

## Interstudy reproducibility of 3D volume selective fast spin echo sequence for quantifying carotid artery wall volume in asymptomatic subjects

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### Abstract

**Purpose:** To determine, in asymptomatic subjects, the interstudy reproducibility of a three-dimensional (3D) volume selective fast spin echo (FSE) cardiovascular magnetic resonance sequence for the assessment of carotid artery wall volume as a measure of atheroma burden.

**Methods:** Interstudy reproducibility was evaluated in 16 asymptomatic volunteers (10 male, 6 female). Both carotid arteries were scanned twice with a median interscan time of 5 days. The images were acquired 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 T1-weighted TWV for the first and second scans was 828 and 821 mm<sup>3</sup>, respectively (mean difference 7 mm<sup>3</sup>,  $p = 0.45$ ). The standard deviation (S.D.) of the differences between the measurements was 38 mm<sup>3</sup> yielding an interstudy coefficient of variation of 4.6%. The time for each study was approximately 30 min. For the longitudinal evaluation of carotid atheroma burden with pharmacological intervention versus placebo, 32 subjects would enable a difference of 38 mm<sup>3</sup> to be detected with a significance level of 5% with 80% power.

**Conclusion:** Volumetric analysis with carotid CMR in asymptomatic subjects using a 3D volume-selective FSE is time-efficient with good interstudy reproducibility, and is well suited for longitudinal studies of carotid atheroma with reasonable sample sizes.

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**Keywords:** Carotid artery; Asymptomatic; Early atherosclerosis; Interstudy reproducibility

### 1. Introduction

Cardiovascular disease (CVD) is an important cause of worldwide mortality accounting for almost 17 million deaths annually predominantly through coronary and carotid artery disease [1]. Coronary heart disease (CHD) is the commonest clinical manifestation of atherosclerosis and frequently presents as sudden cardiac death without a warning prodrome [2]. Treatment of survivors is important but in addition focus is turning increasingly towards the identification of pre-symptomatic disease with risk stratification in asymptomatic individuals.

Risk stratification tools enable a continuum of risk to be established for individuals based on population data. There are several such tools available; one is the Systemic Coronary Risk Evaluation (SCORE) Project which provides a scoring system for use in the clinical assessment of CVD risk in European clinical practice [3]. Other available methods include the Sheffield Tables [4]; the Joint British Societies' Coronary Risk Prediction Chart and associated computer program [5]; and the adult treatment panel (ATP) III 10-year risk estimates for men and women using framingham point scores [6,7]. The predictive value of these risk assessments is variable—the SCORE risk charts when applied to persons aged 45–64 had areas under receiver operating characteristic (ROC) curves ranging from 0.71 to 0.84.

Ultrasound has been used to assess plaque size quantitatively [8,9]. Indicators of carotid stiffness may confer ad-

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ditional prognostic and stratification data and this has been evaluated using B-mode ultrasound [10]. Additionally, ultrasonic determination of carotid plaque area and plaque progression can identify patients at highest risk for the combined 5-year end point of stroke, myocardial infarction, and vascular death [11]. Like ultrasonography, cardiovascular magnetic resonance (CMR) provides quantitative assessment of carotid plaque burden in a noninvasive manner. It also provides tomographic assessment with consistent localization, which enables identification of arterial remodeling over time. Pathological arterial remodeling is an important concept in the pathogenesis of atherosclerotic disease [12]. In this process, the external border of the artery expands and thickens well before luminal encroachment occurs, allowing tomographic vessel wall imaging to identify early atherosclerosis well before conventional luminal angiography. Clinical results using CMR have been reported for the aorta and carotid artery [13–16]. More recently, we have demonstrated that a novel three-dimensional (3D) volume selective fast spin echo (FSE) CMR sequence has good interstudy reproducibility in the quantification of total carotid artery wall volume (TWV) in subjects with known carotid artery atherosclerosis [17]. 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 2D method because of a significantly smaller phase-encode field of view (FOV) [18]. 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 [19]. Using the 3D FSE technique, a total of 56 mm (28 mm above and below the carotid bifurcation) is imaged within 5 min. Since atherosclerosis begins early in life [20], and safe serial identification of plaque burden may be useful for cardiovascular risk stratifica-

tion, prognostication, and assessment of treatments, we evaluated the interstudy reproducibility of 3D volumetric CMR in asymptomatic subjects without known carotid artery disease.

