

## Concise report

**Multi-examiner reliability of automated radio frequency-based ultrasound measurements of common carotid intima–media thickness in rheumatoid arthritis**

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**Abstract**

**Objectives.** To assess the reliability of the automated radio frequency (RF)-based US measurement of carotid intima–media thickness (IMT) performed by rheumatologists and to evaluate the variability between this method and the conventional B-mode US measurement of carotid IMT in RA patients.

**Methods.** Twelve rheumatologists measured in two blinded rounds the IMT of both common carotid arteries (CCAs) of seven RA patients with an automated RF-based method. At each round, a cardiologist measured both CCA-IMTs of the patients using an automated B-mode method. Inter-observer reliability for RF-based IMT measurements was evaluated by the intra-class correlation coefficient (ICC). Intra-observer reliability for RF-based IMT measurements was assessed using the root mean square coefficient of variation (RMS-CV), Bland–Altman method and ICC. Agreement between the two US methods was evaluated by the Bland–Altman method, ICC and RMS-CV.

**Results.** Inter-observer ICCs for the RF-based CCA-IMT measurements were 0.85 (95% CI 0.69, 0.94) for the first round, and 0.77 (95% CI 0.55, 0.91) for the second round. RMS-CVs for the RF-based CCA-IMT measurements varied from 5.6 to 11.7%. The mean intra-observer ICC for the RF-based CCA-IMT measurements was 0.61 (95% CI 0.46, 0.71). In the Bland–Altman analysis for agreement between RF-based and B-mode CCA-IMT measurements, the mean difference varied from  $-0.6$  to  $-19.7 \mu\text{m}$ . Inter-method ICCs varied from 0.57 to 0.83 for 11 rheumatologists. Inter-method RMS-CVs varied from 11.3 to 13.7%.

**Conclusions.** Our results suggest that automated RF-based CCA-IMT measurement performed by rheumatologists can be a reliable method for assessing cardiovascular risk in RA patients.

**Key words:** Ultrasound, Carotid intima–media thickness, Reliability, Rheumatoid arthritis, Radio frequency.

**Introduction**

Atherosclerosis and its consequent cardiovascular (CV) events are largely responsible for the increased morbidity and mortality risk in RA patients [1–5].

US measurement of intima–media thickness (IMT) of the extracranial carotid arteries is widely accepted as a surrogate marker of subclinical atherosclerosis and CV disease, independent of traditional CV risk factors, in observational and interventional studies [6–9]. In RA patients,

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increased IMT of the common carotid artery (CCA) assessed by US has shown independent predictive value in relation to both subclinical atherosclerosis and CV events [10, 11].

In previous literature, the carotid IMT has been mostly measured offline or online from B-mode images by manual, semi-manual or automated detection of the lumen-intima and media-adventitia interfaces over an artery segment [12]. These methods are highly machine and operator dependent, require substantial specific training and can be time consuming. US technology based on radio frequency (RF) provides an automated method for measuring carotid IMT that is uninfluenced by the B-mode image quality and less dependent on the experience in vascular US of the examiner [13].

The objectives of this study were to assess the multi-examiner reliability of the automated RF-based US measurement of carotid IMT performed by rheumatologists non-expert in vascular US and to evaluate the variability between this method and the conventional B-mode US measurement of carotid IMT performed by a highly experienced cardiologist in RA patients.

## Methods

### Patients

Seven consecutive patients [five women, two men; median age 54.5 (52–64) years] with RA according to the ACR 1987 criteria [14] were recruited for the study. The following data were recorded for each patient at study entry: demographics, RA characteristics and CV risk factors and events. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of Hospital Universitario Severo Ochoa. Written informed consent was obtained from all patients before the study.

### Study design

Twelve rheumatologists experienced in musculoskeletal (MS) US and one cardiologist highly experienced in vascular US (C.G.-J.) participated in the study. The rheumatologists had no experience in B-mode US IMT measurements. Their previous experience in automated RF-based US IMT measurements was as follows: six had never performed the above examination, and six had performed 2–50 examinations during the previous 6 months. The study was carried out in 1 day. It took 8 h divided into two sessions, a 4-h morning session and a 4-h afternoon session.

