

ANGIOGRAPHY

## Glagov Remodeling of the Atherosclerotic Aorta Demonstrated by Cardiovascular Magnetic Resonance: The CORDA Asymptomatic Subject Plaque Assessment Research (CASPAR) Project

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### ABSTRACT

*Background:* Aortic atherosclerosis and coronary artery disease (CAD) are closely linked. Early detection of aortic atherosclerosis with the adoption of appropriate preventive measures may therefore help to reduce mortality and morbidity related to CAD. Arterial remodeling, by which the wall adapts to physiological or pathological insults by a change in vessel size, is being increasingly recognized as an important aspect of atherosclerosis. In this prospective longitudinal study we used cardiovascular magnetic resonance (CMR) to detect aortic plaque and to study aortic wall remodeling in asymptomatic subjects. *Methods:* We recruited 175 healthy volunteers (49 years, 110 men) and documented their cardiovascular risk profile. Each subject underwent echocardiogram (ECG)-gated T1-weighted spin-echo imaging of the infrarenal abdominal aorta at baseline and after 2 years. *Findings:* Of the 175 subjects who volunteered at baseline, CMR was successful in 174 (99%), with one (0.6%) failure due to claustrophobia. At 2 years, follow-up scanning was performed in 169 subjects (97%). Infrarenal aortic plaque was identified at baseline in nine (5.2%) subjects. This was reconfirmed in all nine (100%) cases at 2-year follow-up. No new cases of infrarenal plaque were identified at follow-up. The signal characteristics of the plaque on the subtracted images of the Dixon method indicate that all plaques were fibrous. In the nine subjects with infrarenal plaque, the total plaque burden increased as assessed by the total wall volume (561 to 677 mm<sup>3</sup>,  $p=0.0063$ ). The total vessel volume also increased (1737 to 1835 mm<sup>3</sup>,  $p=0.031$ ) but there was no change in the total luminal volume (1175 to 1157 mm<sup>3</sup>,  $p=0.29$ ). *Conclusions:* Cardiovascular magnetic resonance detects subclinical aortic atherosclerosis, can follow plaque burden over

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time, and confirms the presence of Glagov remodeling with preservation of the lumen despite progression of plaque. Cardiovascular magnetic resonance is well suited for the longitudinal follow-up of the general population with atherosclerosis, may help in the understanding of the natural history of atherosclerosis, and in particular may help determine factors to retard disease progression at an early stage.

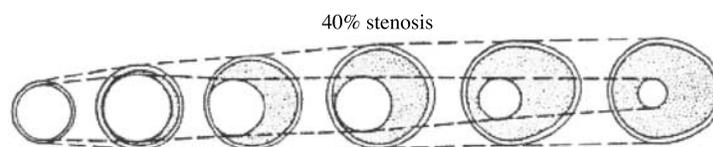
*Key Words:* Glagov remodeling; Atherosclerotic; Cardiovascular magnetic resonance; Asymptomatic Subject Plaque Assessment Research (CASPAR).

## INTRODUCTION

Atherosclerosis is the predominant cause of heart attack and stroke and accounts for the majority of death and disability in the Western world. The concept of arterial wall remodeling in connection with the pathogenesis of atherosclerosis is being increasingly recognized. Arterial remodeling describes the process by which the arterial wall adapts to physiological or pathological insults by a change in vessel size, or area within the external elastic lamina. Increases in this cross-sectional area are termed positive or outward remodeling while a reduction is called negative or inward remodeling. The concept of physiological arterial remodeling was introduced in 1893 when it was noted that blood vessels enlarge to accommodate increased flow to an organ downstream (Thoma, 1893). Almost 100 years later, Glagov presented the concept of arterial remodeling in the pathological process of atherosclerosis in the coronary arteries (Glagov et al., 1987). The Glagov phenomenon describes how the arterial lumen cross-sectional area is preserved in the face of advancing atherosclerosis within the arterial wall (Fig. 1). It was postulated that this occurs by circumferential expansion of arterial wall segments not yet involved in the atherosclerotic plaque formation. However, when the atherosclerotic plaque involved more than 40% of the internal elastic lamina area, progressive luminal encroachment occurs and can lead to significant luminal stenosis. The Glagov phenomenon has been demonstrated in the common carotid artery (Crouse et al., 1994).

