Assesment of Myocardial Perfusion by Cardiovascular Magnetic Resonance: Comparison With Coronary Angiography

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Introduction and objectives. The assessment of regional myocardial perfusion by cardiovascular magnetic resonance imaging makes it possible to detect significant coronary artery lesions. The purpose of this study was to determine the usefulness of this technique in non-selected patients with ischemic heart disease.

Patients and method. The study group included 32 patients (26 men; mean age: 65 years old). Gadolinium (0.05 mmol/kg) for first-pass imaging was administred through a peripheral vein, both at rest and after adenosine infusion (140 mg/kg for 6 min). The presence of a regional perfusion defect was assessed visually, and these images were compared against coronary angiographic images.

Results. Angiography showed 49 significant (> 70%) obstructive lesions in a coronary artery. Magnetic resonance showed a perfusion defect at rest (fixed) in 35 myocardial segments, and only after adenosine infusion (reversible) in 16 additional regions, for a total of 51 segments with perfusion defect. Sensitivity for the detection of an angiographically significant coronary lesion was 78%, with a specificity of 75%. These figures decreased to 54% and 65%, respectively, when only fixed defects were considered. There were no visible defects in 26% of the myocardial territories with proven previous necrosis, although effective reperfusion and patent culprit arteries were frequently seen in these cases.

Conclusions. The detection of a regional myocardial perfusion defect by visual analysis with first-pass gadolinium and cardiovascular magnetic resonance imaging shows good diagnostic accuracy for the presence of significant coronary artery obstruction, provided that both rest and pharmacological stress studies are performed.

Full English text available at: www.revespcardiol.org

This study was supported by a Bayer research grant from the Sociedad Española de Cardiología (2000).

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Received 27 October, 2003.
Accepted for publication 17 March, 2004.

Key words: *Magnetic resonance imaging. Coronary angiography. Coronary disease. Contrast media. Perfusion.*

Estudio de perfusión miocárdica por cardiorresonancia magnética: comparación con la angiografía coronaria

Introducción y objetivos. El estudio de la perfusión miocárdica regional por cardiorresonancia magnética (CRM) permite la detección de lesiones coronarias significativas. El objetivo del presente estudio es determinar la utilidad de esta técnica en pacientes no seleccionados con cardiopatía isquémica.

Pacientes y método. Se incluyó a 32 pacientes (26 varones; edad media de 65 años). Se practicó un estudio de primer paso de gadolinio (0,05 mmol/kg) administrado por vía intravenosa periférica, basalmente y tras infusión de adenosina (140 mg/kg durante 6 min). La presencia de defecto de perfusión regional se estimó visualmente y se correlacionó con la angiografía coronaria.

Resultados. El estudio angiográfico mostró 49 lesiones coronarias significativas (> 70%). El estudio de CRM mostró un defecto de perfusión basal (fijo) en 35 territorios, y tras la infusión de adenosina, únicamente (reversible) en 16 segmentos adicionales, con un total de 51 territorios con defecto de perfusión. La sensibilidad para la detección de una lesión angiográficamente significativa fue del 78% con una especificidad del 75%, que se reducían al 54 y 65%, respectivamente, si sólo se consideraban los defectos fijos. El 26% de los territorios miocárdicos con necrosis previa no mostraba defecto de perfusión, si bien en ellos era frecuente una reperfusión previa y una arteria causante permeable.

Conclusiones. La presencia de un defecto de perfusión miocárdica regional por análisis visual del primer paso de gadolinio por CRM permite la detección de una lesión arterial coronaria significativa con un aceptable grado de exactitud diagnóstica, cuando se practican estudios bajo estrés farmacológico.

Palabras clave: *Resonancia magnética nuclear. Coronariografía. Enfermedad coronaria. Medios de contraste. Perfusión.*

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ABBREVIATION

CMR: cardiovascular magnetic resonance.