The 12 rheumatologists measured the IMT of both CCAs in two rounds (i.e. morning and afternoon), in a blinded fashion, of the seven patients with an automated RF-based US method. At each round, the cardiologist also measured both CCA-IMT of seven patients at the same locations using an automated B-mode US method. Each ultrasonographer was given a maximum of 15 min for measuring the IMT of both CCAs of each patient. The day before the study, the investigators

spent 3 h scanning CCA in B-mode and using the RF technology.

### Carotid IMT measurements

#### *Automated RF-based US measurement of CCA-IMT*

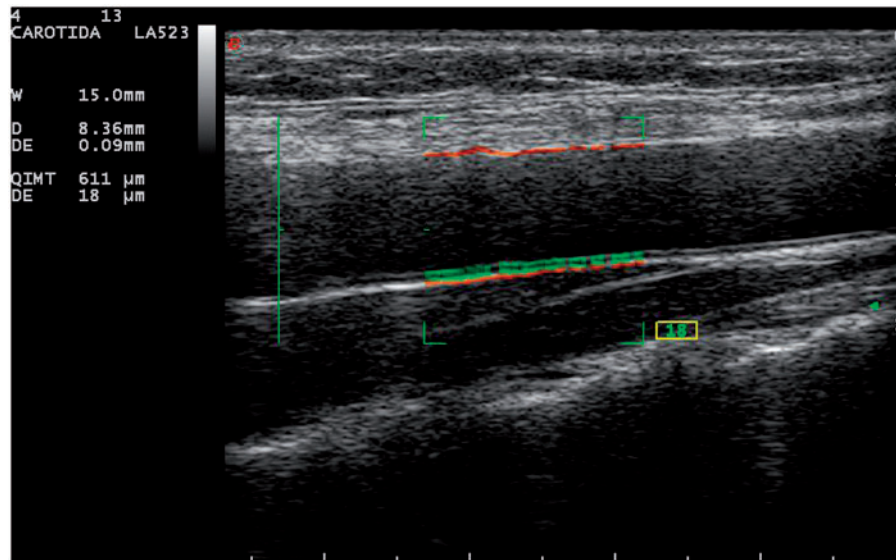
CCA-IMT was measured with seven commercially available real-time scanners (i.e. five MyLab 25 Gold, one MyLab 60 and one MyLab 70; Esaote, Genoa, Italy), equipped with 7–12 MHz linear transducers using the software-guided technique RF-Quality Intima Media Thickness (QIMT; Esaote, Maastricht, Holland). Each patient was randomly assigned to the same scanner during the morning and afternoon sessions.

IMT was measured at the posterior wall of the right and left CCAs, 10 mm from the carotid bifurcation, over the proximal 15-mm-long segment. The patients were placed in the supine position with their heads slightly bent in the opposite direction from the examination side. The right CCA was first identified in B-mode, in a transverse view and followed from the proximal part to the bulb origin. Immediately afterwards, the CCA and the most proximal part of the bulb were imaged in a longitudinal view from a lateral approach (supplementary figure 1, available as supplementary data at *Rheumatology* Online). The QIMT software was enabled by pressing a specific button on the scanner keyboard. A 15-mm-long region of interest (ROI) and a reference line on the left were superimposed on the B-mode image. The vertical reference line was placed on the bulb origin. The distance between this line and the left margin of the ROI was 10 mm. The ROI was positioned so that a marker in the middle of the reference line was located in the centre of the artery lumen. The mean and s.d. of the IMT values from the past six cardiac cycles were continuously calculated by the system and displayed on the left side of the image. According to the manufacturers, the s.d. should be  $<20\ \mu\text{m}$  to maximize the quality and accuracy of the IMT measurements. As soon as the s.d. was  $<20\ \mu\text{m}$  for the first time during the measurement process, the ultrasonographers froze the image and collected the mean IMT value for analysis. The QIMT values were expressed in micrometres. An illustrative example of the RF-based measurement of the CCA-IMT is shown in Fig. 1. This procedure was repeated on the left CCA.