An area of great importance is the prevention of the complications of atherosclerosis, which are major causes of morbidity and mortality. In order to achieve this, it is necessary to detect the disease at an early stage, monitor progression, and find effective treatments that are well tolerated. The longitudinal study of the development of early atherosclerosis is well suited to cardiovascular magnetic resonance (CMR), due to its ability to accurately and noninvasively characterize plaque size and composition. Cardiovascular magnetic resonance has been used to study atherosclerotic plaques in the aorta (Coombs et al., 2001; Yuan et al., 1998, 2002), peripheral arterial tree (Coulten et al., 2000), and coronaries (Botnar et al., 2000, 2001; Fayad et al., 2000a), but almost all of these studies have examined patients with established disease. Jaffer et al. reported the use of CMR to study subclinical atherosclerosis in an asymptomatic population-based cohort to establish age- and sex-specific normative data (Jaffer et al., 2002). The CMR evidence of aortic atherosclerosis was noted in 38% of the women and 41% of the men studied. Plaque prevalence and all measures of plaque burden were shown to increase with age group and were greater in the abdomen than in the thorax for both sexes and across all age groups. The Framingham Coronary Risk Score was significantly correlated with all plaque prevalence and burden measures for women but only for men after age adjustment.

In this prospective, longitudinal study we report the findings of using mobile CMR in asymptomatic subjects to detect subclinical aortic atherosclerotic plaque and to study aortic wall remodeling.



**Figure 1.** Schematic representation of the concept of arterial remodeling as proposed by Glagov et al. (1987). The lumen cross-sectional area of the native nondiseased artery is shown on the left side, and advancing disease is shown with each diagram progressing to the right. Note how the lumen is well preserved in size despite advancing atherosclerosis within the arterial wall until substantial atheroma is present. [Reproduced with permission from Glagov et al. (1987).]



## METHODS

### Subjects

This study reports the results from a subset of the subjects recruited into the CASPAR (CORDA Asymptomatic Subject Plaque Assessment Research) project. The CASPAR project involves the investigation of asymptomatic subjects using CMR with the aim of identifying early vascular disease in order to prevent morbidity and mortality. The project consists of studies that include technical development of atheroma scanning sequences, the longitudinal study of the arterial wall of asymptomatic subjects, the feasibility of operating such research in the community using a mobile CMR scanner, and assessment of the prevention of atherosclerosis progression.

One hundred and seventy-five healthy volunteers (48.8 yrs $\pm$ 5.6 and range 40–62 yrs, 110 male) were recruited from seven companies who agreed to participate in a feasibility project by allowing their staff to be approached for recruitment into the study. At each company, a request for volunteers was posted with the normal pay notification with a simple questionnaire, and responses were collated by the company occupational health department. The inclusion criteria were volunteers of either gender, aged between 40–60 years, with no history or symptoms of vascular disease in any territory. The cardiovascular risk profile was documented for all

the volunteers from the age, gender, the history of hypertension diabetes and smoking, resting 12 lead echocardiogram (ECG), and serum cholesterol. The British Cardiac Society risk program was used to calculate the 10-year risk of coronary artery disease (Joint British Cardiac Society and British Hyperlipidaemia Association and British Hypertension Society, 1998). Subjects from each company were then arbitrarily divided into higher and lower risk on the basis of a 1% per year threshold, and equal numbers of volunteers were randomly selected from each group. Each subject had a baseline CMR scan and a follow-up study after 2 years. In this report, we describe the findings of CMR of the aorta.

### Cardiovascular Magnetic Resonance

We used a mobile CMR scanner designed and constructed at the CMR unit of the Royal Brompton Hospital (Fig. 2). This operated at 0.5 T with actively shielded magnetic field gradient coils on all three axes capable of 20 mT/m at a slew rate of 60 mT/m/ms. Radiofrequency (RF) excitation was generated by a quadrature whole-body resonator and the MR signal was received by a surface coil. A Surrey Medical Imaging Systems (SMIS) Nuclear Magnetic Resonance (NMR) console was used to drive the sequences and acquire the data. All studies were ECG gated. In order to suppress blood signal the imaging sequence was

