Cardiovascular magnetic resonance: twenty-first century solutions in cardiology

Dudley J Pennell

ABSTRACT – Cardiovascular magnetic resonance (CMR) is a rapidly developing new field in cardiology. It is beginning to contribute to greater understanding of diagnosis and management of hitherto difficult clinical conditions and is invaluable for research programmes, where its resolution, accuracy and reproducibility allow studies to be performed more quickly and cheaply than in the past. This article emphasises the use of CMR in preventing cardiovascular disease, such as ventricular remodelling after infarction, the genetic control of left ventricular hypertrophy, cardiomyopathies, high resolution myocardial perfusion in cardiac syndrome X, and detection of early stage atherosclerosis.

KEY WORDS: atherosclerosis, cardiomyopathy, heart, hypertrophy, infarction, magnetic resonance, prevention, syndrome X

Introduction

Cardiovascular magnetic resonance (CMR) is magnetic resonance of the cardiovascular system which yields information on anatomy and physiology of high resolution with exquisite quality and contrast; it is accurate, reproducible, trauma-free and safe. This review covers six areas of recent developments in CMR which have important clinical and research implications.

Left ventricular remodelling and hypertrophy

Remodelling is a term commonly applied to changes in size and shape of the left ventricle (LV) after myocardial infarction. There is a clear relationship between mortality and the LV volumes, and measuring changes in volumes guides treatment options. Over the years, these measurements have mainly been done using two-dimensional echocardiography, but its limitations are problems of acoustic access, inadequate border definition and the assumptions of geometry that have to be made for volume estimations. CMR has advantages because it is a three-dimensional technique, does not depend on geometry, and consistently provides excellent delineation of the endocardium and epicardium. A series of cines is acquired covering the entire LV; simple planimetry is used to define the borders so that the systolic and diastolic volumes and LV mass can be measured, and from this the ejection fraction (EF) and cardiac output are readily calculated (Fig. 1). This valuable technique is widely used for assessing the failing heart.[1,2] It is very accurate[3] and reproducible. Comparisons of reproducibility of CMR and echo show CMR to be substantially superior,[4] and this is best illustrated in the measurement of LV mass. A drug company may wish to study a drug to induce regression of left ventricular hypertrophy aiming for a 10 g change in mass with the active drug versus placebo over six months. The sample size required by 2-D echo is close to 1,000 but only 30 by CMR. If the per-patient cost is £3,000, then the cost difference to the drug company is about £3,000,000, a substantial saving not only in money, but also in terms of speeding up drug development and bringing the drug to market more quickly. This is good for the patient who will be able to benefit sooner, and for the pharmaceutical industry.

The same principles of reproducibility allow CMR to play a role in the investigation of genetic control mechanisms of LV hypertrophy, one of the most important risk factors for cardiac events. This has been investigated through gene–environment interactions, where the effects of natural genetic variations on phenotypic expression are studied. For a number of reasons, one obvious system to investigate is that involving angiotensin converting enzyme (ACE): for example, angiotensin-2 receptors are upregulated in conditions where hypertrophy occurs, such as post myocardial infarction, and ACE antagonists induce regression of LV hypertrophy. There is a polymorphism of the ACE gene with an insertion (I) allele containing an extra series of bases, and a deletion (D) allele. About half of the human population are heterozygous, and 25% each are homozygous for II or DD. The DD genotype expresses higher levels of serum ACE, and is associated with greater increases in LV mass with exercise training.[5]

In order to test this hypothesis in humans, we conducted a collaborative study with the cardiovascular genetics unit at University College London using the

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Coronary Artery Disease Research Association (CORDA) mobile CMR scanner at the army training regiment in Bassingbourn to study 130 army recruits undergoing fitness training, and examined the increase in LV mass over 12 weeks. They were randomly allocated to placebo or an angiotensin-2 receptor blocker (losartan) to see whether the drug interfered with the ventricular growth process.[6] We found no difference in either the DD or II groups between losartan and placebo.