INTRODUCTION

Cardiovascular magnetic resonance (CMR) imaging includes a series of sequences for use in cardiovascular disease, with some designed specifically for the assessment of regional myocardial perfusion. This is accomplished by an analysis of the first-pass kinetics of a paramagnetic contrast agent administered as an intravenous bolus. A deficient increase in signal intensity in a myocardial region indicates a myocardial perfusion defect, as has been demonstrated in experimental studies and clinically in humans.[1]

The perfusion defect is usually the result of severe coronary stenosis, although regional microvascular involvement in previously infarcted segments can also lead to a perfusion defect, even in the absence of an epicardial coronary artery obstruction.[2] Conversely, the presence of collateral circulation can minimize a perfusion defect, even when there are significant coronary lesions.[3]

An obstructive coronary artery lesion may not manifest as a regional myocardial perfusion defect under resting conditions. Therefore, the first-pass gadolinium-enhanced CMR study is also performed under pharmacological stimulation with agents such as dipyridamole or adenosine, and has demonstrated adequate diagnostic performance for the detection of angiographically significant lesions[4] as well as a good correlation with radioactive isotope studies.[5]

Although the technique has advanced and has now attained a certain degree of clinical use by expert CMR teams,[6] experience is still limited and the majority of studies include small series of selected cases, mainly patients with single coronary lesions and no prior episodes of myocardial necrosis.[7]

The aim of this study is to determine the usefulness of first-pass gadolinium regional myocardial perfusion analysis, in baseline assessment and under pharmacological stress conditions, for the detection of angiographically significant coronary lesions in unselected patients with suspected or known ischemic heart disease. The secondary aim was to determine the effect of prior infarction, coronary artery occlusion and collateral circulation on the assessment of myocardial perfusion.

PATIENTS AND METHODS

The study included 32 patients (26 men; mean age, 65 years; range, 32-88 years) scheduled for conventional coronary angiography; CMR examination was performed after receiving their informed consent. Cardiovascular magnetic resonance studies were consecutive, although they depended on the availability of the magnetic resonance system. Patients were included in the study only when there were no contraindications for CMR examination (implanted pacemaker, metal devices, or claustrophobia).

Cardiovascular Magnetic Resonance Assessment

Cardiovascular magnetic resonance assessment was done on a Philips Intera 1.5 T system (Philips, Best, Netherlands), equipped with power gradients (amplitude, 20 mT/m; slew rate, 75 mT/s) and the Release 8 software for cardiac imaging.

Axial, coronal and sagittal scout images of the chest were first obtained, then used to program a series of three parallel short-axis slices of the left ventricle at the basal, mid-ventricular and apical levels. The technique included a hybrid segmented k-space turbo gradient-echo echo-planar imaging sequence, with ECG-triggered single shot acquisition and a prepared presaturation pulse. Three slices in the diastolic phase of each cardiac cycle, up to a maximum of 80 cycles, were obtained during breath holding, with interspersed breathing for predetermined periods. The sequence was acquired with simultaneous administration of 0.05 mmol/kg of gadoteridol (ProHance, Lab Farm Rovi) contrast agent by peripheral intravenous infusion at 4 mL/s using an automatic pump. This protocol was completed twice: immediately after an intravenous infusion of 140 g/kg adenosine over 6 min (stress test), and 15 min later, in this case without giving the drug (baseline study). Because of the limitations for monitoring the patient during the MR examination, adenosine infusion was done with the patient on the examination table, but outside the magnet, to allow immediate access to a portable cardiopulmonary resuscitation unit outside the room, if required.