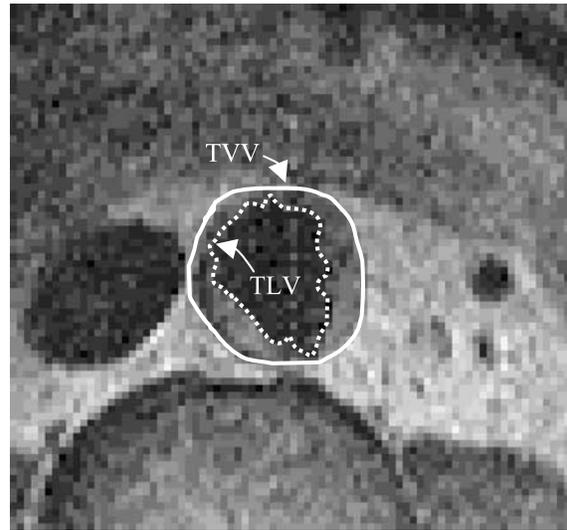


**Figure 2.** The mobile scanner used in this study, which was commissioned by CORDA the Heart Charity. (View this art in color at [www.dekker.com](http://www.dekker.com).)

applied in mid-systole. In addition, a slab-selected blood suppression pulse was applied upstream of the slices prior to the acquisition. The slice order was such that the downstream slice was acquired first to avoid any potential slice interference effects. The images were acquired from two averages of 192 views. The field of view was  $30 \times 30$  cm giving a pixel value of  $1.2 \times 1.6$  mm. Slice thickness was 8 mm. Six contiguous spin-echo images of the infrarenal abdominal aorta were acquired in the transaxial plane using the modified Dixon technique of chemical shift imaging (Dixon, 1984), which we have previously employed (Mohiaddin et al., 1989, 1991). For the modified Dixon technique two images were simultaneously acquired, the first using a conventional spin echo sequence with an echo time of 40 ms, and the second using a modification of the sequence where the  $180^\circ$  pulse was applied 3.5 ms early (16.5 ms after the  $90^\circ$  pulse) but the imaging echo time remained at 40 ms. The first sequence gives “in phase” data, because the protons of fat and water precess with the same phase at the time of the echo and the signal is the sum of that from fat and water. The second sequence gives “out of phase” data because the phases of fat and water protons are diametrically opposed at the time of the echo. The two data sets can be used to reconstruct separate fat and water images, allowing the potential to obtain structural information on the fat or water components of plaques (Yang et al., 1992).

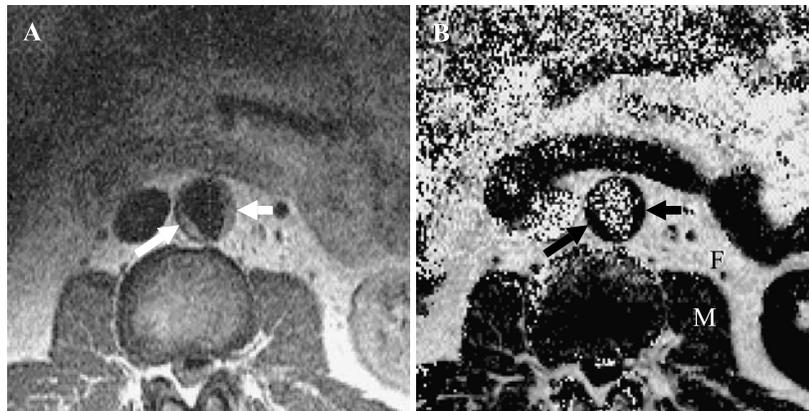
**Image Analysis**

Only patients with CMR evidence of atherosclerotic plaque in the aorta underwent quantitative analysis.



**Figure 4.** Derivation of arterial remodeling parameters from the aorta example shown in Fig. 3 but enlarged. The measurement is shown of total vessel volume (TVV, solid line), and total lumen volume (TLV, dotted line). Total wall volume (TWV) is calculated as TVV minus TLV.

