

Interstudy Reproducibility of Three-Dimensional Volume-Selective Fast Spin Echo Magnetic Resonance for Quantifying Carotid Artery Wall Volume

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Purpose: To assess the interstudy reproducibility of a three-dimensional volume-selective, fast spin echo (FSE) magnetic resonance technique for the assessment of carotid artery wall volume, which is a marker for total carotid plaque volume.

Materials and Methods: Interstudy reproducibility was evaluated in 10 subjects with evidence of carotid artery atherosclerotic disease on carotid Doppler ultrasonography. Subjects were scanned twice with an interscan time of one hour to four days. The carotid artery was imaged in cross-section, and the total carotid arterial wall volume (TWV) was calculated by subtraction of the total carotid lumen volume from the total outer carotid vessel volume.

Results: The mean carotid TWV for the scans was 741 and 734 mm³, respectively, with no significant difference (mean difference 7 mm³; $P = 0.5$). The time for each study was approximately 20 minutes. The standard deviation of the differences between the measurements was 33 mm³, yielding an interstudy coefficient of variation of 4.4%. Sample size calculations showed that 16 patients would enable this difference in plaque volume over time to be detected with 80% power at a P value of 0.05.

Conclusion: Volumetric analysis with CMR of carotid artery plaques using a three-dimensional volume-selective FSE is efficient with good interstudy reproducibility, and is well suited for longitudinal studies of progression of carotid atheroma with reasonable sample sizes.

Key Words: carotid artery; atherosclerosis; interstudy reproducibility; magnetic resonance; 3D fast spin echo
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ATHEROSCLEROTIC DISEASE is a major cause of mortality and morbidity throughout Europe and North America, predominantly through coronary and carotid artery disease. Atherosclerosis starts at an early age—even fetal aortas show signs of early fatty streak formation (1)—and the disease then progresses throughout life. There is considerable interest in identifying patients with the earliest stages of atherosclerosis such that suitable long-term preventive measures can be instituted to arrest, or even regress, the disease. An important concept in the pathogenesis of symptomatic atherosclerotic disease is arterial remodeling (2). In this model of disease, the external border of the artery expands and thickens well before luminal encroachment occurs. Vessel wall imaging, therefore, will identify early atherosclerosis well before conventional luminal angiography. The modalities available for the noninvasive assessment of the vessel wall include carotid ultrasonography, coronary computed tomography, and carotid cardiovascular magnetic resonance (CMR).

CMR is a promising contender for vessel wall imaging and, currently, evaluation of atherosclerosis in the carotid arteries by CMR is superior to that of the coronary vasculature. CMR permits accurate, noninvasive, serial in vivo measurements of artery wall dimensions without the need for ionizing radiation. Also, it provides tomographic assessment with consistent localization, which enables identification of arterial remodeling over time; clinical results have been reported for the aorta and carotid artery (3,4). However, these reports used a two-dimensional fast spin echo (FSE) technique. We have recently developed a three-dimensional volume-selective FSE sequence for arterial wall imaging (5). The primary advantage of this sequence is that it enables greater coverage of the volume of interest in the same amount of time as the equivalent two-dimensional

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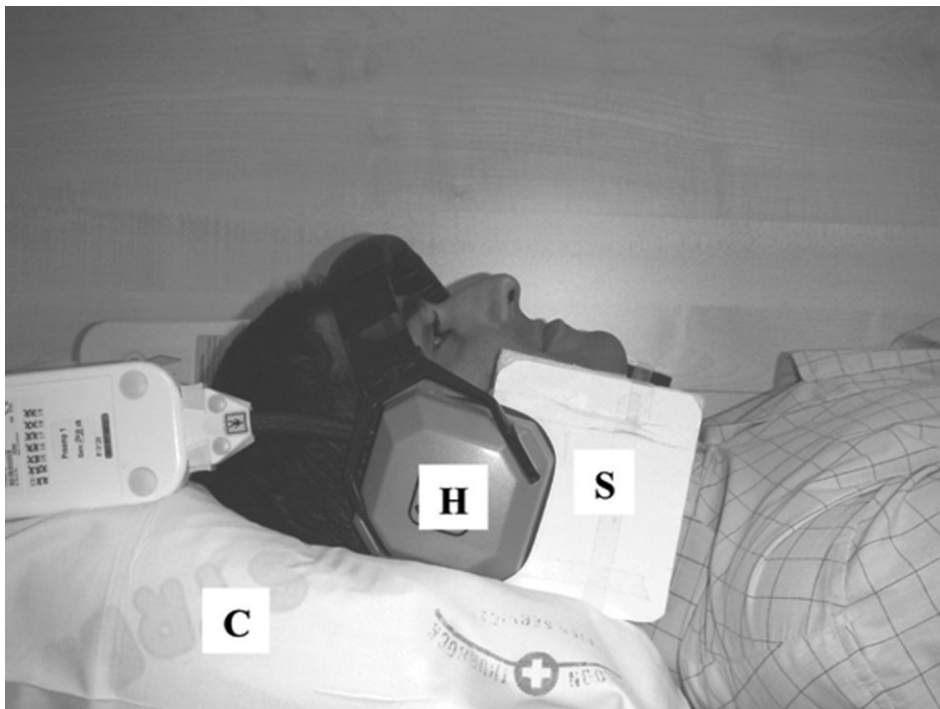