## 2. Methods

### 2.1. Study population

Sixteen asymptomatic volunteers underwent two carotid CMR scans between April and June 2003 with a median interscan period of 5 days (interquartile range 1–8 days). There were 6 females and 10 males with a mean age of 54 years (range 39–70) who were risk stratified using the SCORE system for estimation of 10 year risk of fatal CVD [3]. The median 10 year risk score was 2% (interquartile range 1–4%; Table 1). The study received local ethics committee approval and all participants gave written informed consent.

### 2.2. CMR

CMR was performed using a 1.5T scanner (Sonata, Siemens, Erlangen, Germany), with purpose-built bilateral four channel phased-array surface carotid coils (Machnet B.V., The Netherlands) and a specially designed head and neck cushion for immobilization (Fig. 1). Subjects were scanned in the supine position with the carotid coils in the isocentre of the static magnetic field. The average duration of each CMR study was 30 min. Typical sequence parameters for T1-weighted 3D volume selective FSE were: matrix size = 256, 0.47 mm × 0.47 mm pixels; 28 slices of 2 mm thickness; typical field-of-view = 120 mm × 24 mm; time to echo (TE) = 11 ms; repetition time (TR) according to a sin-

Table 1  
Demographic data on the asymptomatic volunteers included in this study

Subject	Sex	Scan interval	Age	T <sub>c</sub>	HDL	T <sub>c</sub> :HDL	LDL	TG	ECG LVH	FHx	DM	HT	Smoker	Ethnicity	Maximum risk CVD(%)
1	M	4 days	45	5	1.2	4.17	3.35	1	N	N	N	N	N	C	1
2	M	1 day	44	4.6	1.2	3.83	na	na	N	N	N	N	N	C	<1
3	M	8 days	49	4.7	1.3	3.62	2.13	2.8	N	N	Y	N	N	A(i)	2
4	M	2 days	62	4.7	1.1	4.27	3.19	0.9	na	N	N	H	N	A(i)	10
5	F	1 h	65	6.7	2.1	3.19	4.05	1.2	N	N	N	N	N	C	2
6	F	13 days	59	5.2 (treated)	1	5.20	3.06	2.5	N	Y	Y	Y	N	M(i)	15+
7	F	14 days	50	4.4	2	2.20	2.13	0.6	N	N	N	N	Y	c	<1
8	F	1 h	64	8.3	2.5	3.32	na	na	N	N	N	N	N	c	2
9	M	2 days	70	5.7	1.4	4.07	na	na	N	N	N	N	Y	c	9
10	M	6 days	66	5.9	1.3	4.54	3.87	1.6	N	N	N	N	N	A(i)	9
11	F	6 days	59	5.6	1	5.60	3.37	2.7	N	Y	N	N	N	M(i)	2
12	M	7 days	47	5.4	1.5	3.60	na	na	N	N	Y	Y	N	C	2
13	M	13 days	45	4.5	1.5	3.00	2.77	0.5	N	N	N	N	N	c	1
14	F	4 h	50	7.9	1.1	7.18	5.62	2.6	N	N	N	N	Y	c	1
15	M	13 days	39	5.8	1.3	4.46	4.18	0.7	N	N	N	N	N	c	<1
16	M	1 day	51	7.1	1.1	6.45	4.55	3.2	N	N	N	Y	Y	c	4

M: male volunteers, F: female volunteers; T<sub>c</sub>: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, and TG: triglyceride levels; ECG LVH: 12 lead electrocardiogram evidence of left ventricular hypertrophy by the Sokolov–Lyon–Rappaport criteria; FHx: family history of premature ischaemic heart disease; DM and HT: presence of previously diagnosed diabetes mellitus and hypertension, respectively; C: caucasian, A(i): Asian from the Indian subcontinent, na: data not available.