Atherosclerotic plaque was defined as radial wall thickening causing luminal distortion (Fig. 3A). The endoluminal area and the external area of the aorta were outlined manually using in-house designed software (CMRtools ©Imperial College). All slices containing identifiable plaque were analyzed. The areas of the aortic lumen and external aortic outline on contiguous cuts were summed. This enabled the measurement of two



**Figure 3.** A) ECG-gated spin-echo image in a transverse plane perpendicular to the infrarenal abdominal aorta showing a large atheromatous plaque (black arrows). B) The corresponding subtracted Dixon image. The fat (F) and fibrous/muscle (M) tissue appear bright and dark, respectively. This plaque is predominantly fibrous (black arrows).

**Table 1.** Baseline demographics of high and low risk patients, shown as N (%) or mean±SD.

| Risk factor          | High risk N=75 | Low risk N=99 | P value for difference |
|----------------------|----------------|---------------|------------------------|
| Male                 | 61 (81%)       | 48 (49%)      | p<0.001                |
| Age (years)          | 51.8±4.9       | 46.5±4.9      | p<0.001                |
| Systolic BP (mmHg)   | 143.2±19.4     | 128.1±12.9    | p<0.001                |
| Diastolic BP (mmHg)  | 88.1±9.8       | 81.1±9.1      | p<0.001                |
| Smoker               | 34 (44.7%)     | 10 (10.2%)    | p<0.001                |
| Cholesterol (mmol/L) | 6.0±0.84       | 5.1±0.93      | p<0.001                |
| HDL (mmol/L)         | 1.12±0.24      | 1.69±0.42     | p<0.001                |
| Diabetic             | 1 (1.32%)      | 0 (0%)        | P=0.44                 |
| LVH                  | 8 (10.5%)      | 3 (3.1%)      | p=0.06                 |
| 10-year risk score   | 16.3±5.2       | 3.6±2.5       | p<0.001                |

Note: HDL—High Density Lipoprotein, LVH—Left Ventricular Hypertrophy.

parameters of aortic remodeling: total luminal volume (TLV), and total vessel volume (TVV). The total wall volume (TWV) of the aorta (which reflects total plaque burden) was determined by subtraction of TLV from TVV (Fig. 4). This was measured both at baseline and after 2 years. Anatomical landmarks were used to match slices from baseline and follow-up. Atheromatous plaques were classified into lipid rich or fibrous according to signal intensity on subtracted Dixon images (Fig. 3B).

**Statistics**

Data are presented as mean ±1 standard deviation. Arterial remodeling parameters over time are compared using the paired Student’s t-test. Comparison between high/low risk groups and the plaque/no plaque groups was made using the unpaired t-test and the Fisher exact test for categorical values. A threshold of p=0.05 was used for statistical significance.

**RESULTS**

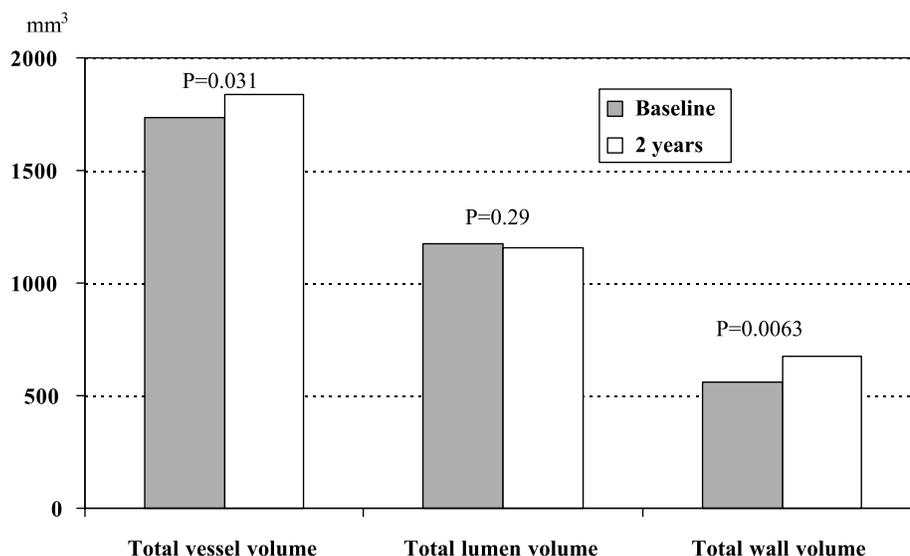
The baseline characteristics of the asymptomatic subjects are shown in Table 1. Of the 175 subjects who volunteered at baseline, CMR was performed in 174 (99%), with one subject scan failure due to claustrophobia. At 2 years, follow-up scanning was performed in 169 subjects (97%). Of the six subjects who were not rescanned, one had claustrophobia, two had onset of other illness, two did not state a reason, and one had moved out of the area. Infrarenal aortic plaque was identified at baseline in nine (5.2%) subjects. The characteristics of these nine subjects, and the comparison with the total group are shown in Table 2.