Figure 1. Normal volunteer with the carotid coil and specially designed cushion. The cushion is filled with polystyrene beads and is partially evacuated, with the headphones in situ, just prior to imaging to allow it to mould to the contours of the subject's head and neck. S = carotid coil, C = custom-made head and neck cushion, H = headphone set.

method because of a significantly smaller phase-encode field of view (FOV). Carotid artery atherosclerotic plaque usually extends from the distal 10–30 mm of the common carotid to the proximal 10–30 mm of the internal carotid artery. Using the three-dimensional FSE technique, a total of 56 mm (28 mm above and below the carotid bifurcation) can be imaged in under five minutes for T1-weighted scans. In order to determine the value of this three-dimensional technique for longitudinal studies, its reproducibility needs to be defined. Therefore we assessed the interstudy reproducibility in subjects with carotid artery atherosclerosis.

MATERIALS AND METHODS

Study Population

Ten patients with carotid artery atherosclerosis, as shown by prior carotid Doppler ultrasonography, underwent two CMR scans. The interscan period was between one hour and four days. The 10 subjects comprised nine males and one female, aged between 65 and 80 years (mean 72 years). Both asymptomatic and symptomatic subjects were included and the severity of carotid artery stenoses varied between 10% and 95%. The study received local ethics committee approval and all subjects gave written informed consent.

Magnetic Resonance

Magnetic resonance was performed using a 1.5-T scanner (Sonata; Siemens, Erlangen, Germany) a purpose-built two-element phased-array surface carotid coil (David Saloner, VA Medical Center, University of California, San Francisco) and a specially designed head and neck cushion for immobilization (Fig. 1). Subjects were scanned in the supine position

with the carotid coil in the isocenter of the static magnetic field. Each CMR study took approximately 20 minutes. Typical sequence parameters were for T1-weighted three-dimensional volume-selective FSE: matrix size 256; pixel size 0.47×0.47 mm; 28 slices of 2-mm thickness; FOV approximately 120×24 mm; time to echo (TE) 11 msec; repetition time (TR) according to the patient's heart rate; echo train length (ETL) 11, fat suppression and 650-msec inversion time following double inversion preparation pulse; and for the T2-weighted three-dimensional volume-selective FSE: matrix size 256, pixel size 0.47×0.47 mm; 28 slices of 2-mm thickness; FOV approximately 120×24 mm; TE 53 msec; TR according to patient's heart rate; ETL 11, fat suppression and 650-msec inversion time following double inversion preparation pulse. The region chosen for measurement was centered on the carotid bifurcation and extended 28 mm in both directions (Fig. 2a–c).

Data was collected as cross-sectional images from which total carotid arterial wall volume (TWV), which is a marker for total carotid plaque volume, was calculated by subtraction of the total carotid luminal volume from the total outer carotid volume (Fig. 3). Slices were matched with respect to their distance from the carotid bifurcation and then judged for adequate signal-to-noise (SNR) ratio. Only if matched T1-weighted images both had adequate SNR were they contoured, separately, and included in the overall analysis. Relevant T2-weighted images were used to help differentiate areas of vessel wall from possible flow artifacts where necessary (Fig. 2b and c). Results were analyzed by a single observer (A.V.) by manual tracing using dedicated display software (CMRTools; Cardiovascular Imaging Solutions, London, UK).

