B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study

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ABSTRACT
Objective. We aimed to determine the diagnostic accuracy of B-mode compression sonography of the temporal arteries (tempCS) and B-mode sonographic measurement of the axillary artery intima media thickness (axIMT) for the diagnosis of giant cell arteritis (GCA).

Methods. After having established measurement of tempCS and axIMT in our routine diagnostic workup, 92 consecutive patients with a suspected diagnosis of GCA were investigated. Clinical characteristics were recorded and wall thickening of the temporal arteries (tempCS) and axillary arteries (axIMT) was measured (mm). Using the final clinical diagnosis as the reference standard, receiver operator characteristics (ROC) analysis was performed. In a subgroup of 26 patients interobserver agreement was assessed using Spearman’s rank correlation.

Results. Cranial GCA, extracranial GCA, and combined cranial/extracranial GCA were diagnosed in 18, 7, and 9 individuals, respectively. For the diagnosis of cranial GCA, tempCS had an excellent area under the curve (AUC) of 0.95, with a cut-off of ≥0.7 mm offering a sensitivity and specificity of 85% and 95%. The AUC of axIMT for the diagnosis of extracranial GCA was 0.91 (cut-off ≥1.2 mm: sensitivity and specificity 81.3 and 96.1%). Applying a combined tempCS/axIMT cut-off of ≥0.7 mm/1.2 mm, we calculated an overall sensitivity and specificity for the final clinical diagnosis of cranial and/or extracranial GCA of 85.3% and 91.4%. Interobserver agreement was strong for both parameters assessed (Spearman’s rho 0.72 and 0.77, respectively).

Conclusion. The combination of tempCS/axIMT allows objective sonographic assessment in suspected GCA with promising diagnostic accuracy.

Introduction
Giant cell arteritis (GCA) is the most common form of the primary systemic vasculitides, typically occurring in individuals aged ≥50 years. In recent years, imaging studies uncovered the systemic nature of the disease by documenting involvement of the thoracic aorta and its major branches in up to 50–70% of cases (1). Stimulated by the landmark study by Schmidt et al. in 1997, colour duplex sonography (CDS) of the temporal arteries and subsequently also of the axillary arteries has been studied extensively in the diagnostic workup of GCA (2, 3). Applying modern ultrasound equipment experienced centres reported a sensitivity and specificity of up to 80% and 100%, respectively (4). However, CDS is highly dependent on the operator’s expertise (4, 5). The role of CDS of the extracranial arteries still has not been formally established.

High frequency ultrasound probes allow exact delineation of the vessel wall even in small arteries. Most recently, cut-off-values of the intima-media-thickness of the temporal arteries and axillary arteries to discriminate between patients with and without GCA have been proposed (6). In 2013, Aschwan­den et al. introduced B-mode-compression sonography of the temporal arteries (tempCS) in the diagnosis of cranial GCA (4). These authors documented a diagnostic accuracy of tempCS comparable to that of temporal artery CDS. Combining the simple and promising B-mode ultrasound techniques of tempCS and intima-media-thickness measurement of the axillary arteries (axIMT), the present study aimed to determine the diagnostic accuracy of objective cut-off-values of temporal and axillary artery wall thickness for the diagnosis and exclusion of GCA.
Patients and methods

In October 2014 we implemented B-mode sonography with determination of temporal artery wall thickness (tempCS) and axillary artery wall thickness (axIMT) in our routine diagnostic workup of patients suspected of having cranial or extracranial GCA. Since then, all consecutive patients underwent a standardised B-mode sonographic examination in addition to CDS, as outlined below.

All examinations were performed by one of two experienced sonographers (M.C., A.S.). For sonographic evaluation a GE LOGIC E9 ultrasound unit (GE Healthcare, Munich, Germany) with a 5–16 MHz broadband linear transducer was used. B-Mode and CDS settings were dynamically adjusted to achieve optimal visualisation of the arterial wall. CDS examination included cross-sectional and longitudinal evaluation of the bilateral common superficial arteries and their parietal and frontal branches as well as both axillary arteries at the origin of the subscapular arteries. A hypoechogenic circumferential wall thickening (halo) in any segment of the temporal arteries or the axillary arteries was considered a positive CDS finding for GCA (2, 3).

