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Compensatory enlargement of human coronary arteries identified by magnetic resonance imaging

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Abstract

The aim of the present study was to evaluate the role of magnetic resonance imaging (MRI) for the non-invasive detection of coronary abnormalities and specifically the remodeling process in patients with coronary artery disease (CAD). MRI was performed in 10 control healthy subjects and 26 patients with angiographically proven CAD of the right coronary (RCA) or left anterior descending (LAD) artery; 23 patients were within two months of acute coronary syndromes, and 3 had stable angina with a positive test for ischemia. Wall thickness (WT), vessel wall area (VWA), total vessel area (TVA), and luminal area (LA) were measured. There were significant increases in WT (mean ± SEM, RCA: 2.62 ± 0.75 *vs* 0.53 ± 0.15 mm; LAD: 2.21 ± 0.69 *vs* 0.62 ± 0.24 mm) and in VWA (RCA: 30.96 ± 17.57 *vs* 2.1 ± 1.2 mm^2; LAD: 19.53 ± 7.25 *vs* 3.6 ± 2.0 mm^2) patients compared to controls ($P < 0.001$ for each variable). TVA values were also greater in patients compared to controls (RCA: 44.56 ± 21.87 *vs* 12.3 ± 4.2 mm^2; LAD: 31.89 ± 11.31 *vs* 17.0 ± 6.2 mm^2; $P < 0.001$). In contrast, the LA did not differ between patients and controls for RCA or LAD. When the LA was adjusted for vessel size using the LA/TVA ratio, a significant difference was found: 0.33 ± 0.16 in patients *vs* 0.82 ± 0.09 in controls (RCA) and 0.38 ± 0.13 *vs* 0.78 ± 0.06 (LAD) ($P < 0.001$). As opposed to normal controls, positive remodeling was present in all patients with CAD, as indicated by larger VWA. We conclude that MRI detected vessel wall abnormalities and was an effective tool for the noninvasive evaluation of the atherosclerotic process and coronary vessel wall modifications, including positive remodeling that frequently occurs in patients with acute coronary syndromes.

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Key words
- Coronary disease
- Coronary remodeling
- Magnetic resonance imaging

Introduction

Since 1957, contrast angiography has been the "gold standard" for the detection of coronary artery stenosis (1) despite being an invasive and imperfect method. Angiographic imaging depicts the coronary artery as a simple two-dimensional projection of the lumen (2), and may reveal advanced lesions, plaque disruption, luminal thrombosis, and

calcification. However, vessel wall characteristics cannot be assessed clearly by the luminogram (3). It is often assumed that the vessel is normal when the lumen is preserved. Post-mortem studies of acute coronary syndromes have revealed that culprit lesions showed large atherosclerotic plaques (4,5), but serial angiographic studies have revealed that myocardial infarctions frequently occurred in non-obstructive stenosis (6,7). Probably, these "small" vulnerable plaques are underestimated by angiography. Vessel enlargement in plaque sites, first identified as remodeling by Glagov et al. (8) and later confirmed by intravascular ultrasound (IVUS; 9,10), is a characteristic of this process. The noninvasive identification of vessel wall abnormalities and especially remodeling may be relevant for both long-term and routine patient care. In fact, an invasive study has reported differences in coronary remodeling between stable and unstable syndromes (11). Magnetic resonance imaging (MRI) is a new noninvasive method that can detect morphologic characteristics of coronary arteries *in vivo* in animals and humans (12-15) and also allows the identification of arterial remodeling in experimental atherosclerosis (16,17). Hence, in the present study, we investigated the efficacy of MRI for the assessment of vessel wall abnormalities and coronary artery remodeling in patients with coronary artery disease (CAD).

Table 1. Demographic and clinical characteristics of patients with coronary artery disease and a healthy control group.

	CAD patients (N = 26)	Control group (N = 10)
Age (years)	54.04 ± 11.07*	27.0 ± 5.72
Male/female	23/3	8/2
Unstable angina	22/26 (84.6%)	–
NSTEAMI	1/26 (3.9%)	–
Stable angina	3/26 (11.5%)	–

CAD = coronary artery disease; NSTEAMI = non-ST elevation acute myocardial infarction.
*P < 0.001 compared to control group (Student *t*-test).