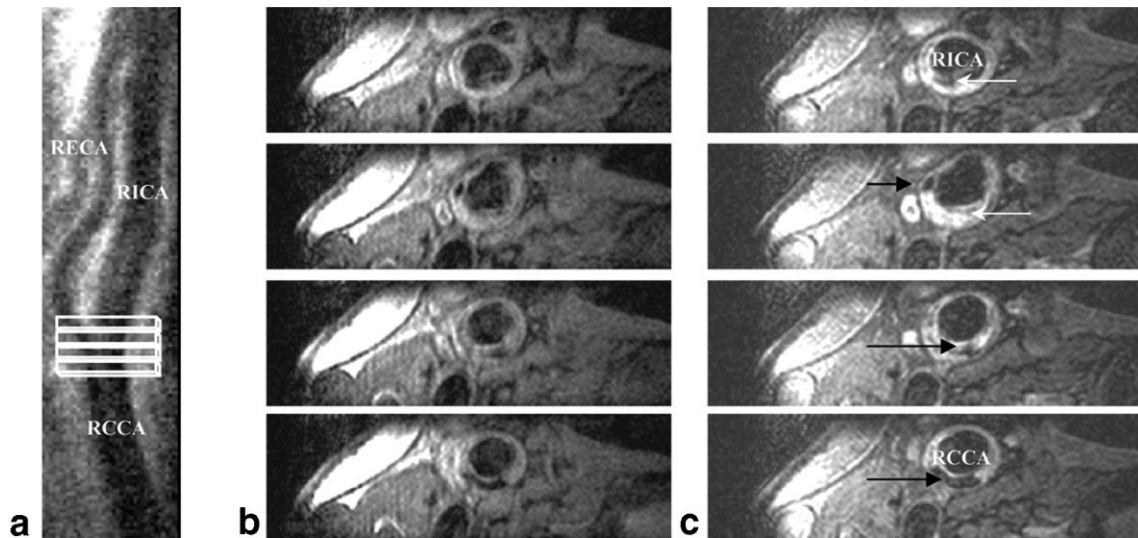


Figure 2. a: In-plane fast spin echo image through the right common carotid artery (RCCA), where it bifurcates into the right internal (RICA) and external carotid (RECA) arteries. The four slices shown at the bifurcation correspond to the adjoining T1- and T2-weighted images in (b) and (c). **b:** Examples of four T1-weighted contiguous 2-mm image sections from the distal RCCA to the proximal RICA and RECA using a right-sided positioning of the carotid coil. **c:** Comparative T2-weighted image sections; the white arrows delineate areas of periluminal flow artifact around the level of the carotid bifurcation and into the proximal RICA. The areas of focal, reduced signal intensity in the bottom three panels of the T1-weighted images (b) and the T2-weighted images (c; black arrows) are likely to represent areas of calcification (21).

Statistical Analysis

The standard deviation (SD) of TWV between matched image was calculated and divided into the mean TWV to determine the coefficient of variation (COV). The paired two-tailed Student’s *t*-test was used, and a *P* value of <0.05 was taken to represent statistical significance. The agreement between successive CMR scans was assessed using the intraclass correlation coefficient (*r*) and a Bland-Altman plot. Spearman’s ρ rank correlation coefficient (r_s) was used to determine any correlation between interscan times and the percentage difference between successive measurements. The *r* and r_s were determined using SPSS (Statistical Package for the Social Sciences) version 10.0 for Windows, while the remainder of the statistical analysis was performed on Microsoft Excel 2002. Power calculation was performed using the nomogram described by Altman (6).

RESULTS

The mean TWV for the two MR scans was 741 and 734 mm³, respectively, which were not significantly differ-

ent from each other (mean difference 7 mm³, *P* = 0.5). The SD of the differences between the measurements was 33 mm³, yielding a COV of 4.4%. The correlation between the two scans was high (*r* = 0.99; Fig. 4) and there were narrow limits of agreement on the Bland-Altman plot (Fig. 5). R_s was -0.68 with a *P* value of 0.85, indicating no significant relationship between the interscan times and percentage difference between successive measurements. The average number of matched slices having adequate SNR for analysis was 14 (range 3–26).