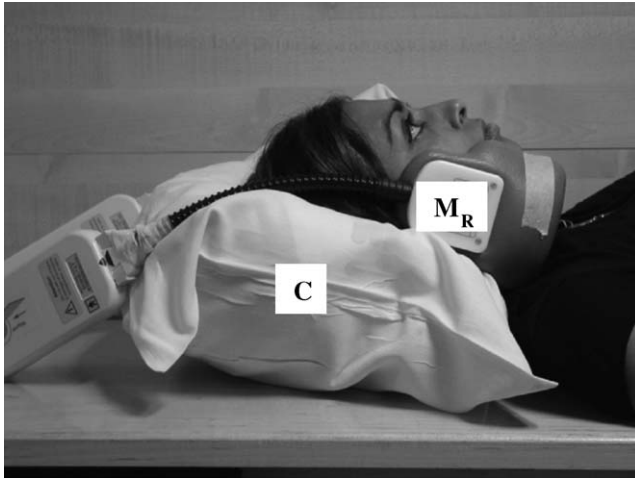


Fig. 1. Positioning of a volunteer using bilateral carotid coils and a specially designed cushion. The cushion is filled with polystyrene beads and is partially evacuated, with the coils in situ, just prior to imaging to allow moulding to the contours of the subject's head and neck.  $M_R$ : right carotid coil; C: custom-made head and neck cushion.

gle multiple of the subject's R–R interval ( $1 \times RR$ ); echo train length (ETL)=11; fat suppression; and 650 ms inversion time following double inversion preparation pulse. For T2-weighted 3D volume selective FSE, parameters were similar excepting a TE of 53 ms and a  $TR = 2 \times RR$ . The region chosen for measurement was centered on the carotid bifurcation and extended 28 mm in both directions (Fig. 2).

Data was collected as cross-sectional images from which TWV, a marker of total carotid plaque volume, was calculated by subtraction of the total carotid luminal volume from the total outer carotid volume. Only if matched T1-weighted images both had adequate signal-to-noise (SNR) were they included in the analysis. Relevant T2-weighted images were used to help differentiate areas of vessel wall from possible flow artifacts where necessary. Results were analyzed by a single observer (AV) by manual tracing using dedicated display software (CMRtools, Cardiovascular Imaging Solutions, London, UK; Fig. 3).

### 2.3. Statistical analysis

The standard deviation (S.D.) of TWV between matched T1-weighted image was calculated and divided into the mean TWV to determine the coefficient of variation (COV). To compare the two sets of TWV measurements, 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 evaluated by comparison of the measurements with the line of identity and a Bland–Altman plot [21]. Power calculation was performed using the nomogram described by Altman [22]. Results are shown as mean  $\pm$  S.D., or median with interquartile range as appropriate.

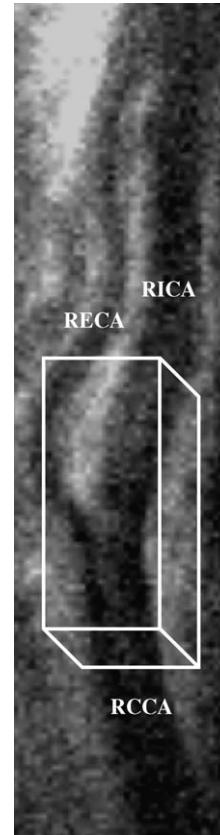


Fig. 2. In-plane FSE image through the right common carotid artery (RCCA) where it bifurcates into the right internal (RICA) and external (RECA) arteries. The volume highlighted indicates the area of interest for serial imaging.

## 3. Results

The mean TWV for the two CMR scans was  $828 \pm 572 \text{ mm}^3$  and  $821 \pm 560 \text{ mm}^3$ , respectively, which were not significantly different from each other (mean difference  $7 \pm 38 \text{ mm}^3$ ,  $p=0.45$ ). The interstudy COV was 4.6%. Agreement between the two measurements was good as shown by the close approximation of the values to the line of identity and the narrow limits on the Bland–Altman plot (Figs. 4 and 5).