The frontal and parietal branches of the temporal arteries were evaluated with tempCS, as described by Aschwanden et al. (4). The maximum thickness of the temporal artery wall remaining visible after transducer-induced compression was measured in the mid portion of each arterial segment evaluated in the transversal plane (Fig. 1). Measurement of the axillary artery intima-media complex (axIMT) was performed on the near and far wall of the axillary arteries proximally to the origin of the subscapular arteries. B-Mode sonography visualises three arterial layers, two hyperechoic layers with a hypoechoic layer in between. The inner two layers closer to the arterial lumen are referred to as IMT (7).

B-Mode- and CDS-findings were compared against the final clinical diagnosis which was based on the American College of Rheumatology classification criteria and/or a positive temporal artery biopsy (TAB) for cranial GCA (8) and on non-invasive cross sectional imaging (magnetic resonance imaging or positron emission tomography) for extracranial GCA (1). Both sonographers were not involved in making the final clinical diagnosis. All patients with a final clinical diagnosis of GCA were classified according the disease pattern (cranial GCA only vs. extracranial GCA only vs. combined cranial and extracranial GCA). Clinical and laboratory characteristics of patients with and without a final clinical diagnosis of GCA were recorded.

For statistical analysis, SPSS v. 21.0 (SPSS Inc., Chicago, IL, USA) was applied. Univariate group comparisons were performed using χ² test (categorical variables) and unpaired t-test (continuous variables). Two-sided p-values <0.05 were considered significant. Using receiver operator characteristics (ROC) analysis, we aimed to determine the optimal cut-off-values of tempCS for the diagnosis/exclusion of cranial GCA and of axIMT for the diagnosis/exclusion of extracranial GCA. Applying 2 x 2 contingency tables, the sensitivity and specificity of the combined threshold values of tempCS + axIMT for the final clinical diagnosis were calculated.

A subgroup of patients was examined independently by both sonographers. Interobserver-agreement was assessed using Spearman’s rank correlation (continuous variables).

Results

Patient’s characteristics

Between October 2014 and October 2015, a total of 92 patients were referred for sonographic examination because of clinically suspected GCA. The proportion of subjects investigated under corticosteroid treatment was 47.8%, with a mean daily Prednisolone dose of 492±474 mg in these patients. Twenty-two patients (23.9%) had already received one or more applications of high dose prednisolone (500 to 1000 mg) intravenously because of cranial ischaemic complications. Fourteen patients were on corticosteroids for more than 7 days before the sonographic examination because of previously diagnosed polymyalgia rheumatica (mean daily dose 10.8±9.8 mg; mean duration in these patients 72±63 days, range 10 to 210 days). One of these patients was treated with methotrexate 15 mg once weekly in addition to prednisolone 5 mg per day.

A final diagnosis of GCA was established in 34 patients (37%). Isolated cranial GCA, isolated extracranial GCA, and combined cranial and extracranial GCA were diagnosed in 18, 7, and 9 individuals, respectively. Out of 48 corticosteroid-naive patients, 30 patients treated between 1 to 7 days, and 14 patients on corticosteroid treatment for longer than 7 days, GCA was diagnosed in 13 (27.1%), 19 (63.3%), and 2 (14.3%), respectively. Compared to patients without a final diagnosis of GCA, those eventually diagnosed with GCA were more frequently under corticosteroid treatment (61.8% vs. 39.7%), with a higher mean Prednisolone dose (658±447 mg vs. 341 mg±447 mg) but a shorter mean treatment duration (7.6±15.8 days vs. 28.5±55.7 days). Intravenous corticosteroid pulse therapy had been started prior to US in 41.2% of patients with a final diagnosis of GCA versus 13.8% without a final diagnosis of GCA.
Clinical characteristics of patients with and without a final clinical diagnosis of GCA are compared in Table I.

**Colour duplex sonography (CDS)**

CDS had an overall sensitivity of 82.4% and specificity of 100% for the final clinical diagnosis of GCA. For the diagnosis of cranial GCA, a sensitivity of 81.5% and specificity of 100% were calculated, while the respective values were 86.7% and 100% for the diagnosis of extracranial GCA.

Six patients without positive CDS findings eventually got a final clinical diagnosis of GCA. Four of these patients fulfilled 3 or more of the ACR classification criteria and thus were classified as suffering from cranial GCA. TAB was negative in 3 out of these 4 patients, whereas one TAB revealed a histological pattern consistent with subsided arteritis. According to results of cross sectional imaging studies the remaining two CDS-negative patients fulfilling less than 3 ACR classification criteria were diagnosed with extracranial GCA.