Fortunately, the power of the study using CMR allowed further analysis of the data, specifically looking at the role of the kinin system, which is intricately linked with, but separate from, the angiotensin system. Kinins inhibit growth, and are broken down by ACE. Thus the higher levels of ACE in DD subjects might explain the higher LV mass growth with exercise through the Kinin system. The subjects were therefore genotyped for the polymorphism in the bradykinin 2 receptor gene. There is greater gene expression for -9 genotype (missing 9 bases compared with the +9 genotype). The -9/-9 homozygous subjects therefore have the most active inhibitory kinin system and would be expected to show the greatest effect if growth stimulation was mediated through this pathway. Analysis showed that there was substantial inhibition of LV mass growth in the II group with the -9/-9 genotype.[7] This strongly suggests that the kinin system is important in LV growth and is the first such evidence *in vivo* in man. Thus, in considering how to manage left ventricular hypertrophy, we need to consider this kinin pathway as well as the better known angiotensin pathway.

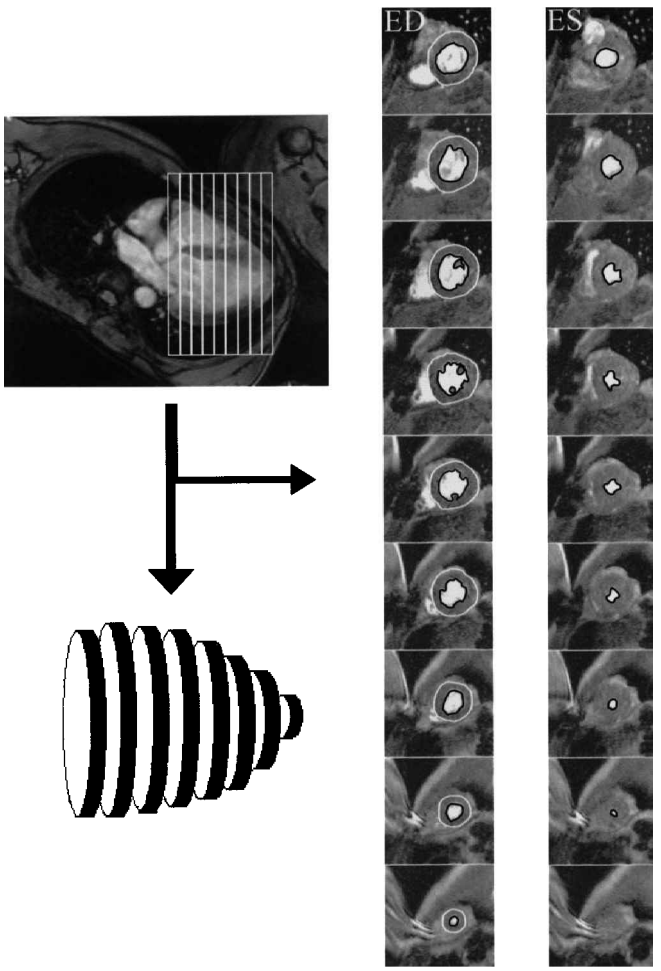

Fig 1. CMR measures ventricular volumes by three-dimensional coverage in the short axis plane. Planimetry of the epicardial and endocardial borders, which are well defined, and addition over all slices yields accurate and reproducible results. (Reproduced with permission from Rajappan *et al.*,[2] copyright 2000, with permission from Elsevier.)