Subjects and Methods

Subjects

Thirty-six subjects were studied: 10 healthy asymptomatic volunteers aged on average 27 years (range: 20 to 40 years), 8 men and 2 women considered as controls, and 26 patients (23 men) referred to our Institution for coronary by-pass graft intervention, aged on average 54 years (range: 36 to 77 years). Twenty-three of the 26 patients (88%) had unstable coronary syndromes according to Braunwald's classification (18), 22 had unstable angina and 1 had non-ST elevation acute myocardial infarction; 3 patients (12%) had stable angina with a positive EKG stress test (Table 1). Conventional contrast angiography was performed in all patients, and ≥50% stenosis was detected in at least one of the coronaries. For ethical reasons coronary angiography was not performed in the volunteers. MRI angiography without contrast was carried out in all subjects and five cross-sectional slices of the proximal portion of the left anterior descending (LAD) artery and right coronary artery (RCA) were acquired. All subjects signed a written informed consent form and the Institutional Ethics Committee approved the protocol.

Magnetic resonance imaging

MRI scans were performed with a 1.5 Tesla whole-body system (Sigma Cvi-GE Medical Systems, Milwaukee, WI, USA), within 4 weeks of the coronary angiogram. Fast gradient echo scouts on coronal, axial and sagittal planes were used for location. Subsequently, EKG triggering sequences were used in the following order for data acquisition: spiral breath-held sequences were used to visualize the coronaries longitudinally in order to prescribe cross-sectional views;

2-D breath-held black-blood double-inversion-recovery fast-spin-echo sequences, using a constant time of repetition (TR) of twice the R-R, were performed at end diastole. Image acquisition was possible within a time period of less than 25 s. The sequence parameters were: T2W; TR and time of echo = 2RR' and 42 ms; receiver bandwidth ± 62.5 Hz; echo train length 32 ms; field of view 18-20 cm; matrix 256 x 192 interpolated to 512 x 384; slice thickness 3 mm; 2 signal averages. An additional saturation pulse sequence was used to eliminate the epicardial fat signal and thus enhance the definition of the vessel boundaries. The in-plane resolution was 0.35 x 0.45 x 3 mm. The 2-anterior elements of a cardiac phased-array receiver surface coil were selected for these acquisitions to improve the signal-to-noise ratio.

Image analysis

The images were transferred to an off-line workstation (Sun Microsystems Ultra 60, Santa Clara, CA, USA), and the maximum wall thickness (WT), vessel wall area (VWA), luminal area (LA), and total vessel area (TVA) were analyzed. All cross-sectional slices acquired by MRI for RCA and LAD were reviewed and the best slice was selected for analysis. The circumflex artery was not studied because of technical reasons related to image acquisition. Maximal WT was defined by visual inspection and thickness was measured with a caliper. The vessel wall was depicted and the internal (LA) and external surfaces (vessel area) were traced; planimetric values were displayed automatically (Figure 1). Remodeling was identified on the basis of the LA/TVA ratio. Data for controls and patients were compared by the unpaired two-tailed Student *t*-test and Mann-Whitney test, with the level of significance set at $P < 0.05$.

Results

MRI allowed analysis of 25/26 RCA and 19/26 LAD arteries in patients and of all these arteries in control subjects, representing a total of 64/72 arteries (88.8%) assessed.