#### *Automated B-mode US measurement of CCA-IMT*

A Philips CX50 CV was used equipped with a linear 11.0 MHz transducer (Philips Medical Systems, Andover, MA, USA). With the same patient position as used for the RF-based US measurements, the segments of the CCAs 10 mm proximal to the carotid bifurcation were scanned. The image was focused on the posterior carotid wall in longitudinal view. The images were stored digitally for subsequent offline analysis. For measurement of the IMT, the distance between the leading edges of the lumen-intima interface and the media-adventitia interface of the B-mode frame was taken. Software (Qlab; Philips Medical Systems, Andover, MA, USA) that analysed the IMT automatically at 64 points within a segment of 10 mm

**Fig. 1** RF-based measurement of the CCA-IMT. The green discontinuous box represents the ROI. The green mark is positioned at the centre of the artery lumen. The green vertical line is placed on the bulb origin. The green horizontal thick line appears superimposed on the B-mode image of the intima-media of the CCA far wall. On the left side of the image the following data are displayed: width of the ROI (W), mean and s.d. (DE) of the vessel diameter (D) from the last six cardiac cycles, and mean and s.d. of the CCA-IMT from the last six cardiac cycles. The QIMT value is expressed in micrometres. The number in the yellow box indicates the s.d. which is shown in green if  $<20$ .



was adopted; the value given was the arithmetic mean IMT calculated. An ECG recording during the US examination was obtained for all patients. All measurements were performed in the end diastole [12, 15].

#### Statistical analysis

Statistical analysis was performed using SPSS, version 15.0 (SPSS, Chicago, IL, USA). To summarize patient characteristics, quantitative variables were presented as the median or mean (s.d.) and range.

#### Inter-observer reliability

Inter-observer reliability for RF-based IMT measurements was evaluated by calculating the intra-class correlation coefficient (ICC) using a two-way mixed model. ICC values  $<0.40$  were considered poor,  $0.40$ – $0.75$  good to optimal and  $>0.75$  excellent [16].

#### Intra-observer reliability

Intra-observer reliability for RF-based and B-mode IMT measurements was assessed as follows. Short-term precision was calculated using the formula for the root mean square coefficient of variation (RMS-CV). The difference between the measurements from the two rounds was plotted against the mean of the paired measurements according to Bland-Altman for disaggregated visual analysis of agreement [17]. The limits of agreement (i.e. there is a 95% probability that the difference between two measurements will be in this interval) were also

estimated. In addition, the intra-observer ICC (one-way model) was calculated.

#### Agreement between RF-based and B-mode IMT measurements

Agreement between the two US methods was evaluated by the Bland-Altman method [17] and by calculating the ICC (two-way mixed model) for each investigator who performed the RF-based method (i.e. 12 rheumatologists). In addition, the inter-method RMS-CV was estimated for each rheumatologist.  $P < 0.05$  was considered statistically significant.

## Results

#### Patient characteristics

Median disease duration was 50 (20–600) months. Six patients were RF positive, five were CCP positive and four had radiographic erosions. All patients were taking DMARDs, four were taking biologic therapy and three were taking systemic CSs. Six patients had been diagnosed with traditional CV risk factors. One patient smoked. No patient had suffered from CV events.

#### CCA-IMT

We took the measurements performed by the cardiologist as the reference for describing the CCA-IMT in each patient. The mean (s.d.) of the right and left CCA-IMT measurements ranged from 502.5 (35.9) to 865 (157)  $\mu\text{m}$ .

### Inter-observer reliability of RF-based CCA-IMT measurements

Inter-observer ICCs for the RF-based CCA-IMT measurements were 0.85 (95% CI 0.69, 0.94) for the first round, and 0.77 (95% CI 0.55, 0.91) for the second round.

### Intra-observer reliability of RF-based and B-mode CCA-IMT measurements

RMS-CVs for the RF-based CCA-IMT measurements taken by the rheumatologists varied from 5.6 to 11.7% and the global RMS-CV was 9.3%. RMS-CV for the B-mode CCA-IMT measurements taken by the cardiologist was 4.8%. Overall, the results from the rheumatologists did not depend on their previous experience in the procedure (Table 1).

Intra-observer ICC for the RF-based CCA-IMT measurements was 0.61 (95% CI 0.46, 0.71). Intra-observer ICC for the B-mode CCA-IMT measurements was 0.98 (95% CI 0.95, 0.99). The mean difference between the RF-based CCA-IMT measurements from the two rounds was 3.3  $\mu\text{m}$  (95% CI  $-8.5$ , 15.1  $\mu\text{m}$ ) (Supplementary figure 2, available as supplementary data at *Rheumatology* Online). The limits of agreement were  $-146.8$  and 153.4  $\mu\text{m}$ .