DISCUSSION

In the United Kingdom (UK) alone, coronary artery disease (CAD) accounts for over 117,000 deaths per year, accounting for approximately one in five deaths in men and one in six deaths in women. Around 270,000 people in the UK have a myocardial infarction (MI) each year and approximately 2 million people suffer from angina (7). There are clear pathological links between CAD and stroke. Both commonly result from athero-

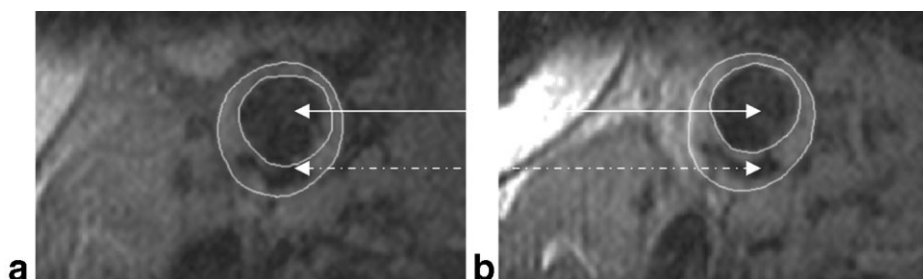


Figure 3. a, b: Analysis of total carotid arterial wall area (TWA). The dashed lines connect corresponding total carotid wall areas, while the solid lines connect the carotid lumens. The total carotid arterial wall volume for each slice is obtained by multiplying the TWA by the slice thickness. The total wall volume (TWV) is determined by summing this product over all usable slices imaged.

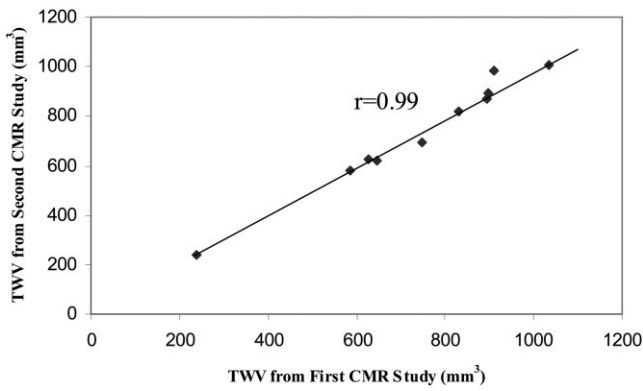


Figure 4. Correlation of TWV measurements for successive CMR scans. The line of identity is shown (solid line). There is good correlation and a good fit to the line of identity.

sclerosis of the feeding artery; transient ischemic attacks are harbingers for MI (8) and the risk factors for atherosclerosis at both sites share many similarities (9). It has been demonstrated that increased carotid artery intima-medial thickness is directly associated with increased risk of MI and stroke (10). This suggests that study of the carotid artery will also yield important insights into atherosclerosis affecting the coronary arteries.

The phenomenon of pathological arterial wall remodeling, as first described by Glagov et al (2), is a process by which the arterial wall adapts to progressive atherosclerotic disease by an initial change in overall vessel cross-sectional area prior to luminal narrowing. Increases in arterial cross-sectional area are termed positive or outward remodeling, while reduction is called negative or inward remodeling. Since luminal encroachment may not occur until approximately 40% of the arterial internal elastic lamina is involved in the disease process, tomographic assessment of the arterial wall can detect atherosclerosis at an earlier stage than conventional luminal angiography. This was well illustrated in the Familial Atherosclerosis Treatment Study (FATS), which assessed the angiographic regression of coronary artery disease in men at high risk for cardiovascular events following either intensive lipid lowering with lovastatin and colestipol or conventional therapy (11). After 2.5 years of treatment, there was a reduction of only 3% in the severity of proximal coronary artery stenoses, but a 73% reduction in the clinical event rate in the intensively treated group. More recently, Corti et al (3) used CMR to study the effects of simvastatin on the vessel wall of the aorta and carotid arteries of asymptomatic patients with hypercholesterolemia. Following two years of therapy, they noted up to a 20% reduction in vessel wall area compared with only a slight increase of 4% to 6% in luminal area. These findings imply that negative remodeling may play an important role in effecting the outcome benefits of statin therapy despite little anticipated change in any symptoms attributable to ischemia. Similar tomographic assessment of arterial remodeling changes induced by other drug therapies may prove useful markers of their clinical potential.