In the RCA, patients had significantly greater WT (2.62 ± 0.75 *vs* 0.53 ± 0.15 mm), VWA (30.96 ± 17.57 *vs* 2.1 ± 1.2 mm^2) and TVA (44.56 ± 21.87 *vs* 12.3 ± 4.2 mm^2) than controls ($P < 0.001$ for each variable). Similar differences were found for the LAD: WT (2.21 ± 0.69 *vs* 0.62 ± 0.24 mm), VWA (19.53 ± 7.25 *vs* 3.6 ± 2.0 mm^2) and TVA (31.89 ± 11.31 *vs* 17.0 ± 6.2 mm^2) in patients *vs* controls ($P < 0.001$ for each parameter). In contrast, LA did not differ between control subjects and patients either in the RCA (13.68 ± 8.0 *vs* 10.1 ± 3.7 mm^2; $P = 0.08$) or

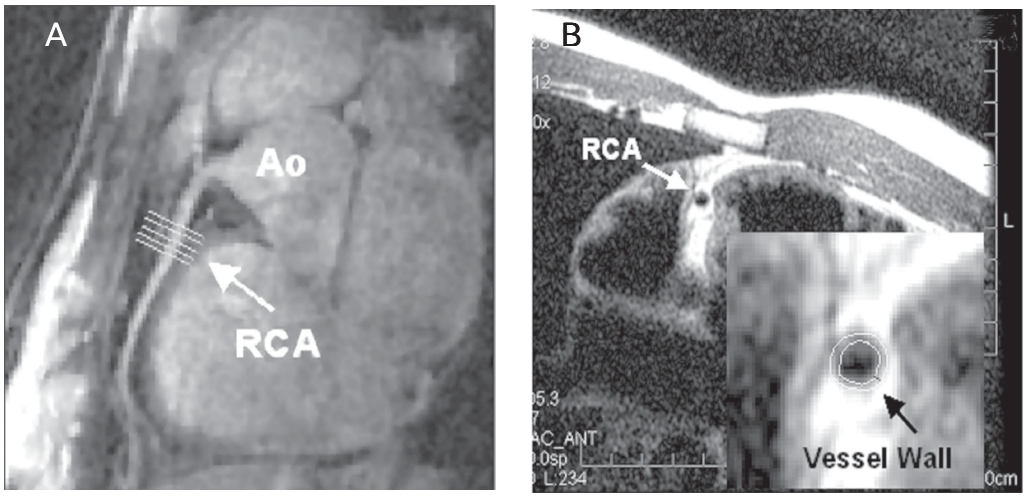


Figure 1. Magnetic resonance imaging (MRI) of a 26-year-old healthy male subject. Double-oblique view of the right coronary artery (A) with transverse prescription and cross-sectional black-blood magnetic resonance images of circular lumen and thin wall in magnified view (B). Ao = aorta; RCA = right coronary artery.

LAD (12.37 ± 6.87 *vs* 13.3 ± 4.8 mm^2; P = 0.70). These results are illustrated in Figure 2A and B.

When LA was adjusted for vessel size by using the LA/TVA ratio, a significant decrease was observed in CAD patients compared to control subjects: 0.33 ± 0.16 *vs* 0.82 ± 0.09 in the RCA and in 0.38 ± 0.13 *vs* 0.78 ± 0.06 in the LAD (P < 0.001 for both), demonstrating that positive remodeling or vessel enlargement had occurred in CAD, as shown in Figure 3.

Discussion

In the present study, MRI permitted the detection of coronary vessel wall modifications, i.e., increases in WT, VWA and TVA in almost all patients with CAD. Interestingly, the LA was preserved in these patients despite large plaque volumes. A reduction in the LA/TVA ratio was identified in patients, thus establishing a clear distinction between diseased coronaries and vessels from asymptomatic healthy, young volunteers. We assumed that these volunteers would have normal coronary arteries; for ethical reasons, coronary angiography was not performed on them. In agreement with this assumption, Fayad et al. (13) and Botnar et al. (14) obtained similar results regarding the coronary WT of healthy subjects.

Visualization of the vessel wall and the plaque itself rather than the lumen only is necessary for the best evaluation of the coronary artery lesion. Plaque characteristics are important to identify early lesions and vulnerable plaques (3). IVUS allows characterization of some features of atherosclerosis, being accurate in determining the thickness and echogenicity of vessel wall structures, but it does not consistently provide actual tissue characterization (19); in addition, it is an invasive method that cannot be performed routinely.

