Signal intensity was determined for all dynamics and segments (Fig. 1) and the upslope of the resulting signal intensity time curve was determined by the use of a linear fit (Fig. 2). To correct for possible differences of the input function, the results of the myocardial segments were corrected for the input function by dividing the upslope of each myocardial segment by the upslope of the left ventricular signal intensity curve, which was regarded as a measure of the input function. An index for myocardial perfusion reserve was calculated by dividing the results at maximum dobutamine infusion by the results at rest.[26]

Two experienced observers blinded to the results of MR examination decided from the angiographic appearance which of the six myocardial segments was supplied by which coronary artery. Segments 1 and 6 were always assigned to the left anterior descending coronary artery (LAD), segment 3 to the left circumflex coronary artery (LCX), and segment 5 to the right coronary artery (RCA). Segment 2 was either assigned to the LAD or the LCX, depending upon the angiographic appearance, and segment 4 was assigned in the same manner either to the LCX or to the RCA (Fig. 2).

Perfusion reserve index was calculated for all segments. Patients without coronary artery disease were used as controls and a threshold value was determined from all myocardial segments of controls by subtracting two standard deviations from the mean value. Segments with an index below the threshold value were defined as ischemic. MR was regarded as true positive if at least one segment within the territory of the stenotic coronary artery was found to be ischemic. Segments with an index above the threshold value were defined as nonischemic.

Statistical Analysis

If not otherwise referred to, continuous data are given as mean ± 1 standard deviation. An unpaired two-tailed Student's *t*-test was used for differences between examinations in myocardial segments supplied by

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Table 1

Patient Population

	CAD+, $n = 23$	CAD−, $n = 4$
Male/female	16/7	2/2
Age (years)	59 ± 8	53 ± 9
BSA (m^2)	1.95 ± 0.16	2.01 ± 0.12
CI ($l/min/m^2$)	3.9 ± 1.5	4.0 ± 1.3
Ejection fraction (%)	61 ± 9	62 ± 5

CAD+ = patients with significant coronary artery disease; CAD− = patients without significant coronary artery disease; BSA = body surface area; CI = cardiac index; EF = ejection fraction determined by planimetric evaluation of the ventriculographic examination. Continuous values are presented as mean ± 1 standard deviation.

stenotic and nonstenotic coronary arteries. A p-value of <0.05 was regarded as statistically significant.

RESULTS

The clinical data of the patient population are given in Table 1. Four patients (2 males, 2 females, age 53 ± 9 years) did not have a significant coronary artery stenosis ≥ 75% area reduction. Three of these patients had small coronary changes with stenosis not exceeding 50% area reduction. Twenty-three patients (16 males, 7 females, age 59 ± 8 years) had significant coronary artery disease (LAD = 11, LCX = 11, RCA = 10). Median area reduction was 88%, mean reference vessel diameter was 3.2 ± 7 mm. Fourteen patients had coronary single vessel disease and nine had double vessel disease.

Table 2

Mean Hemodynamic Data of All Patients at Rest and Under Maximal Stress

	Rest	Stress	p
Heart rate (beats/min)	74 ± 12	107 ± 13	<0.0001
Systolic blood pressure (mmHg)	131 ± 16	159 ± 24	<0.001
Diastolic blood pressure (mmHg)	81 ± 8	79 ± 15	n.s.
Rate pressure product ($mmHg/min \times 10^3$)	9.7 ± 2.2	17 ± 3.2	<0.0001

Dobutamine stress magnetic resonance perfusion imaging was successfully performed in all patients. Besides the known minor side effects of dobutamine no major adverse effects occurred during the angiography or the CMR examination. Hemodynamic data of patients at rest and dobutamine stress are listed in Table 2.

In 268 (89%) segments, a linear fit could adequately be performed. Because calculation of the upslope is based on a few data points, a reduced acquisition at this particular time will affect analysis substantially. Rapid breathing, patient motion, or rapid cardiac motion lead to significant noise or artifacts and prohibited adequate fitting, mainly during dobutamine infusion (25 of 32 segments that could not be fitted).