### 3.1. Discussion

Atherosclerosis starts very early in life [20], and is progressive. Progression can however be retarded or reversed by therapies such as lipid lowering [23,24] Targeting such potentially lifelong and costly therapy is an important step which may be problematic in individuals who have yet to manifest clinical symptoms. CVD risk assessment models incorporating factors such as age, gender, smoking history, blood pressure and total and high-density lipoprotein cholesterol, group a large proportion of individuals into an intermediate-risk category rather than high-risk (needing treatment) and

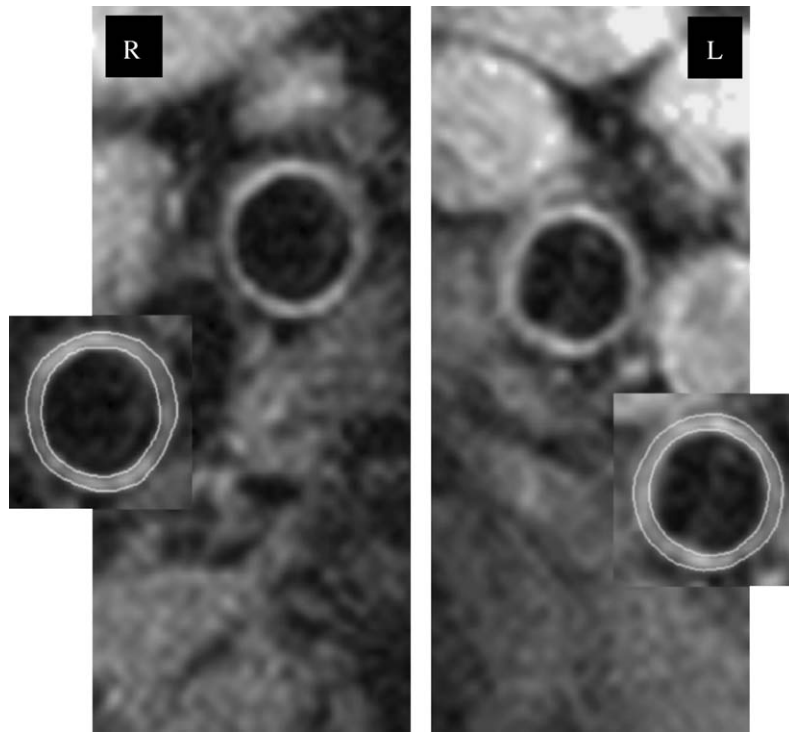


Fig. 3. Cross-sectional carotid CMR slices through the right (R) and (L) common carotid arteries for one subject. Inset are the contours drawn from each image, with the inner circles demarcating carotid luminal areas and the outer circles representing total carotid artery wall areas. The areas are summated from all usable slices for both sides and multiplied by the 2 mm slice thickness to provide one TWV measurement.

low risk (treatment not currently needed). Emerging methods for establishing those who are most vulnerable within this large intermediate-risk group include carotid CMR.

Current CMR technology can readily study disease at the carotid artery in a serial manner, which is non-invasive and free from radiation. At any fixed point in time, such CMR data can be used as an adjunct to risk stratification and/or screening while serial data could be used in follow-up [10,23,24].

Prerequisites for such use of CMR include determination of normal ranges and assessment of interstudy reproducibility in individuals with and without significant disease.

Volumetric analysis with carotid CMR in subjects with known carotid atherosclerotic disease using a novel 3D volume selective FSE sequence had an interstudy reproducibility of 4.4% [17]. This is comparable to the COV of 4.6%