Dilated cardiomyopathy

One of the key issues in managing patients presenting with dilated cardiomyopathy (DCM) is to exclude coronary artery disease as the cause. This is because treatments to prevent complications and outcomes differ in these two conditions. In addition, the genotypes are very different and we are moving into an era of screening family members for DCM genes before the phenotype is expressed. In many institutions, patients presenting with DCM undergo invasive coronary angiography to exclude coronary disease. CMR may be able to prevent this, saving costs and avoiding patient trauma. In order to do this, it uses a new technique called *late hyperenhancement gadolinium imaging*. After gadolinium injection, areas of infarction or fibrosis can be seen as intensely bright spots after a delay of about 15 minutes, when the gadolinium has largely washed out of the normal myocardium. The high resolution of CMR allows for the first time *in vivo* the description of the transmural distribution of infarction,[8] and detection of the smallest infarcts easily missed by other techniques.[9] This has been extensively validated in animals.[10]

We tested whether this could be applied to prevent the need for coronary angiography in DCM by studying 63 patients with DCM who had normal coronary angiography, and 27 patients with established angiographic coronary disease.[11] All the patients with coronary disease had infarctions, which always involved the subendocardium extending outwards towards the epicardium, as is well established. However, of the patients with DCM, 59% had completely clear myocardium, and 28% had longitudinal fibre fibrosis at the base of the heart which was clearly different from the infarction pattern in which the subendocardium was not involved (Fig. 2). Finally, 13% of the

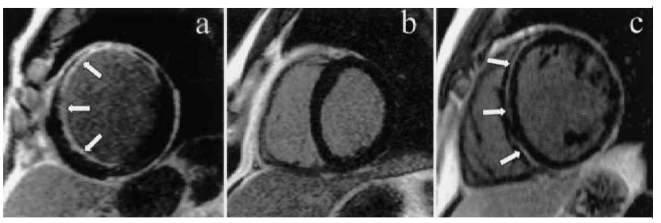

Fig 2. Late gadolinium hyperenhancement (short axis plane) of (a) infarction, showing subendocardial involvement of the anterior and septal walls, with extension towards the epicardium anteriorly, (b) dilated cardiomyopathy with no enhancement, and (c) dilated cardiomyopathy with mid-wall fibrosis in the anterior wall and septum. Note how dilated cardiomyopathy in both cases is readily distinguishable from the ventricular dilation caused by coronary disease.

DCM patients had typical myocardial distribution of gadolinium for infarction, strongly suggesting that the clinical diagnosis was either wrong and the patients were being managed as if they had DCM when actually they were suffering from coronary disease, or potentially the patients had dual pathology. We believe from this data that CMR could replace coronary angiography as the first line test to exclude coronary disease in new patients presenting with DCM. The DCM patients in whom the fibrosis is present may well need aggressive management for arrhythmias possibly with the cardioverter defibrillators, as the fibrosis is a likely substrate for re-entrant ventricular tachycardia. Identifying such patients accurately, in particular those who would benefit most, may have considerable cost-saving implications.

Hypertrophic cardiomyopathy

CMR is an ideal technique for the diagnosis of hypertrophic cardiomyopathy (HCM). This is a condition where some patients die suddenly, while others progress to terminal heart failure. Predicting which patients are at risk of sudden death is difficult. Some clinical risk factors are known (severe hypertrophy, abnormal blood pressure response to exercise, ventricular tachycardia, family history of sudden death, syncope) but some patients with no risk factors die suddenly and some patients with risk factors do well. We studied patients with HCM using the gadolinium hyperenhancement technique to determine if fibrosis was present, and to determine its relationship to clinical risk. The amount of hyperenhancement in patients with progression towards heart failure was higher that in those with no progression. This was especially evident in patients over 40 years old (Fig. 3). In younger patients, the gadolinium uptake predicted the presence of risk factors for sudden death.[12] We believe that the amount of gadolinium in young people is the arrhythmogenic substrate for sudden death; in older patients, it also indicates the onset of progressive systolic dysfunction. This technique may lead to improved clinical risk assessment, with rational application of cardioverter defibrillators and early institution of aggressive heart failure therapy in those patients who show the most fibrosis. It may lead to a better understanding of why patients progress to heart failure in HCM and may enable us to test new therapies to evaluate whether reversal of myocardial fibrosis is achievable or useful.