**Compression sonography of the temporal arteries (tempCS)**

In total, 359 out of 368 temporal artery segments (97.6%, bilateral frontal and parietal branches) could be evaluated sufficiently with CS. The mean residual wall thickness measured during compression did not differ significantly between the single branches (data not shown). The mean tempCS was 1.03±0.03 in the group finally diagnosed with cranial GCA and 0.44±0.13 in the group classified as not suffering from cranial GCA (p<0.01). According to ROC-curve analysis, a tempCS of ≥0.7 mm (maximum of all temporal artery branches evaluated in a single patient) showed the best diagnostic accuracy for the diagnosis of cranial GCA, with a sensitivity of 85% and a specificity of 95%, respectively (Fig. 2-3). The corresponding area under the curve was excellent (0.95; 95% CI 0.90-1.0).

**IMT-measurement of the axillary arteries (axIMT)**

Assessment of axIMT on both sides could be performed in all patients. Due to the presence of focal eccentric, hyperechoic arterial wall thickening consistent with arteriosclerotic plaques of the near wall of one or both axillary arteries in 8 patients (8.7%), axIMT values of the far axillary artery wall (maximum of both sides) were used for analysis only. The mean axIMT was 1.64±0.61 mm in the group finally diagnosed with extracranial GCA and 0.87±0.18 mm in the group without a final diagnosis of extracranial GCA (p<0.01). ROC-curve analysis revealed an AUC for axIMT of 0.91 (95% CI 0.82-1.0), and an axIMT-cut-off (maximum of both axillary arteries in a single patient) of ≥1.2 mm had a sensitivity and specificity of 81.3% and 96.1% for the diagnosis of extracranial GCA (Fig. 2, 4). An axIMT-value of ≥1.2 mm in one or both axillary arteries was found in 6 of 7 patients with the final clinical diagnosis of isolated extracranial GCA.

**Combination of B-Mode sonographic parameters**

For the final clinical diagnosis of GCA (cranial and/or extracranial disease) the combination of tempCS (cut-off ≥0.7 mm) and axIMT (cut-off ≥1.2 mm) had a sensitivity and specificity of 85.3% and 91.4%, respectively. Sensitivity was 92.3%, 84.2% and 50% in subjects without corticosteroid treatment, corticosteroid treatment between 1 and 7 days, and treatment longer than 7 days, respectively. The respective values for specificity according to treatment duration were 94.3%, 72.7%, and 100%.

**Interobserver agreement**

Interobserver agreement was tested in a subgroup of 26 patients and was strong for tempCS (maximum value of all temporal artery branches evaluated in a single patient; Spearman’s
Discussion

To our knowledge, this is the first study evaluating the combined diagnostic yield of B-mode sonography of the temporal and axillary arteries within a consecutive cohort of subjects suspected of suffering from GCA. According to our study results we propose thresholds of tempCS (≥0.7 mm) and the axIMT (≥1.2 mm) for the diagnosis of cranial and extracranial GCA. Applying the combined threshold of tempCS and axIMT, we calculated a sensitivity and specificity of 85.3 and 91.4% for the final clinical diagnosis of GCA independent from the settings relevant for CDS such as pulse repetition frequency, wall filter and colour gain. Aschwanden et al. nicely demonstrated that a temporal artery halo can easily be provoked in a normal temporal artery, and that a halo can be missed in a diseased temporal artery when applying insufficient CDS settings (4). B-mode sonographic assessment bears the potential of broader establishment of ultrasound as a first line imaging method in the diagnostic workup of suspected GCA in routine clinical practice. Interestingly, in another study from Aschwanden et al. tempCS had excellent interobserver agreement, even when compared between experienced vascular sonographers and rheumatologists not familiar with vascular ultrasound who had undergone a short training course (5). Interobserver agreement was substantial in our study as well. Aschwanden et al. used a binary discrimination of the tempCS (fully compressible vs. not fully compressible) (4, 5). However, it is our experience that in this population of elderly patients the temporal artery wall frequently remains visible under compression also in subjects not suffering from GCA. Nonetheless, the diagnostic accuracy observed in that study was comparable to what we report here. Our approach certainly necessitates the use of high frequency ultrasound probes, whereas qualitative evaluation of the tempCS may have the advantage of being broader applicable even with standard linear transducers.