### Agreement between RF-based and B-mode IMT measurements

Supplementary table 1 (available as supplementary data at *Rheumatology* Online) shows the agreement between methods from the Bland-Altman analysis (i.e. mean difference between methods and limits of agreement) for each rheumatologist. All the 95% CI included 0, indicating that the data are consistent with a theoretical inter-method difference of 0.

Most ICCs between the two methods were  $>0.6$  and only one rheumatologist obtained an ICC  $<0.4$ .

**TABLE 1** Precision of CCA-IMT measurement

Ultrasonographers	RMS-CV between rounds, %	No. of previous IMT measurements
Rheumatologist 1	5.6	50
Rheumatologist 2	8.3	50
Rheumatologist 3	9.1	10–15
Rheumatologist 4	10.6	10–15
Rheumatologist 5	10.2	$<5$
Rheumatologist 6	11.7	$<5$
Rheumatologist 7	10.5	None
Rheumatologist 8	9.9	None
Rheumatologist 9	7.6	None
Rheumatologist 10	7.6	None
Rheumatologist 11	9.0	None
Rheumatologist 12	9.7	None
Cardiologist	4.8	800

RMS-CV between rounds, and previous experience in IMT measurement for each ultrasonographer.

Inter-method RMS-CVs varied from 11.3 to 13.7%. Again, there were no relevant differences in the inter-method variables according to rheumatologists' previous exposure to RF-based US technology (supplementary table 2, available as supplementary data at *Rheumatology* Online).

## Discussion

The growing body of evidence of increased CV risk in RA patients has led the rheumatologist community to recognize the importance of this in clinical practice and research [1–5, 18].

Several CV scientific societies have reported that IMT measurement should be included in the routine assessment of CV risk [8, 12]. The criterion validity of US IMT measurement has been established in histological studies [19]. The added value of carotid IMT in CV risk assessment has been shown also in RA patients [10, 11]. In addition, later stages of atherosclerosis (i.e. plaque, stenosis and occlusion) can also be identified by carotid US [6].

Over the past decade, increasing numbers of rheumatologists have incorporated MSUS as a bedside diagnostic tool into their routine clinical practice. Most of the US scanners widely used in MSUS have the facility of incorporating software for vessel wall assessment. Among these software programs, RF-based systems permit the acquisition of RF data in real time as raw US signal. B-mode is used only to locate the artery and optimize the angle of insonation in order to correctly place the RF ROI [13].

We tested, for the first time, the multi-examiner inter- and intra-observer reliability of CCA-IMT measurement with an RF-based method performed by rheumatologists in representative RA patients. We obtained good to excellent inter-observer reliability in both RF-based CCA-IMT assessment rounds. It is noteworthy that most of the rheumatologist ultrasonographers, although experts in MSUS, had minimal or no experience in IMT measurements.

The intra-observer reliability of RF-based CCA-IMT measurements, although not at the level achieved by our vascular expert cardiologist, was good to optimal. The precision results in our study showed similar RMS-CVs to that obtained by vascular expert ultrasonographers with RF-based US in patients with CV disease [20].

The comparison between RF-based and B-mode CCA-IMT measurements showed good to excellent agreement based on the ICC obtained by 11 out of 12 rheumatologists. Our ICCs, differences and limits of agreement between both methods were in accordance with those of the study by Schreuder *et al.* [20] who evaluated the relationship between B-mode and RF measurement of CCA-IMT taken by expert ultrasonographers in 136 patients recently diagnosed with CV disease.

In conclusion, our results suggest that RF-based US measurement of CCA-IMT performed by rheumatologists may be a reliable, feasible and relatively easy to learn method in rheumatology practice and multicentre epidemiological and interventional studies for assessing CV

risk in RA patients. Training rheumatologists in this system and implementation of this technology in routine rheumatology US could provide additional value to current US in rheumatology.

#### Rheumatology key messages

- US measurement of carotid IMT performed by rheumatologists may be reliable and feasible.
- Rheumatologists can assess carotid IMT in practice and multicentre epidemiological and interventional studies.
- Implementation of carotid intima-media assessment could provide additional value to current US in rheumatology.

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### Supplementary data

Supplementary data are available at *Rheumatology* Online.

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