Analysis of Cardiovascular Magnetic Resonance Images

The perfusion studies were analyzed on a specialized workstation (MASS, Medical Imaging Solutions, Leiden, Netherlands). The analysis consisted in qualitative assessment of the myocardial signal increase (Figure 1) in each of the 16 sectors comprising the 3 slices of the left ventricle[8] (Figure 2). Two observers evaluated by consensus the presence or

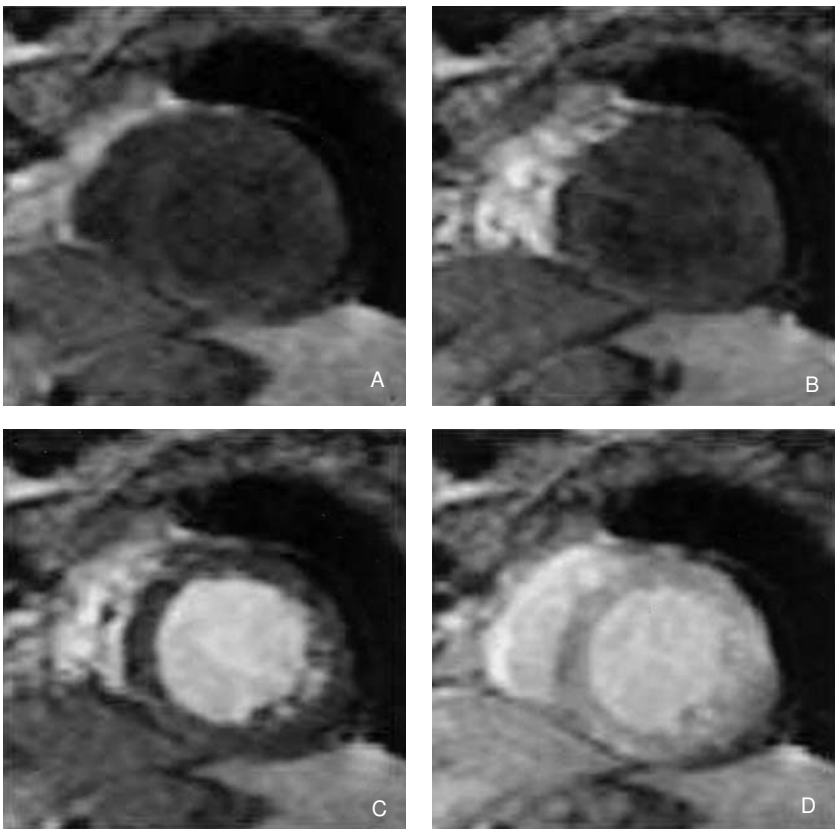

Fig. 1. Phases of a first-pass gadolinium-enhanced myocardial perfusion study in 1 of the 3 slices in the sequence, corresponding to the mid-ventricular segment. A. Baseline, immediately before contrast injection. Because of the characteristics of the sequence, both the myocardium and blood flow show a low signal intensity. B. Contrast reaches the right ventricle. C. Contrast reaches the left ventricle. D. Contrast reaches the myocardium, and a uniform increase in signal intensity is observed in all the regions, indicating normal myocardial perfusion.

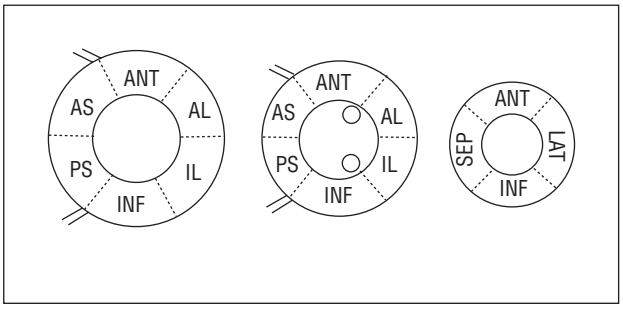

Fig. 2. Division of the left ventricle into segments as seen on basal (left), mid-ventricular (center), and apical (right) slices according to the diagram and nomenclature proposed by Cerqueira et al.[8]
AL indicates anterolateral; ANT, anterior; AS, anteroseptal; IL, inferolateral; INF, inferior; LAT, lateral; PS, posteroseptal; SEP, septal.

not of a perfusion defect and determined its location, subendocardial or transmural extension, involvement of more or less than 50% of the wall thickness, respectively, and whether the defect was reversible (only provoked after stress) or fixed (present at rest and stress) (Figure 3). Based on the theoretical distribution of the coronary vessels (Figure 4), the presence of significant coronary occlusion was attributed to the vessel feeding a territory showing any type of perfusion defect.