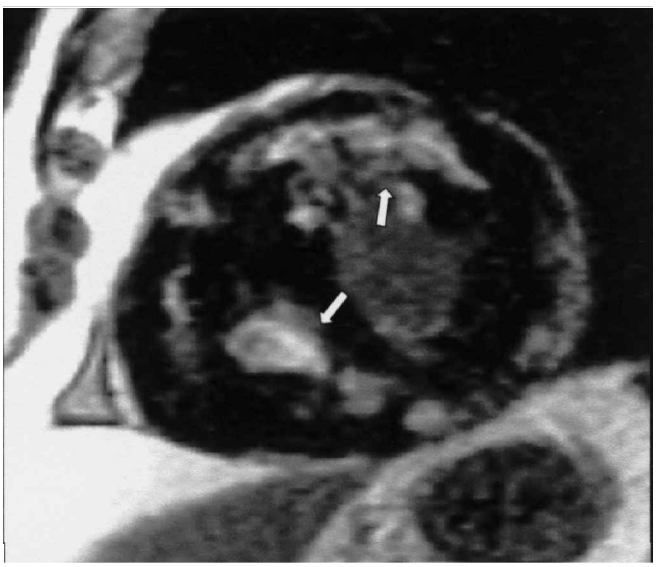

Fig 3. Late gadolinium enhancement of the left ventricle in hypertrophic cardiomyopathy shown in the short axis plane (arrows). Substantial fibrosis is evident, and this is linked to increased risk of sudden death and heart failure.

Key Points

- **Cardiovascular magnetic resonance (CMR) is a major new tool for assessing structure and function of the heart and vessels with safe high-resolution, high-quality imaging**
- **Reproducibility of CMR is excellent because of definition of epicardial and endocardial borders, allowing faster (and therefore) cheaper drug development through small clinical trial sample sizes**
- **CMR is valuable in determining the diagnosis and prognosis of hypertrophic, dilated and siderotic cardiomyopathy**
- **High-resolution myocardial perfusion and infarct CMR are likely to have a substantial clinical impact in management of coronary disease in the future**
- **The earliest signs of structural abnormality in early atherosclerosis can be identified with CMR of plaque, and this may lead to improved prevention at younger ages**

Siderotic cardiomyopathy in thalassaemia

Thalassaemia affects large numbers of people around the world including the Mediterranean basin, India, China and Indonesia. The problem with this disease is that to prevent death from anaemia, regular blood transfusions are required, but these cause tissue iron overload. Despite iron chelation therapy, a recent report showed that only 50% of patients in the UK survive to 35 years, and up to 71% of deaths are due to heart failure.

The conventional management of cardiac iron has been by measuring iron in a liver biopsy, measuring the serum ferritin, or by following ventricular function over time using echocardiography. However, using these techniques, diagnosing iron overload cardiomyopathy is difficult as patients are usually asymptomatic until the cardiomyopathy is advanced, the echo is often normal until the late stages, and the liver iron and ferritin are not good predictors. Once cardiomyopathy has developed the outlook is extremely poor.

We attempted to assess myocardial iron using CMR to measure the relaxation parameter T2* in the myocardium. In control patients the T2* is greater than 20 ms, and in thalassaemia patients the ejection fraction fell with T2* below the normal range, and this was associated with a much enlarged end

systolic volume.[13] There was no correlation between heart T2* and liver iron and serum ferritin, explaining why conventional management of cardiac risk had proven problematic (Fig. 4).