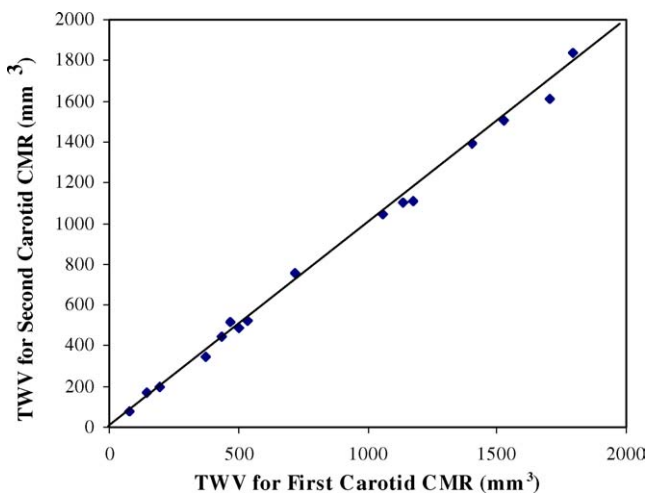


Fig. 4. Comparison of results of TWV between successive carotid CMR scans. There is close agreement with the line of identity.

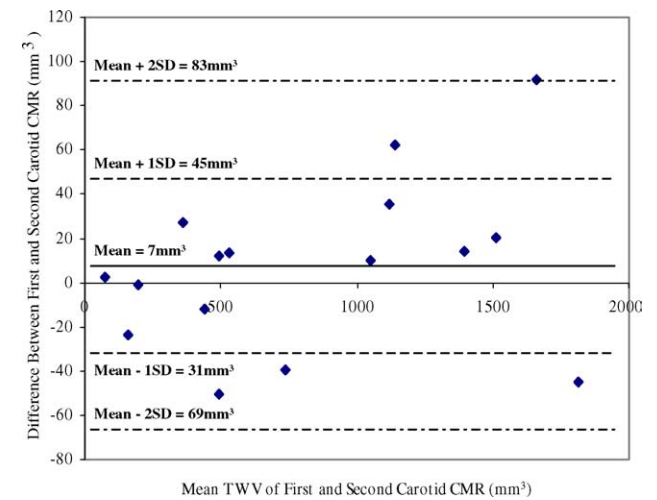


Fig. 5. Bland–Altman plot of the means of the two TWV values against their difference. The mean difference and limits of 1 and 2 standard deviations are indicated.

obtained using this sequence on the carotid arteries of asymptomatic volunteers without known carotid artery atherosclerotic disease in whom the burden of disease is markedly lower. Notwithstanding these good results, more residual blood signal was encountered in this asymptomatic group than in subjects with known disease. This is as a result of several factors; more distensible carotid arteries which have increased recirculation of blood within the carotid bulb and permit greater variability in vessel circumference during systole and diastole, and the lack of high velocity jets from stenoses which when present allow better flow suppression using black-blood imaging methods. One potential solution for flow artifacts is velocity sensitive phase reconstruction, which aims to highlight and thereby eliminate slow flow [25]. Motion artifacts from swallowing and head movement were once again infrequent. This is a reflection of the successful use of the specially designed head and neck cushion and clear subject instruction and motivation. Where such motion artifacts do arise, the addition of navigators placed at the base of the tongue will prove useful [26]. It is hoped that such lingual navigation will also allow compensation for the heart rate variability noted during swallowing, which in turn will reduce flow artifacts.

The results of this pilot study indicate that the newly described 3D carotid CMR sequence has good reproducibility and can detect small changes in the carotid arterial wall volume in subjects with a low overall carotid plaque burden. Future work will evaluate the accuracy of this technique by comparison of TWV measures made using carotid CMR on cadaveric carotid artery specimens of predetermined volume. Power calculation indicates that a sample size of 32 subjects would allow a placebo-controlled trial of a therapeutic intervention to detect a difference in plaque volume between groups of 38 mm<sup>3</sup> with a significance level of  $p < 0.05$  and 80% power. Such high reliability in the carotid artery is due to the combination of high-resolution 3D imaging, fixation to the anatomical landmark of the carotid bifurcation, and accurate cross-sectional imaging.

#### 4. Conclusion

Volumetric analysis with CMR of the carotid arteries in asymptomatic volunteers without known carotid artery disease using a 3D volume-selective FSE is time efficient and reproducible with an interstudy coefficient of variation of 4.6%. This suggests that this novel sequence is suitable for longitudinal studies in similar individuals for the quantification of atherosclerosis and the serial assessment of the progression or regression of carotid artery atherosclerotic plaque burden following drug or other interventions.

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