Angiographic Study

Conventional coronary angiography was performed within 1 week of CMR imaging in 90% of the cases and did not exceed 1 month in any case. An experienced observer interpreted the images without knowledge of the CMR results and determined the presence, location and degree of coronary artery occlusion, expressed as a percent reduction of the arterial lumen with respect to an adjacent segment of the vessel considered healthy. Coronary artery lesions causing occlusion of more than 70% were considered significant. In addition, the presence and degree of collateral circulation were assessed, the arterial territory irrigated was recorded and the collateral network was classified as limited or extensive.

Statistical Analysis

To determine the diagnostic value of CMR myocardial perfusion assessment for the detection of coronary artery lesions deemed significant by angiography, sensitivity was defined as the percentage of coronary artery vessels with significant lesions detected by the presence of a perfusion defect on CMR study, and specificity was defined as the percentage of arteries without significant angiographic lesions that showed no myocardial perfusion defect on

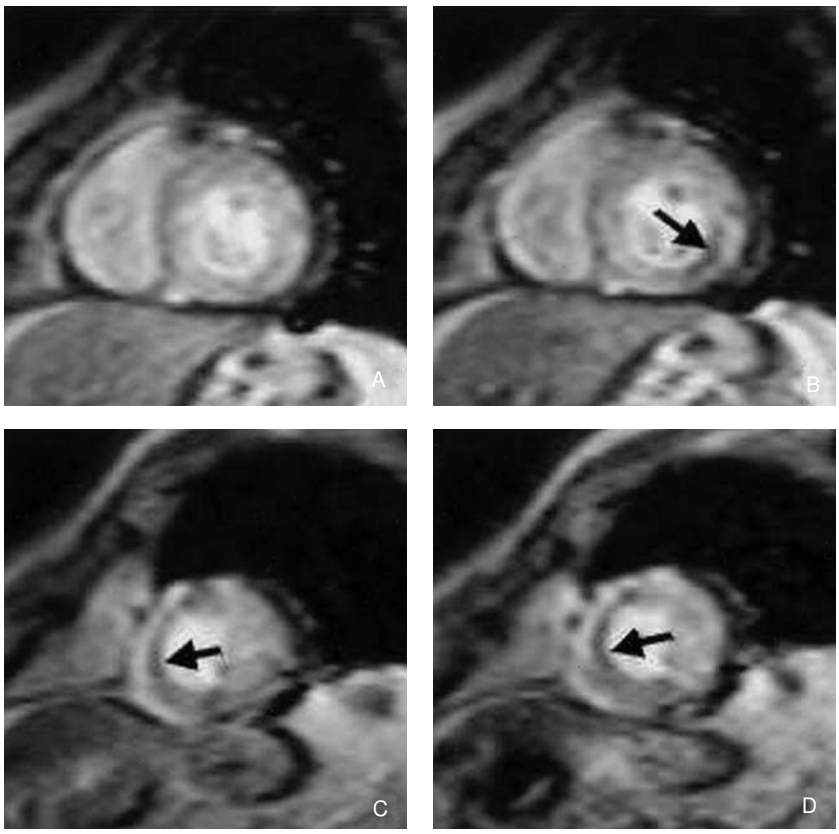

Fig. 3. Reversible perfusion defect. A. Baseline study, with no apparent defects. B. Stress study shows a subendocardial defect in the lateral wall (arrow). Fixed perfusion defect. C. Baseline study, shows a transmural defect in the septal region (arrow). D. Stress study with persistence of the defect in the same area (arrow).

the CMR study. The sensitivity and specificity of the method with 95% confidence intervals (CI) were calculated, as well as the positive and negative predictive values.

