Ultrasound for diagnosis and follow-up of chronic axillary vasculitis in patients with long-standing giant cell arteritis

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Abstract

Aims: To assess intima-media thickness (IMT) changes measured by ultrasound in axillary arteries of giant cell arteritis (GCA) patients over time and to calculate an ultrasound cut-off value for the diagnosis of chronic axillary artery involvement in patients with long-standing GCA.

Methods: Ultrasound of both axillary arteries was performed in 109 GCA patients at time of diagnosis and at several follow-up visits and in 40 healthy controls (HCs). IMT determined at the prospective follow-up visit was compared between GCA patients with (axGCA) and without (non-axGCA) vasculitis of axillary arteries at baseline, as well as with HCs. Changes in IMT were depicted. Receiver operating characteristics were performed for cut-off calculations. Inter-/intra-rater agreement was evaluated using stored images and intraclass correlation coefficient (ICC).

Results: Seventy-three patients were in the axGCA and 36 in the non-axGCA group. Pathological IMT of axillary arteries (axGCA) declined in the first 18 months of treatment by −0.5 mm, (range −2.77 to 0.50), independent of age and gender. Median IMT, after median disease duration of 48 months (16–137), was 0.90 mm (0.46–2.20) in axGCA and 0.60 mm (0.42–1.0) in the non-axGCA group pooled with HCs. An IMT of 0.87 mm was highly specific (specificity 96%, sensitivity 61%) for diagnosis of chronic axGCA. Intra-rater and inter-reader agreement of ultrasound images were good [ICC 0.96–1.0 (three readers) and 0.87, respectively].

Conclusion: Pathological IMT of the axillary artery declined under treatment. An IMT of 0.87 mm is highly specific for diagnosis of chronic vasculitis of axillary arteries in long-standing GCA patients.

Keywords: giant cell arteritis, imaging, large vessel vasculitis, outcome measure, Ultrasound

Introduction

Large-vessel vasculitis (LVV) of extra-cranial large arteries, such as the aorta and its major branches, is a manifestation of giant cell arteritis (GCA) occurring in up to 70% of patients.1–5 Patients with predominant LVV often present clinically with polymyalgia and constitutional symptoms and only infrequently with headache, visual symptoms, or jaw claudication.6,7 Evaluating the presence of inflammation in extracranial arteries is of clinical importance not only for diagnostic purposes as suggested by European League Against Rheumatology (EULAR) and British Society for Rheumatology recommendations,8,9 but also for identifying a subset of GCA patients with a worse clinical outcome: studies demonstrated that GCA patients with large vessel involvement require a higher cumulative glucocorticoid (GC) dose and are at an increased risk for relapses and aneurysm development.10 In clinical practice, patients with predominant large-vessel GCA (LVGCA) are often worked-up only weeks or months after GCs have been started. Patients may, for example, initially present with polymyalgia rheumatica, but...
then respond insufficiently to initial GC doses or suffer from frequent relapses, leading to re-evaluation of the initial diagnosis. While ultrasound of axillary arteries is well established to diagnose GCA in the acute phase, and we have a validated cut-off value of 1.0 mm for measurement of the intima-media thickness (IMT) in acute GCA patients, the value of ultrasound in a chronic phase of the disease still needs to be evaluated.11–13 In the present study, we identified an IMT cut-off value of axillary arteries for diagnosis of vasculitis in patients with longstanding GCA treated with GCs. In addition, we evaluated IMT changes over time in patients with LVGCA of the axillary artery (axGCA).

Methods

Patients

This is an observational study with a mixed, retrospective and prospective design. Patients with GCA and GC treatment ≥1 year, who were diagnosed based on clinical, laboratory and ultrasound results between 2006 and 2015, were contacted and invited to participate in this study. Patients who agreed were examined once between November 2016 and May 2017 in a tertiary rheumatology centre (Immanuel Krankenhaus Berlin Buch, Berlin, Germany). The study complied with the Declaration of Helsinki, was approved by the local ethics committee of the Berlin Board of Physicians (Ethik-Kommission der Ärztekammer Berlin – Eth.52/16) and written informed consent was obtained from each patient.

For the present analysis we included only GCA patients with an ultrasound examination of the axillary arteries at the time of diagnosis (baseline) and at one prospective follow-up visit. For the calculation of the diagnostic value of ultrasound we used this final prospective follow-up visit, whereas all visits between baseline and the prospective study visit were utilized to explore the change of IMT over time and for sensitivity analyses, testing the identified cut-offs at different time points (the latter being part of the retrospective phase of the study). Clinical data and information on diagnosis (from 2006 until 2015) were retrieved by chart review, while all clinical and ultrasound data after 2016 were obtained prospectively. The diagnosis of GCA was made clinically by the physician performing baseline (but not necessarily follow-up) ultrasound examinations. No formal criteria were applied to establish the diagnosis, and the decision whether or not to request additional tests (e.g. biopsy) was at the discretion of the treating physician. The cut-off values for IMT of temporal and axillary arteries had not been published yet when the diagnosis of GCA was made; rather, the ultrasound image was interpreted visually during the examination for the presence or absence of the halo-sign.14

The index test for this study was the measurement of IMT by ultrasound of axillary arteries at the prospective study visit. The reference standard was the judgment of the sonographer for the presence or absence of vasculitis of the axillary artery (binary evaluation) at the baseline visit (i.e. at time of diagnosis).

Patients were divided into two groups: the axGCA group, in the case of vasculitis of one or both axillary arteries being found at baseline, and the non-axGCA group, in the case of neither at baseline nor at any follow-up visit was ultrasound considered positive for vasculitis of the axillary arteries. Patients which could not be assigned to either of these two groups, or in the case of missing data, were excluded. Patients with normal axillary arteries at every visit, except for the prospective study visit, where the results were considered “indeterminate” (n = 5), were included in the group of non-axGCA patients for the main analysis, but sensitivity analyses excluding these patients were conducted as outlined below.