Aortic plaque was reconfirmed in all nine (100%) cases at 2-year follow-up. No new cases of infrarenal plaque were identified at this time. In the nine subjects with infrarenal plaque, the total wall volume (TWV; 561 to 677 mm<sup>3</sup>, p=0.0063) increased significantly, as did the total vessel volume (TVV; 1737 to 1835 mm<sup>3</sup>,

**Table 2.** Comparison of risk factors for patients with and without plaque formation, shown as N (%) or mean±SD.

| Risk factor          | With plaque N=9 | No plaque N=165 | P value for difference |
|----------------------|-----------------|-----------------|------------------------|
| Male                 | 9 (100%)        | 101 (61%)       | p=0.027                |
| Age (years)          | 52.9±3.1        | 48.6±5.6        | p=0.024                |
| Systolic BP (mmHg)   | 136.6±20.6      | 134.4±17.6      | p=0.72                 |
| Diastolic BP (mmHg)  | 81.7±10.9       | 84.2±9.9        | p=0.46                 |
| Smoker               | 8 (89%)         | 36 (22%)        | p<0.001                |
| Cholesterol (mmol/L) | 5.6±0.61        | 5.5±1.0         | p=0.77                 |
| HDL (mmol/L)         | 1.17±0.28       | 1.46±0.45       | p=0.058                |
| Diabetic             | 0 (0%)          | 1 (0.6%)        | p=1.0                  |
| LVH                  | 0 (0%)          | 11 (6.7%)       | p=1.0                  |
| 10 year risk score   | 17.1±5.7        | 8.7±7.3         | P<0.001                |

Note: Abbreviation as in Table 1.



**Figure 5.** Changes in total vessel volume, total lumen volume, and total wall volume from baseline to 2-year follow-up. The increase in wall volume does not affect the lumen, but leads to an increase in vessel volume (external remodeling).

$p=0.031$ ). However, there was no change in the total luminal volume (TLV; 1175 to 1157 mm<sup>3</sup>,  $p=0.29$ , Fig. 5). Lipid analysis showed predominantly fibrous plaques with no significant changes between baseline and follow-up.

## DISCUSSION

This study shows the feasibility of using CMR to detect and follow the progression of aortic atherosclerotic plaque in asymptomatic healthy volunteers. This is important because the absence of atherosclerosis in the thoracic aorta has been shown to indicate absence of significant coronary artery disease (Parthenakis et al., 1996). In addition, aortic and coronary artery atherosclerosis have a long subclinical phase (Holman et al., 1958; Napoli et al., 1997; Tuzcu et al., 2001), and therefore effective measures to retard progression or to induce regression of atherosclerosis at an early stage may reduce the incidence and severity of sequelae such as myocardial infarction and stroke. Because of its safety, CMR is ideally suited to the study of early atherosclerosis and its progression in asymptomatic subjects. This makes possible the study of the natural history of early disease prior to therapy in a wide variety of arterial locations. It is also possible to envisage the use of CMR to identify safe and simple measures that might retard progression of atherosclerosis. This could

include the assessment of lifestyle interventions such as exercise; supplementary antioxidant (Azen et al., 1996; Salonen et al., 2003) or B vitamins (Hackam et al., 2000; Spence et al., 2001); conventional drug therapy for established disease such as angiotensin converting enzyme inhibitors (Lonn et al., 2001), or statins (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995), and for which longitudinal studies by CMR in hypercholesterolemic patients have been reported (Corti et al., 2001).