RESULTS

The patients included in the study group presented the following prevalence of cardiovascular risk factors: hypertension 53%, smoking 72%, hypercholesterolemia 53%, and diabetes 31%. Eighteen patients (56%) had a history of myocardial infarction before the CMR study, as demonstrated by clinical and electrocardiographic criteria and cardiac enzyme analytical results. Three patients (9%) had undergone coronary artery bypass grafting and 6 (19%) had undergone coronary angioplasty.

Angiographic Studies

Visualization of all the coronary vessels was achieved in all patients. Some degree of coronary artery disease was detected in 27 patients (84% of the study group), and in 23 of them (72%) the lesions were significant. Considering the three main coronary vessels and their branches as independent territories, a total of 96 vascular territories were assessed and 49 significant lesions were detected (14 in the left anterior descending artery, 17 in the circumflex and 18 in the right coronary). Among

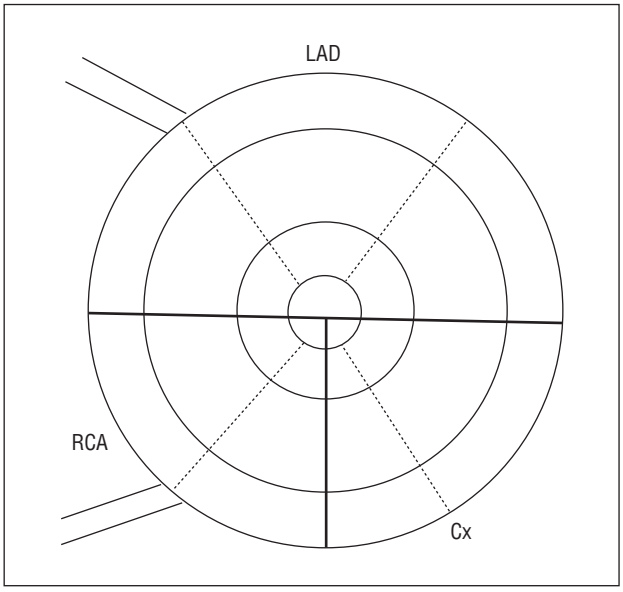

Fig. 4. Theoretical distribution territory of the main coronary arteries in the myocardial segments visualized in the cardiovascular magnetic resonance study: the diagram shows concentrically the basal, mid-ventricular and apical slices depicted in Figure 2. RCA indicates right coronary artery; Cx, circumflex; LAD, left anterior descending.

these, 20 were occlusive lesions (7 in the left anterior descending artery, 4 in the circumflex, and 9 in the right coronary).

The 3 patients who had undergone coronary artery revascularization had a total of 5 grafts; 2 were occluded and 3 were patent. Among the latter, the respective territory was considered to have no lesion for the purpose of comparison with the perfusion study, even when the native vessel had presented coronary arterial occlusion.

One patient had a 70% lesion in the left main coronary artery as well as significant additional lesions in the left anterior descending and circumflex arteries. In another case there was an anatomically dominant left coronary artery. Hence, the lower segments of the left ventricle were considered to be dependent on the circumflex artery and not the right coronary artery in this patient.

Collateral coronary circulation was estimated to be extensive in 15 territories and limited in 6 others.

Cardiac Magnetic Resonance Studies

The complete CMR protocol was performed in all patients with no complications due to pharmacological stress. Ten patients (31%) mentioned chest discomfort during adenosine administration that improved in all cases after infusion was completed. No patients required discontinuation of infusion.

The quality of the studies was judged to be good in 22 patients (69%). In the remaining ten it was considered only adequate due to the presence of magnetic susceptibility artifacts or because the cardiac walls in regions affected by prior infarction were thin. Nevertheless, these problems did not hinder the analysis in any case.

A total of 512 myocardial segments were assessed which, attributed to the main coronary vessels, allowed estimation of perfusion in 96 myocardial territories with theoretically independent coronary irrigation. Fixed perfusion defects (present at rest and under stress) were observed in 35 territories, and reversible defects (not present at rest) were observed after adenosine infusion in 16 additional segments, making a total of 51 (53%) territories with fixed or reversible perfusion defects. Forty-eight of the 51 territories (94%) were affected by a subendocardial perfusion defect and only three by a transmural defect.