CMR has also been used to guide chelation therapy. Chelation in this condition is not straightforward because desferrioxamine is given either subcutaneously overnight for 5 to 7 days a week or intravenously in patients in heart failure. It has marked toxicity in excess and, as compliance with a complex regimen during adolescence can be poor, iron overload is common. There are second-line chelators such as deferiprone which are used far less but, being oral treatments, they have the advantage of greater compliance. We compared 15 patients on long-term deferiprone due to problems with desferrioxamine, with 30 matched patients on desferrioxamine. The mean T2* of the heart in the deferiprone patients was significantly better than in the desferrioxamine group. This showed in the EF results (70% vs 63%), and the odds ratio for excess iron was 5.5 for using desferrioxamine.[14] These unexpected findings suggested that deferiprone should be further evaluated for cardioprotection, and show the importance of techniques which directly indicate the causative pathology rather than surrogate measures. We believe that an early diagnosis and improved management using T2* of the heart will prevent death from heart failure.

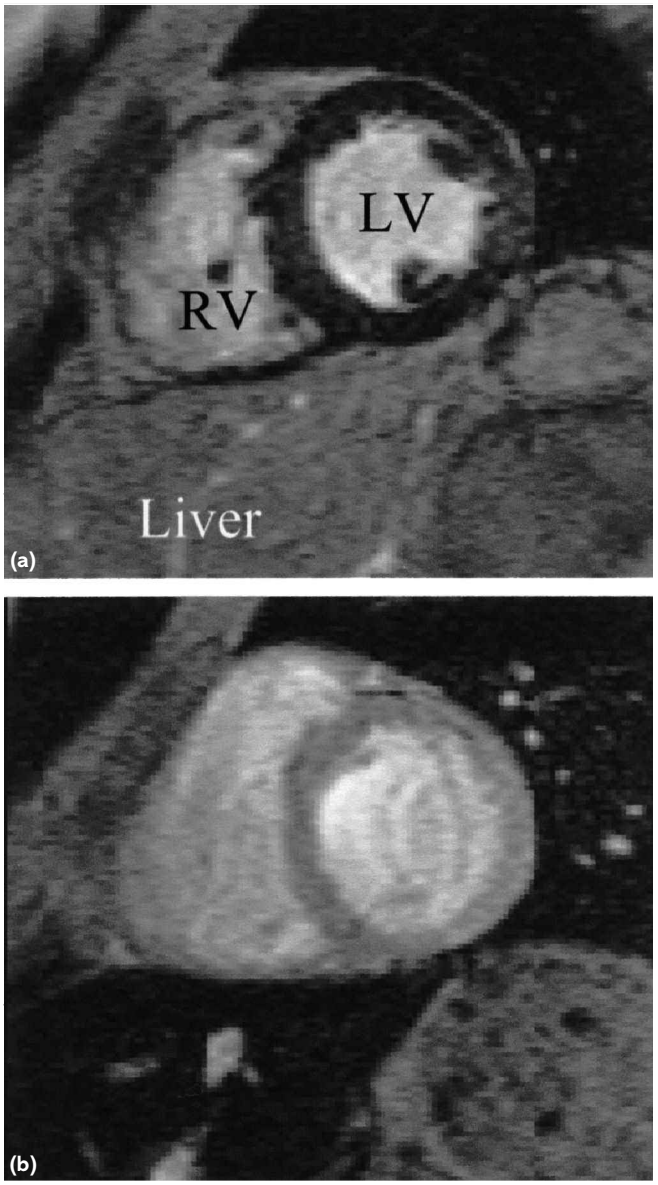

Fig 4. In thalassaemia, there is discordance between heart and liver iron deposition: (a) the myocardium is dark (high iron – low T2*) and the liver is light (low iron – high T2*) and (b) light myocardium and dark liver. The patient shown in (a) is at risk of heart failure from the myocardial iron, but liver biopsy would fail to identify this. (Reproduced with permission from Anderson *et al.*,[13] copyright 2001, with permission from Elsevier.)