In this study, we have also demonstrated that CMR can be used in a mobile fashion to study subjects in the community setting. This is valuable for population studies and for access to unusual cohorts, where bringing the scanner to the subjects may have significant advantages (Brull et al., 2001; Myerson et al., 2001). The cardiovascular risk was significantly higher in the asymptomatic subjects who were shown to have plaque, than in those who had no plaque (10-year risk of coronary artery disease  $17.1 \pm 5.7\%$  vs.  $8.7 \pm 7.3\%$ ,  $p < 0.001$ ). This suggests that established cardiovascular risk factors are important even in early disease, but there was overlap between the groups. While this suggests that ideal separation is not possible, it would be possible to enrich a study population of asymptomatic subjects using this risk evaluation. However, it is important to recognize that the study of one site of atherosclerosis does not necessarily mean the presence of atherosclerosis elsewhere, but as a systemic disease



the likelihood of abnormality in an unknown territory certainly increases when significant abnormality is found in another territory.

Another important aspect of this study is the confirmation of the Glagov hypothesis in the aorta of asymptomatic healthy volunteers with subclinical atherosclerosis. The results show that there was an increase in the aortic plaque burden as measured by the total wall volume, and this was associated with an expansion of the total vessel volume, but not the total lumen volume. We believe that this is the first longitudinal CMR study of the human aorta to confirm the Glagov hypothesis, although CMR has been used to assess aortic plaque in humans in cross-sectional studies (Fayad et al., 2000b), and in longitudinal studies in animals (Helft et al., 2002; Worthley et al., 2000). There have been clinical studies corroborating the Glagov phenomenon in the coronary arteries. Gradus-Pizlo used two-dimensional, high-resolution transthoracic echo to assess the left anterior descending (LAD) coronary artery wall thickness and external diameter in normals in comparison with 26 patients with abnormal x-ray coronary angiography (Gradus-Pizlo et al., 2001). They found a correlation between arterial wall thickness and external diameter, with the presence of coronary atherosclerosis. In addition, patients with subclinical LAD disease had equally increased arterial wall thickness and external diameter as compared to patients with angiographically significant LAD stenoses. Hermiller et al. used intravascular ultrasound (IVUS) to demonstrate arterial remodeling in vivo within the coronary arteries of 44 consecutive patients undergoing interventional treatment (Hermiller et al., 1993). However, IVUS is an invasive tool that usually precludes serial assessment of asymptomatic subjects, leading to a paucity of longitudinal, prospective data outside of trials in coronary disease (Nissen, 2002). More recently Kim et al. published a cross-sectional study of 12 human subjects in which evidence for Glagov remodeling was demonstrated by coronary CMR (Kim et al., 2002). Although CMR resolution is low compared with vessel size for the coronaries, this indicates the potential of this noninvasive technique for the future.

### Limitations

The aims of the CASPAR project are to establish assessment and prevention techniques in the community, and therefore from its inception this project was designed to be performed using a mobile CMR scanner. Jaffer et al. recently reported the use of CMR to study age and sex distribution of

subclinical aortic atherosclerosis and demonstrated a higher rate of detection of atherosclerotic plaque than reported in our study (Jaffer et al., 2002). The likely explanation for this discrepancy is that our technique was less sensitive for detection of smaller lesions due to poorer spatial resolution ( $1.2 \times 1.6 \times 8$  mm vs.  $1.03 \times 0.64 \times 5$  mm). At the time of the design of the mobile scanner and initiation of this project, the highest practical field strength and gradient power designs were used, but technological development has enabled improvements in resolution and in field strength in mobile scanners. The imaging methods used were those available on the mobile scanner, and newer techniques are now in use at higher field strengths, and these newer methods may have yielded more sensitive results. Despite this, significant findings have been made in the study population, and further studies are now underway using a more modern mobile scanner. Detailed plaque characterization and aortic wall imaging using intrinsic contrast phenomenon or extrinsic contrast agent would have been desirable, but this was not performed because of time constraints. Also, for the same reason the study was limited to the infrarenal abdominal aorta and the thoracic and upper abdominal aorta were not included.

### CONCLUSION

Cardiovascular magnetic resonance detects subclinical aortic atherosclerosis and shows aortic remodeling in asymptomatic subjects over time, confirming the Glagov hypothesis in this large vessel. The noninvasive nature of CMR is well suited for the longitudinal follow-up of the general population with atherosclerosis and may help in the understanding of the atherosclerosis process in particular factors that may lead to progression or regression of this disease.

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