The sensitivity of the presence of a perfusion defect in the CMR study (whether reversible or fixed) for the detection of an angiographically significant coronary artery lesion was 78%, with a specificity of 75%, a positive predictive value of 71% and a negative predictive value of 81%. Table shows the results for each coronary territory. When an analysis was made only of the fixed defects and the pharmacological stress test was excluded, the diagnostic power of the method decreased notably, with a sensitivity of 54% and a specificity of 65%.

Effect of the Presence of Previous Infarction on Myocardial Perfusion

The CMR perfusion studies in the 18 patients who had a clinically manifested myocardial infarction (19 episodes in all; since 1 patient had a history of 2 separate infarctions) showed defects in 14 (74%) of the territories with previous necrosis; half the defects were fixed and half were reversible. The vessels causing the infarction in these 14 cases were occluded in 9, presented significant lesions in 3, and presented non-significant lesions in 2, 1 treated with fibrinolysis in the acute phase of infarction and 1 with successful primary angioplasty.

Five patients (26%) showed apparently normal myocardial perfusion in territories with clinical evidence of prior infarction. Three of these patients had undergone apparently successful fibrinolysis during the acute phase of the infarction episode; in fact, no significant residual lesions were seen on coronary angiography.

Coronary Artery Occlusion Versus Significant Obstruction

Specific analyses were also done on the perfusion studies in territories dependent on occluded arteries and arteries with significant obstructive lesions. Among territories with occluded vessels (n=18), 14 had perfusion defects (7 fixed and 7 reversible) and 4 had apparently normal perfusion. In territories with patent, but significantly obstructed vessels (n=28), 22 had perfusion defects (16 fixed and 6 reversible) and 6 studies showed no visible defect.

Effect of the Presence of Collateral Circulation

A separate analysis was done on perfusion study results in territories where a significant coronary lesion had been detected, but where evident collateral circulation was visualized (n=15). In these cases, the CMR perfusion study showed a defect (true-positive) in 13 patients (9 fixed and 4 reversible) and an apparently normal image (false-negative) in only 2 patients.

DISCUSSION

The results of this study demonstrate that estimation of regional myocardial perfusion by visual analysis of first-pass gadolinium CMR images allows detection of significant coronary lesions with a good degree of precision, provided that both baseline and stress

TABLE 1. **Comparison Between the Presence of Perfusion Defects by Cardiac Magnetic Resonance (CMR) and Angiographically Significant Arterial Lesions, Considering the 3 Main Coronary Vessels Separately***

	Left Anterior Descending		Circumflex		Right		Overall	
	Angiography+	Angiography–	Angiography+	Angiography–	Angiography+	Angiography–	Angiography+	Angiography–
CMR+	10	6	11	6	15	3	36	15
CMR–	2	14	5	19	3	11	10	44
S, %	83		69		83		78	
95% CI	55-95		44-86		61-94		64-88	
SP, %	70		76		79		75	
95% CI	48-85		57-88		52-92		62-84	
PPV, %	63		65		83		71	
NPV, %	87		79		79		81	

*SP indicates specificity; 95% CI, 95% confidence interval; S, sensitivity; NPV, negative predictive value; PPV, positive predictive value.

perfusion studies are performed in each case.

Even though the technique is relatively complex, we were able to apply it and interpret the results in all the patients studied. There were no complications attributable to induction of ischemia, probably because the stress agent used was adenosine, which has a pharmacological profile known to be safe, particularly because of its short half-life.