In the 14 patients with single coronary artery disease (Fig. 3), myocardial perfusion reserve index in segments supplied by a stenotic coronary artery was significantly lower than the remote segments (0.90 ± 0.18 vs. 1.73 ± 0.32, $p < 0.0001$) or segments of the control patients without coronary artery disease (2.0 ± 0.39, $p < 0.0001$). No difference was found between the segments of patients without significant coronary stenosis and the remote control segments of patients with single vessel disease ($p = 0.67$). In all patients with coronary artery disease ($n = 23$), perfusion reserve index in segments supplied by a stenotic coronary artery was significantly lower than segments of patients without significant coronary artery disease (0.97 ± 0.20 vs. 2.0 ± 0.39, $p < 0.001$) (Fig. 4).

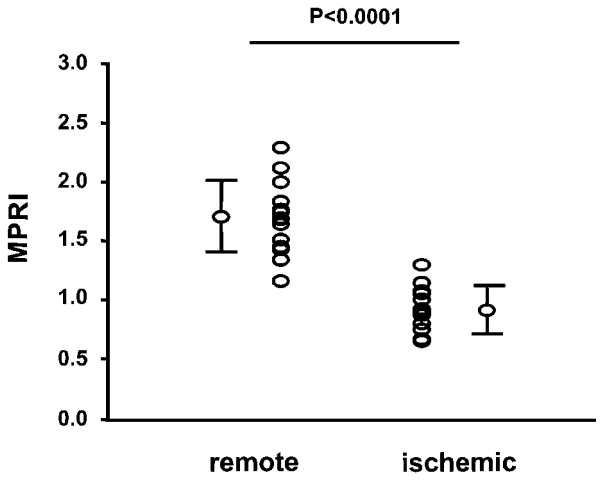

Figure 3. Myocardial perfusion reserve index in patients with single vessel disease comparing ischemic (ischemic) with remote to ischemic segments (remote). Presented as single values and mean ± 1 standard deviation.

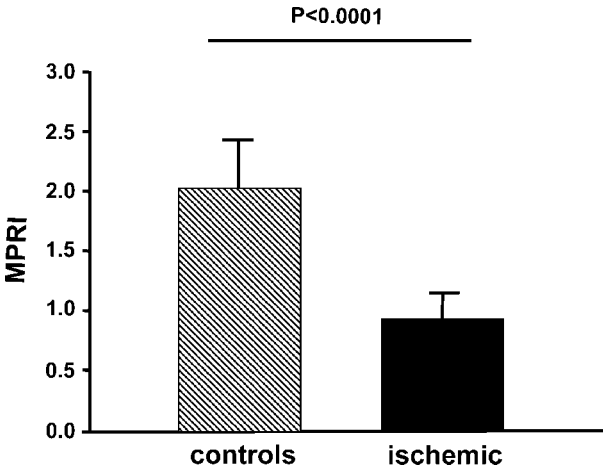

Figure 4. Myocardial perfusion reserve index in ischemic segments of all 23 patients with coronary artery stenosis (ischemic) compared with segments of the control patients without significant coronary stenosis (controls).

A threshold value of 1.22 was calculated from the segments of patients without coronary artery disease. Using this threshold in the patients with coronary artery disease, a significant coronary artery stenosis of $\geq 75\%$ area reduction was correctly diagnosed in 26 of 32 stenotic coronary arteries. Twenty-seven of the 37 coronaries without significant stenosis were correctly identified resulting in a sensitivity and specificity of 81 and 73%, respectively, and a diagnostic accuracy of 77% (Table 3). None of the segments in patients without coronary artery disease had an index < 1.22.

DISCUSSION

Alterations of myocardial perfusion can be assessed with CMR using dobutamine stimulation, which is feasible for the detection of significant coronary stenosis.