High-spatial-resolution black-blood MR methods have been used to visualize coronary arterial lumen and wall in humans (13-15), and have shown good correlation with histopathology in swine coronary lesions induced by balloon angioplasty (12). In the present study, we were able to analyze a large number of RCA and LAD segments (88.8%), demonstrating the power of this approach to assess the proximal segments of the coronary arteries. We did not study plaque composition, but only morphology; yet, this is an important information. Thinner coronary walls and smaller VWA were consistently found in healthy subjects compared to CAD patients.

Remodeling

Our data showed larger VWA in almost all patients, but no differences were found in LA compared to controls. This "preserved" lumen may be explained by adaptive enlarge-

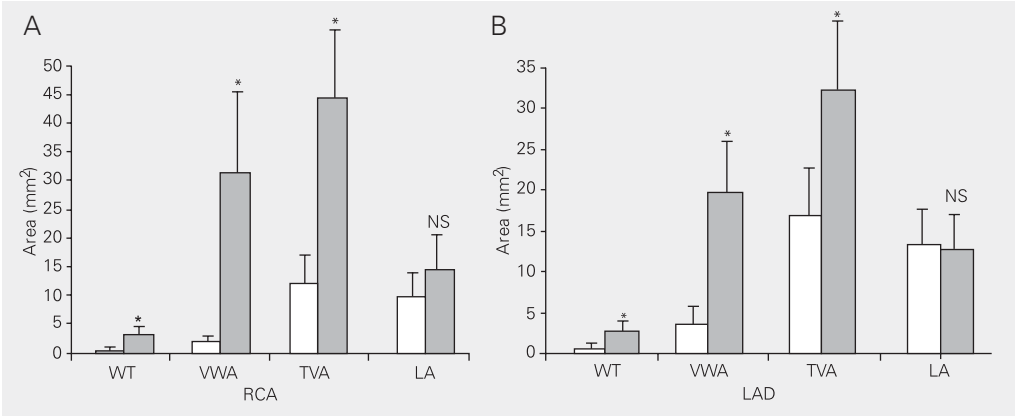


Figure 2. Areas of the right coronary artery (RCA) (A) and left anterior descending artery (LAD) (B) parameters obtained by magnetic resonance imaging. Patients: filled columns; control subjects: open columns. WT = wall thickness (mm); LA = luminal area (mm^2); VWA = vessel wall area (mm^2); TVA = total vessel area (mm^2); NS = not significant. *P < 0.001 compared to control (Student *t*-test).

ment of the vessels. As first reported by Glagov et al. (8) in a histological post-mortem study, human coronary arteries are enlarged at plaque sites, and frequently there is no change in lumen size because of outward displacement of the vessel wall. This "remodeling" phenomenon can explain why several investigators have demonstrated that low angiographic grade lesions represent the most important source of acute coronary syndromes (6,7,20). Probably, these culprit lesions were not "small" but rather large plaques, which may not produce significant luminal stenosis but may undergo rupture with subsequent thrombosis (21). A post-mortem study underscored the importance of the lesion/lumen relationship and angiographic limitations to identify vulnerable plaques, and confirmed that atherosclerotic plaques, which cause fatal thrombosis, are more frequently positively remodeled and tend to be larger than non-culprit plaques, but have the same degree of cross-sectional stenosis (22). We did not necessarily study culprit lesions, or at least not always. Most patients in this study were within 2 months of unstable coronary symptoms and only a small percentage had stable angina.

We have demonstrated that using MRI to determine the LA/TVA ratio is a noninvasive method for detecting coronary vessel wall modifications including remodeling and clearly differentiate patients with CAD from healthy subjects despite a similar lumen. Kim et al. (23) have recently reported the detection of this outward arterial remodeling by 3-D MRI in the proximal RCA of patients with nonsignificant CAD. Enlargement of atherosclerotic human coronaries and other arteries has been demonstrated *in vivo* by epicardial echocardiography (24) and IVUS (9,10,25). A recent IVUS study demonstrated that in unstable patients both TVA and plaque areas were significantly larger than in stable patients (11). Positive remodeling is more frequent in unstable disease and negative remodeling is more prevalent in stable disease (11). We did not demonstrate negative remodeling in our patients with stable angina, in disagreement with previous IVUS studies (11,26,27). The three patients in this latter group had similar large vessel areas when compared to unstable patients. An example of positive remodeling is illustrated in Figure 4.