In the analysis of the first-pass gadolinium CMR images, some authors have advocated the use of semi-quantitative methods, such as determination of the myocardial perfusion reserve index, which is the ratio of the maximum upslope of myocardial signal intensity curves at rest and under stress.[3,9-11] Although these studies have demonstrated good diagnostic precision for the detection of significant stenosis, in our experience the semi-quantitative technique has proved to be laborious and requires imaging studies of optimal quality. As an alternative, we chose qualitative estimation of regional myocardial perfusion, an approach also taken by other authors in clinical research studies[7,12] as well as clinical protocols for the use of CMR.[6]

Visual analysis of first-pass perfusion images showed that the defects were mainly subendocardial in nature, as has been reported in other studies.[13] This finding is in keeping with the accepted pathophysiological concept that the subendocardium is more susceptible to myocardial ischemia.[14] The fixed or reversible character of the lesion was also identified. Although some authors have suggested that fixed defects are associated with coronary occlusion,[11] our series showed fixed or reversible defects both in territories with coronary occlusion and with significant obstruction. Moreover, fixed defects were not more frequent in patients with prior infarction, and collateral circulation did not have an influence on the dynamic nature of the defect. We believe that these findings can be attributed to the fact that the study population was mainly comprised of patients with advanced ischemic heart disease, with episodes of infarction, and often with prior interventions, in whom a perfusion disorder might depend not only on the current degree of coronary stenosis, but also on residual microcirculation alterations following a previous ischemic episode or infarction.

It is interesting that in the group of infarction patients, 26% of cases had perfusion studies with no apparent defect, an observation reported by other authors[15] and considered by some[16] to indicate myocardial viability. In 3 of the 5 patients with this finding, apparently successful reperfusion treatment had been administered in the acute phase of infarction, and culprit arteries were angiographically patent at the time of the imaging study.

Overall, although the first-pass perfusion technique proved useful for the detection of significant coronary lesions, a certain number of false-positive and false-negative observations were recorded (Table). The false-positive findings may have been related to perfusion defects in the microcirculation of patients with a prior infarct and a patent epicardial artery.[3] This was the case in 2 patients with evident prior infarction and an open artery on coronary angiography (Figure 5). With regard to the false-negatives, it has been reported that development of an adequate collateral network can prevent perfusion defects, even in patients with significant coronary stenosis.[3,13] Specific analysis of this point in our series shows that 13 of 15 patients with coronary obstruction apparently "protected" by collateral circulation showed a defect in the first-pass perfusion study, a fact that explains why there were only 2 false-negative cases. It is difficult to determine what degree of collateral development is required to counterbalance a defect in myocardial perfusion at rest or exertion, but in our series of patients with advanced ischemic heart disease and probable microcirculation alterations, the presence of collateral circulation did not seem to influence the detection of perfusion defects by the CMR technique. A relatively higher percentage of false-negative results was observed in the circumflex artery, resulting in