Table 3

Diagnostic Accuracy of MR Perfusion Measurements

	CAD+	CAD−
MPRI+	26	10
MPRI−	6	27
	Sensitivity = 81%	Specificity = 73%

MPRI+ = myocardial perfusion reserve index ≤ 1.22; MPRI− = myocardial perfusion reserve index > 1.22; CAD+ = coronary artery stenosis $\geq 75\%$; CAD− = coronary artery stenosis $< 75\%$.

From the upslopes of the signal intensity time curves a myocardial perfusion reserve index of < 1.22 was defined from patients without significant coronary artery stenosis as an ischemic threshold and resulted in a sensitivity of 81%, a specificity of 73%, and a diagnostic accuracy of 77% compared with quantitative angiography when used for prospective evaluation of 23 different patients with single and double coronary vessel disease. Dobutamine MR perfusion analysis in patients with coronary artery disease is comparable with other techniques such as echocardiography or scintigraphy.[27,28]

Effects of Dobutamine on Myocardial Blood Flow in Intermediate Doses

Any increase of cardiac performance, as induced by dobutamine infusion, is paralleled by an increase in myocardial blood flow.[29,30] However, coronary vasodilatory reserve downstream from a stenosis might be already exhausted under rest conditions to maintain adequate perfusion. Thus, a higher stimulation of blood flow is not possible in these areas and differences between territories of stenotic and normal coronary arteries may be found with intermediate doses of dobutamine.[15]

In normal coronary arteries, dobutamine causes a similar increase of myocardial flow in subepicardial and subendocardial myocardium by dilating the distal coronary arterioles,[13] whereas in diseased coronary arteries the increase of blood flow is less pronounced in subendocardial myocardium leading to a vertical steal effect which is already seen in small doses of 10–15 μg/kg body weight of dobutamine.[12,18,31,32] Furthermore, there is a horizontal steal effect in collateral dependent myocardium, since the decrease in pressure in the coronary arteries will lead to a decrease in collateral flow to the territory of the stenotic coronary artery. In a study performed with 13 *N* ammonia PET imaging,[14] it was shown that myocardial blood flow responses to dobutamine and adenosine are linearly correlated over a wide range and dobutamine induces a coronary steal effect with a frequency approaching that of adenosine.

In contrast to the detection of wall motion abnormalities,[33] which can be achieved with sufficient sensitivity only at high dose stress, it has been shown that diagnostic techniques that depend on the detection of myocardial perfusion defects may achieve high diagnostic accuracy even during submaximal stress because hypoperfusion occurs earlier in the ischemic cascade

than wall motion abnormalities.[34,35] Since significant alterations of myocardial blood flow and the induction of perfusion defects have been shown with intermediate doses of dobutamine,[15,20,21,36] and the induction of wall motion abnormalities was not the aim of the current study, an intermediate dose of 20 μg/min/kg body weight dobutamine was given to stimulate blood flow.

Comparison with Dipyridamole Stress

The results observed in this study differ from previous own results[2] using the same MR technique with dipyridamole stimulation in two points.

First, the ischemic threshold of myocardial perfusion reserve index derived from four control patients with symptoms but without significant coronary artery disease was lower with dobutamine in comparison to dipyridamole. This may be explained only in part by the heart rate dependency of the application of a 180° preparation pulse. With higher heart rates, as achieved during dobutamine stress, radio frequency pulsing is performed faster and consequently the steady state longitudinal magnetization is lower. As a result, the maximal achievable signal intensity and its upslope are lower at higher heart rates. However, this is only the case for patients with a strong increase in heart rate during dobutamine stress because at stress examination image acquisition was performed of every other heartbeat. Furthermore, the increase of cardiac output during dobutamine stress results in different signal intensity curves of the input function. Because calculation of the upslope is based on a few data points, a reduced acquisition at this particular time may affect the maximal upslope for which the slopes of myocardial signal intensities were corrected. Consequently, there will be a stronger influence on the perfusion reserve index than during dipyridamole stress. Other approaches of correction for the input function such as deconvolution[9] can result in an error due to loss of linearity between concentrations of gadolinium-DTPA and signal intensity at peak concentrations that might be achieved in the left ventricular cavity during first pass. This, however, requires evaluation in more detail in further studies.