Second, investigating not only the temporal but also the axillary arteries is part of clinical routine in most experienced centres. Arteriosclerosis of the axillary arteries is uncommon, whereas in GCA the axillary arteries are affect-
ed in up to 50% of patients (3, 9). Temporal artery CDS and TAB are negative in more than 50% of cases with extracranial GCA (9). In these cases, the additional diagnostic yield of imaging the axial arteries is undoubtedly, yet not formally established. In our series, every fifth patient with a final clinical diagnosis of GCA was classified as having isolated extracranial GCA. Applying a cut-off of ≥1.2 mm for the axIMT, ultrasound examination correctly classified 6 out of 7 of these patients. Proper sonographic evaluation of the axillary arteries of course requires CDS and PW-Doppler assessment in order to detect and graduate axillary artery stenoses.

The question on how and to which extent corticosteroid treatment influences the results of B-Mode sonography in the diagnosis of GCA cannot be finally answered with our study. One reason is the application of a combined diagnostic approach of two different arterial territories (with normal wall thickness in one location possible despite vasculitic wall thickening in the other location), prohibiting simple analysis of wall thickness measures according to time under treatment. Moreover, subgroups were too small to determine meaningful differences. With this regard, the low sensitivity (50%) of the combined diagnostic approach in patients on corticosteroid treatment longer than 7 days was related to the small number (n=2) of patients with a final diagnosis of GCA in this group. It can be assumed, that similar to CDS, the diagnostic accuracy of CS of the temporal artery decreases over time, whereas the wall thickening of the axillary arteries usually persists (13, 14).

CDS and/or CS of the temporal arteries may have the potential to replace TAB in many cases of suspected cranial GCA. The bilateral halo sign has been shown to have a specificity reaching 100% for the diagnosis of GCA in the most recent meta-analysis (10). However, there remains one clinical scenario which still makes TAB indispensable. This is the patient suffering from typical symptoms of cranial GCA but having a negative CDS/CS-study of the temporal arteries. It has been shown in histopathological studies that there are distinct histological patterns of GCA not showing a transmural inflammation but a small-vessel vasculitis of the vasa vasorum and/or the perivascular small vessels (11). Patients exhibiting these disease patterns seem to have a very low rate of positive CDS-studies of the temporal arteries compared to those patients with classical transmural arteritis of the temporal arteries, despite similar clinical characteristics (12). Thus, currently TAB still has its role in the diagnostic workup of patients with suspected giant cell arteritis.

Recently, the results of a large multicentre prospective observational cohort study (TABUL: Temporal Artery Biopsy vs. Ultrasondoing Diagnosis of GCA) were published (15). This study primarily aimed at determining the diagnostic accuracy of temporal artery CDS in comparison to TAB in the diagnosis of GCA. Experience with vascular ultrasound was no prerequisite to participate as a CDS operator in the study, but sonographers were required to pass a training program and to provide scan recordings of the patients investigated for central reading. Clinicians were kept blinded to the US results. Compared to the final clinical diagnosis in 381 patients included in the primary analysis, the sensitivity/specificity of CDS and TAB were 54%/81% and 39%/100%, respectively. Of note, discrepant results between CDS and TAB were noted in as much as 30% of cases. Evaluation of the diagnostic yield of axial artery CDS was a secondary study objective, and the rate of axillary involvement by CDS criteria was somewhat lower (13.9%) than in previous monocentric studies (3, 9). The rather disappointing diagnostic accuracy of CDS in TABUL was most probably related to the limited experience of a significant proportion of sonographers. B-mode sonographic assessment including tempCS may be more useful in this setting, as it eliminates many of the potential methodological pitfalls of CDUS and seems to be less dependent on the operator’s experience (5, 18).

Some limitations of our retrospective study must be mentioned. First, the number of patients included in our study was limited and the number of subjects with a final diagnosis of GCA was somewhat lower (one third) compared to previous US-studies which investigated the cranial and extracranial arteries in suspected GCA (about 50%) (16, 17). Second, the rate of patients who underwent TAB was considerably low in our cohort, particularly in those patients without a final clinical diagnosis other than GCA. Finally, the combined threshold of ≥0.7 mm for the tempCS and of ≥1.2 mm for the axIMT determined in our study needs to be validated in prospective studies before implementation in clinical routine ultrasound protocols can be discussed.

In conclusion, our study results suggest a high diagnostic accuracy of a combined B-mode sonographic strategy of compression sonography of the temporal arteries and measurement of the intima media thickness of the axillary arteries for the diagnosis of GCA. The objective cut-off values established (≥0.7 mm for compression sonography of the temporal arteries and ≥1.2 mm for axIMT) for the diagnosis of GCA warrant investigation in prospective studies.

References
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