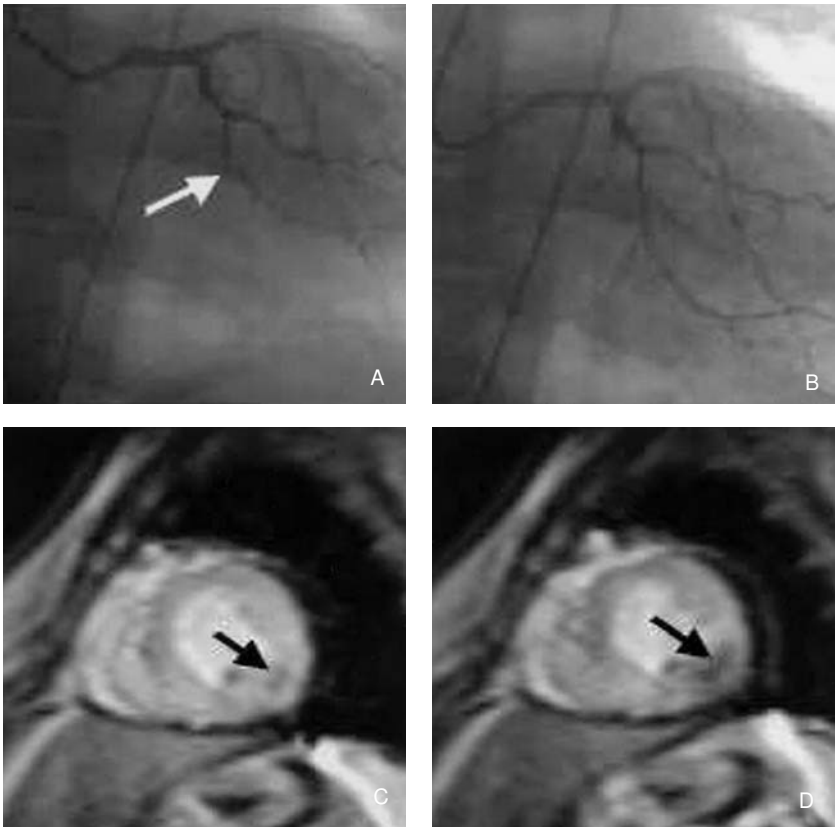

Fig. 5. Circumflex artery occlusion (arrow in A), which is patent after angioplasty (B). Cardiovascular magnetic resonance after the procedure shows a perfusion defect in the lateral wall both at baseline (arrow in C), and, more markedly, after adenosine infusion (arrow in D).

lower sensitivity of the technique for this vessel (Table). This may be because the extension of the myocardial territories irrigated by the right coronary and circumflex artery branches is subject to anatomic variation.

In any case, it is necessary to consider the relationship between the degree of coronary artery stenosis and the decrease in regional myocardial perfusion, which is known to be non-linear. Coronary artery stenosis of at least 40% on angiography is required for perfusion to be compromised,[17] whereas a 70% lesion results in a 50% reduction in coronary flow reserve.[18] A decrease of this magnitude is detectable by first-pass gadolinium technique in experimental animal models using semi-quantitative methods to measure myocardial signal intensity.[19] However, under clinical conditions with qualitative readings, the sensitivity would not be the same. This would explain why there are as many false-positives as false-negatives when 70% angiographic stenosis is used as the cut-off point, as in the present study.

One limitation of this study is that estimation of the presence of perfusion defects was done by visual analysis. However, as mentioned above, semi-quantitative analysis of multiple signal intensity curves and their sensitivity to artifacts in each case is a cumbersome tool, whose use is limited to the experimental area, in our opinion. In addition, the visual analysis was done by consensus between 2 observers instead of separately, and therefore interobserver differences could not be calculated. This design was adopted taking into consideration that the recent implementation of the technique implied a common learning curve between the observers that made interobserver analysis unrealistic. However, this aspect should be considered in future studies.

Comparisons between the diagnostic accuracy of CMR perfusion study and the accuracy of other techniques for the detection of ischemia, such as those using radioactive isotopes or stress echocardiography,[20] is not especially favorable for CMR according to the results of the present study, although other reports[7] in selected patients have found better diagnostic performance than with isotope techniques. In any case, it does not seem probable at this time that conventional techniques will be displaced by CMR perfusion for detecting induced myocardial ischemia in clinical practice. As we see it, the place for CMR perfusion study is within the framework of the entire array of methods for assessing ischemic heart disease with CMR. First-pass perfusion analysis is an additional element to be used along with assessment of overall and regional ventricular function by cine sequences, and myocardial viability and necrosis by delayed contrast sequences, which allow a comprehensive study of patients with ischemic heart

disease[21] and are now a part of the protocols for practical application of the technique.[6]

In conclusion, the presence of a regional myocardial perfusion defect by visual analysis of first-pass gadolinium-enhanced CMR images allows the detection of significant coronary lesions with an acceptable degree of diagnostic accuracy, providing the study is performed both at rest and under pharmacological stress. From the viewpoint of practical clinical applications, other factors besides angiographic stenosis must be taken into consideration, such as prior myocardial necrosis, revascularization and collateral circulation, which can influence the regional myocardial perfusion visualized by this technique.

ACKNOWLEDGEMENT

The authors would like to acknowledge the excellent work of Marc Gómez and Ricard Cullell, the radiology technicians who performed the CMR studies.

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