Cardiac syndrome X

Angina is caused by obstruction in the epicardial coronary arteries usually from atheromatous deposits and is most common in men of middle age and above. In cardiac syndrome X, however, it is typically younger female patients who present with chest pain just like angina and abnormal exercise ECGs suggestive of ischaemia but, paradoxically, they have normal coronary angiography. This causes diagnostic problems, frustration for the doctor, and often psychological trauma for the patient. One theory of its causation is angina from abnormal small vessels. Others have postulated a low pain perception threshold. Cardiac investigations into syndrome X have been unhelpful or inconsistent, with normal myocardial perfusion, wall motion scans and metabolic tests. However, it is now possible to examine myocardial perfusion using CMR with resolution which is considerably higher than current radionuclide studies, potentially allowing visualisation of subendocardial ischaemia in these patients. In a study of 20 syndrome X patients and matched controls, the controls showed no abnormality during stress with adenosine, but the syndrome X patients showed subendocardial ischaemia (Fig. 5).[15] The controls increased both endocardial and epicardial perfusion with adenosine, but the syndrome X patients showed no change in endocardial perfusion while the epicardium developed luxury perfusion. These data lend considerable credence to the hypothesis that in well characterised patients with syndrome X an abnormality lies in the small resistance vessels which leads to myocardial ischaemia. This development may lead to a better understanding of the disease, and a diagnostic test that would differentiate this small proportion of patients from the total number of patients who have chest pain of non-cardiac origin. In addition, new treatments can be tested rationally in patients with ischaemia, whilst other therapy is given to patients with non-cardiac causes for their chest pain.

Atherosclerosis: improved assessment

In the last few years, CMR has been making considerable progress in assessment of the arterial wall as a means of identifying early atherosclerosis and also risk of plaque rupture in established disease. These two key areas have undergone considerable changes in thinking as a result of pathological, angiographic and

intra-coronary ultrasound studies. Glagov first suggested that luminal narrowing is a late stage event in the natural history of atherosclerosis development and that vessel wall atheroma burden was considerable prior to clinical symptoms and events.[16] It was also shown that myocardial infarction usually occurs due to thrombosis on plaques of <50% diameter stenosis.[17] The emphasis has therefore changed from assessment of the vessel lumen to the wall, and to identifying *vulnerable* plaque, that is plaque which is prone to rupture and thrombosis. It is easier for CMR to image this large atheroma build-up in the arterial wall than it is to see inside the small lumen to determine percent luminal narrowing. In addition, the atheromatous plaque can be characterised using a combination of CMR scanning techniques to allow the visualisation of the size and location of the cholesterol pool and the thickness of the overlying fibrous cap to assess vulnerability. Therefore both aspects of this new approach can be assessed by CMR.

We performed a project called CASPAR (CORDA Asymptomatic Subject Plaque Assessment Research) to determine whether CMR vessel wall imaging could detect atheroma in asymptomatic people in the community, and to determine progression over two years of follow-up. The artery studied was the infrarenal aorta, and images were taken from just below the renal arteries to the bifurcation into the iliacs. In each slice, the total external area and the total lumen area of the aorta was outlined. The difference between these is called the total wall area, which reflects the burden of atheroma. The total atheroma burden is the sum of the total wall area in each slice over the imaging field. Significant early atheroma was identified in 5% of the asymptomatic individuals. Over two years, we found that there was no change in the volume of the lumen. However, the wall volume (representing plaque) increased significantly, nearly doubling in amount. This change in the vessel wall was entirely accommodated by the outside of the vessel enlarging. This study confirms Glagov's hypothesis of external remodelling of the vessel as the atheroma burden increases even in very early stage disease.

CMR can also be performed in smaller arteries to examine risk in specific organ systems. The best studied to date is the carotid at its bifurcation, but early studies of coronary arteries are now being performed (Fig. 6). In the carotid, Yuan has shown that all the plaque components can be differentiated using a mixture of T1, T2 and proton density weighted CMR.[18] The thickness of the fibrous cap has been linked with clinical symptoms such as stroke and transient ischaemic attack.[19] In the smaller coronary arteries, wall thickening and intra-plaque detail such as cholesterol pools have been identified.[20]

Conclusion

CMR is progressing in both the clinical and research arenas on a broad range of fronts. Its high resolution, versatility and safety make it a powerful technique both for today and increasingly in the future. By using CMR, we are likely to understand new and existing pathologies better, and this will help in patient management and therapy. In addition, as disease is found earlier in its phenotypic expression using CMR, the possibilities greatly increase for prevention of complications not only in affected patients, but also in family members in heritable conditions.