The results of the current pilot study indicate that the newly described three-dimensional CMR sequence has good reproducibility and can detect small changes in carotid arterial wall area. Power calculation indicates that a sample size of 16 would enable a significant difference over time ($P < 0.05$) in a plaque volume of 33 mm³ to be detected with 80% power. Such high reliability in the carotid artery is due to the combination of high resolution imaging centered on the fixed anatomical landmark of the carotid bifurcation. One limitation of this pilot study is that the interstudy reproducibility was only determined for a single trained observer.

The potential area of coverage with this technique is 56 mm, but in practice was reduced to an average of 28 mm along the length of the carotid artery, with a range of 6–52 mm. Taken together with the reproducibility data, this variability in the degree of coverage limits this technique to the serial rather than isolated evaluation of carotid atherosclerotic disease. The images included in the analysis had adequate SNR, judged predominantly by the outer and inner carotid arterial walls showing continuity and being clearly defined. With the use of a head and neck cushion for immobilization, motion artifacts from swallowing and head movement were infrequent in this study. This reflects the care taken to ensure patient comfort and head immobilization with the custom-made cushion. SNR can be increased by optimization of local coil placement and design and increasing the FOV in the phase-encode direction. Up to a doubling of the initial phase-encoded FOV, and therefore doubling of the scan time for that sequence, can be easily tolerated for T1-weighted imaging without swallowing motion artifact becoming problematic. Flow artifacts were distinguished by reviewing relevant time of flight and T2-weighted slices. Where there remained a problem, altering the direction of the phase-encoding gradient by 90° was helpful, as was comparison with images acquired during systole. Inadequate juxtaluminal flow suppression was in comparable regions between scans, leading to consistent overestimation of plaque burden, and did not compromise interstudy reproducibility. In an attempt to increase the

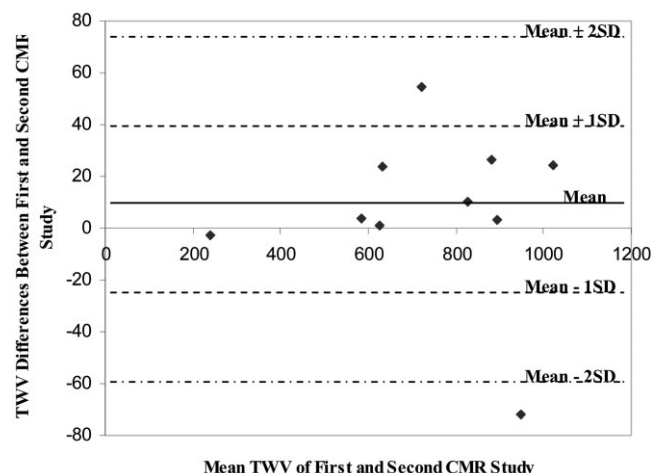


Figure 5. Bland-Altman plot of TWV differences vs. mean values for successive CMR scans.

future accuracy of this technique, we have recently developed a velocity-sensitive phase reconstruction method that can identify and remove residual signal from slow-flowing blood (12). Acquisition time for this method is identical to the current T1-weighted sequence. A further future modification is the addition of navigators positioned at the base of the tongue to help reduce motion artifact (13). Initial experience with such navigators is encouraging and indicates that overall scan time is not greatly increased. Both these changes may increase the average coverage of this technique. Further coverage could also be obtained with the introduction of automated software that can interpolate missing slices in a robust manner.

Previous CMR work in atherosclerosis assessment has recommended that at each matched location, comparison of images with the highest quality is more important than analysis based on T1-weighting, proton density-weighting, or T2-weighting (14). Others have shown that carotid arterial wall area measurements taken from T1-weighted and proton density-weighted images can be used interchangeably, but T2-weighting provides smaller values and could underestimate arterial area and consequently carotid arterial plaque burden (15). In this study, we compared successive T1-weighted images.

As well as the tomographic assessment of atheroma burden by T1-weighted FSE, multiple contrast-weighted CMR, or multispectral CMR, can identify fibrous cap rupture (16), distinguish advanced from early atheromatous lesions (17), and identify plaques that have a lipid rich necrotic core (18). The use of contrast agents such as gadolinium (19) and ultrasmall superparamagnetic particles (USPIOs) (20) can highlight areas of greater plaque neovasculature and macrophage density, respectively. Such additional information will identify and stratify increasing plaque and therefore patient vulnerability to symptoms (16). We hope to evaluate T1-weighted and T2-weighted three-dimensional volume selective FSE for similar multispectral analysis in conjunction with gadolinium and USPIOs.

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