Study limitations

The absence of coronary angiography in control subjects may represent a limitation;

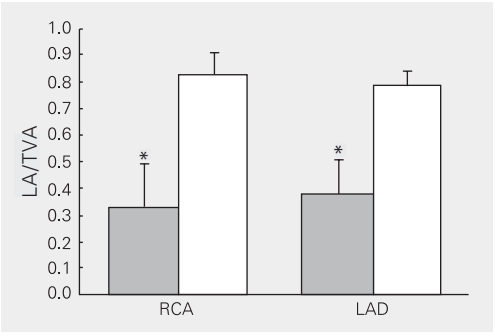
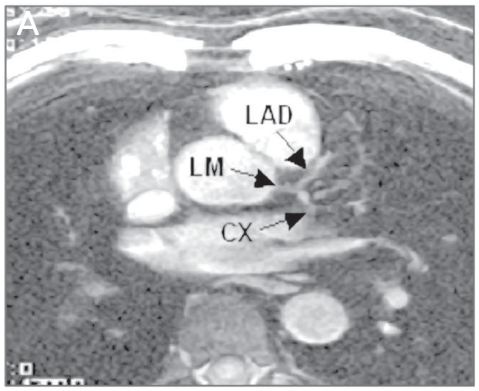


Figure 3. LA/TVA ratio for the right coronary artery (RCA; left) and left anterior descending artery (LAD; right) of patients and controls. Patients: filled columns; control subjects: open columns. The reduced ratio for patients with coronary artery disease was due to vessel enlargement. LA = luminal area; TVA = total vessel area. *P < 0.05 compared to control subjects (Mann-Whitney test).



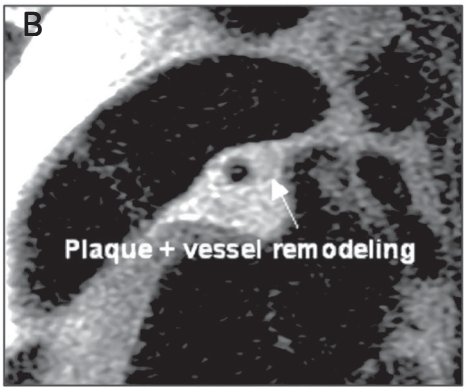


Figure 4. Magnetic resonance image of a 43-year-old male patient. *A*, View of the left main (LM), left anterior descending (LAD) and circumflex (CX) arteries. *B*, A cross-sectional view of the LAD with a clearly positive remodeling (arrow) between 1 and 5 h (total vessel area = 37 mm^2).

however, since they were asymptomatic and young, the probability of atherosclerosis was small, and thus a thin vessel wall was expected. The small coronary WT found in our control group by MRI suggests the absence of coronary stenosis, as also reported by other investigators (13,14). The plaque sites were not compared to a reference segment at the same vessel and we cannot be absolutely sure that the sites studied were the most stenotic ones. The 2-D breath-held technique may cause slice displacement during multiple breath-held even though the images were acquired at the end of expiration, a procedure that may produce the slice acquisition most consistent with the prescribed planning. Culprit lesions could not be determined in most of our patients; however, identification of culprit lesions was not the objective of this study. Finally, circumflex arteries were not examined and not all RCA and LAD were visualized by MRI.

Coronary disease is not a disease of the lumen, at least initially, but of the vessel wall. The development, progression, and stability or instability of plaque determine its natural history (28). The present study demonstrated the ability of MRI to detect vessel wall abnormalities and, importantly, showed positive remodeling in CAD patients. Therefore, MRI appears to be an efficient and safe tool that could be applicable to evaluate CAD noninvasively and longitudinally. Demonstrating coronary vessel wall modifications and positive remodeling could potentially discriminate high-risk patients, allowing more effective prevention.

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