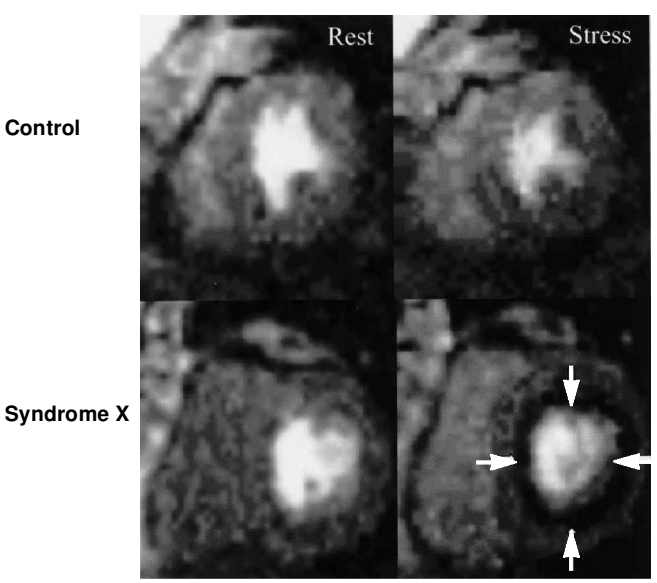

Fig 5. Subendocardial ischaemia in syndrome X is seen as a dark subendocardial region (arrows) during adenosine stress only, which is not seen in the controls. This can only be shown using the resolution of CMR. (Reproduced with permission from Panting *et al.*,[15] copyright © 2002 Massachusetts Medical Society. All rights reserved.)

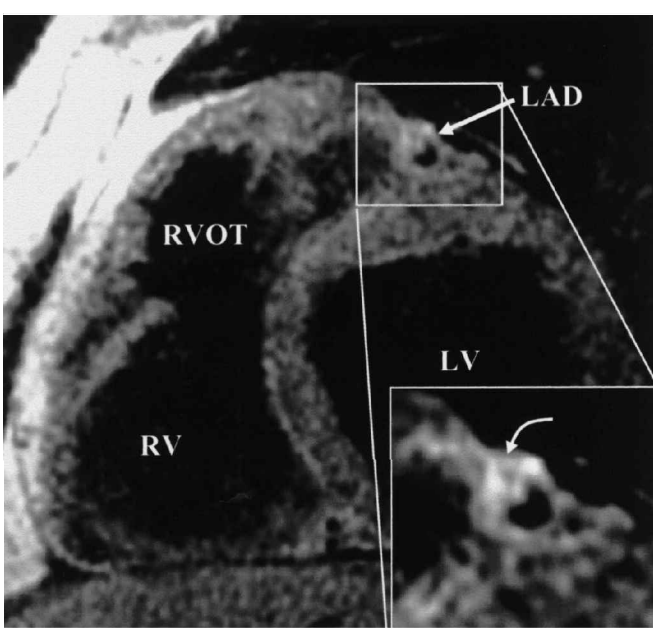

Fig 6. CMR of coronary plaque. The short axis of the left ventricle (LV) is shown (RV = right ventricle; OT = outflow tract), and the left anterior descending artery (LAD) is seen in cross section in the anterior interventricular groove. The inset shows an enlargement of the LAD and the eccentric atheromatous plaque (curved arrow), which is very evident despite rather little luminal encroachment. (Reproduced with permission from Fayad *et al.*)[20]

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