The second difference to dipyridamole in this study is that sensitivity and specificity of dobutamine were lower than those achieved with dipyridamole. This can be explained by the following: (1) Vasodilation at an intermediate dose of dobutamine may not be comparable to that achieved by dipyridamole. It was recently shown that a submaximal dose of dobutamine fully exhausts myocardial resistance, with no additional increase by intracoronary adenosine infusion in patients pretreated with molsidomine.[15] Thus, in our patient population, which was not treated with nitrates the effect of 20 μg dobutamine may be submaximal. (2) Dobutamine has a higher influence on cardiac hemodynamics due to its positive inotropy. This causes alterations in the passage of the contrast agent through the left ventricle. In the current study, the myocardial signal intensity time curves were corrected for the left ventricular input function to minimize this effect. However, the correction for the input function may result in larger deviations than with dipyridamole and thus a higher influence on diagnostic accuracy. This effect is a drawback of dobutamine in comparison with dipyridamole and may explain perfusion reserve indices below 1 in many ischemic segments. (3) Another possible explanation is the smaller patient population. The differences between dipyridamole and dobutamine could be due to chance resulting from the limited sample size in this study.

A critical point for an MR examination during pharmacological stress may be the safety of the patients. During intermediate doses of dobutamine major side effects are rare, however, an ECG rhythm strip, blood pressure monitoring, and frequent communication with the patient are required. In addition, resuscitation equipment and a physician trained in emergency situations are essential at the MR scanner.

Limitations

The main limitation of the current study is the evaluation of a single slice only. However, as only patients with proximal or medial stenoses of a major coronary artery were included, a rather large perfusion defect was expected. New developments and faster techniques allow to acquire several slices during one heart beat even during a dobutamine induced tachycardia, which may further increase sensitivity.[37] The second limitation is the long acquisition time that results in a significant through plane motion during image acquisition and may result in discrepancies in the assignment of the segments to the territories and an error in comparing similar segments. However, large segments were compared rather than a pixel to pixel analysis, which will be more sensitive to through plane motion. Furthermore, high heart rate results in an image acquisition of only every second heart beat. Improvements of the MR technique allow much faster acquisition, which will minimize this effect. The acquisition at higher heart rates affects the shape of

ventricular signal intensity curves and leads to the problems in the correction for the input function, because the correlation between the slope and cardiac output is not linear.

The patient population included in this study is highly selected and thus the results cannot be extrapolated to a general patient population. Patients with previous myocardial infarction, low ejection fraction, or high-grade valvular heart disease were excluded for safety reasons and to guarantee a homogeneous study population. The impact of dobutamine MR perfusion in an unselected patient population needs to be determined in further studies which in addition should define normal values in a larger cohort.

Another general limitation for the validation of noninvasive diagnostic tests for the detection of myocardial ischemia is the comparison to angiography as differences between luminal morphology and myocardial perfusion may occur. However, quantitative angiography was performed to reduce the known errors due to visual analysis.[38]

Conclusions

In this study, it has been shown that the assessment of myocardial perfusion with dobutamine using CMR is feasible and yields sufficient diagnostic accuracy. Even though several drawbacks of dobutamine in comparison with adenosine remain, such as the influence on hemodynamics and the increase of heart rate, this agent might be used for an integrative cardiac examination combining the detection of wall motion abnormalities and the assessment of myocardial perfusion. The value of such an integrative examination has yet to be determined in further studies. Dobutamine stress can be performed for the assessment of myocardial perfusion in patients with intolerance to adenosine or dipyridamole.

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