Healthy controls with a comparable age and sex distribution in respect to GCA patients and with a single ultrasound examination of the axillary arteries were also included. These individuals were originally recruited for another study.11 The ultrasound examiners were not blinded to clinical data.

Ultrasound examination

Ultrasound of the right and left axillary arteries was performed at the prospective follow-up visit by one of two rheumatologists with 25 years (W.A.S.) or 10 years (V.S.S.) of ultrasound experience, or by the medical student (K.D.S.) under supervision of one of the rheumatologists. All ultrasound examinations were performed according to a previously described protocol.11 Briefly, ultrasound examinations were performed with an
Esaote MyLab Twice eHD or an Esaote MyLab 70 ultrasound machine. IMT measurement of the axillary arteries was performed manually in grey scale (without Doppler) at the level of the middle humeral head. Ultrasound examinations at baseline and at follow-up visits during the retrospective part of the study were performed by four sonographers at the same rheumatology unit over a time span of 9 years (2006–2015).

**Statistical analysis**

Descriptive statistics were used to summarize the data. For continuous data, we present either mean and standard deviation or median and range; categorical data are summarized using absolute and relative frequencies. Comparisons between two independent groups were conducted using the t or Mann–Whitney U test. For comparisons between three independent groups, the Kruskall–Wallis test with post-hoc Mann–Whitney U tests was used, using a Bonferroni–Holm correction for multiple testing. Group differences regarding categorical data were analysed using the $\chi^2$ or Fisher’s exact test. Receiver operating characteristics (ROC) analysis was performed, to determine the optimal IMT cut-off values at the prospective follow-up. We were searching for a cut-off value with maximum sensitivity given a minimum specificity of 95%. As sensitivity analyses, IMT cut-off values were analysed (1) between all GCA patients and healthy controls (HCs) (2) separately for male and female patients, (3) using a different optimality criterion (Youden Index), (4) separately for different time points since GC initiation (for this analysis, IMTs were taken from all available visits) and (5) excluding those five patients with indeterminate results at the prospective follow-up visit. In the case of only one of the two axillary arteries being affected at baseline, the affected artery was used for the axGCA group in the analyses. Cut-offs were calculated for right and left arteries separately as well as for both arteries pooled. To estimate the reproducibility of IMT values, three raters (W.A.S, V.S.S. and K.D.S.) each doubly assessed stored pictures of (left and right) axillary artery walls of 30 selected patients using the graphics program GIMP (Version 2.10). We performed intra- and inter-rater agreement analyses by means of the intraclass correlation coefficient (ICC). The analyses were performed using R version 3.6.1. In particular, the packages “cutpoint”, “me4” and “irr” were used. Whenever appropriate, 95% confidence intervals (CIS) are presented.

**Results**

**Patient selection**

Out of the 360 GCA patients whose diagnosis had been confirmed with ultrasound between 2006 and 2015, 179 agreed to participate in the prospective part of the study. Seventy of them were excluded (1) due to missing data ($n=31$), (2) because they had never received GCs ($n=1$), (3) because they could not be assigned to any of the two groups (axGCA or non-axGCA) as axillary artery ultrasound results were considered unclear at baseline ($n=9$), or (4) because axillary artery ultrasound was negative at baseline but considered positive at any follow-up visit ($n=29$). Finally, 109 GCA patients were included in the main analysis. Supplemental material Figure 1 online depicts the flowchart for patient selection and group allocation.

**Patient characteristics.** Seventy-three (67.0%) patients were diagnosed with vasculitis of at least one axillary artery at baseline; they formed the axGCA group. The non-axGCA group consisted of 36 (33.0%) patients, 31 (86.1%) of which had normal axillary arteries at every ultrasound visit, and five (13.9%) had normal axillary arteries at every ultrasound visit, except for the prospective follow-up, where ultrasound was reported indeterminate (visits with normal axillary arteries: median 2, range 1–3). Furthermore, 40 HCs were included. The axGCA and control group (non-axGCA and HC pooled) were similar according to age, sex and other demographic and clinical parameters at the prospective follow-up visit, as outlined in Table 1.

**IMT at diagnosis and follow-up**

In the axGCA group, 131/146 (89.7%) axillary arteries were considered pathological at baseline, in comparison with none out of the 72 and 80 arteries of the non-axGCA group and HC group, respectively.

IMT at baseline was available for 101/131 (77.1%) axillary arteries from 58/73 (79.5%) axGCA patients. Median baseline IMT in these patients was 1.70 mm (range 1.00–3.60).

For the prospective study visit, IMTs of all patients were available. As outlined in Figure 1, median IMT in the axGCA group (0.90 mm, range 0.46–2.20) was higher than that in non-axGCA patients (0.65 mm, range 0.43–1.0) and HCs (0.59 mm, range 0.42–0.86). IMT was also slightly higher in
### Table 1. Demographic data at the prospective follow-up visit.

| Variable                        | axGCA Value ± SD/Range | axGCA n | Non-axGCA Value ± SD/Range | Non-axGCA n | HCs Value ± SD/Range | HC n | p value<sup>b</sup> |
|---------------------------------|-------------------------|---------|-----------------------------|-------------|----------------------|------|---------------------|
| Age, years                      | 72.8 ± 7.5              | 73      | 76.2 ± 6.7                  | 36          | 72.0 ± 6.7           | 40   | 0.32                |
| Female, n (%)                   | 52 (71.2)               | 73      | 19 (52.8)                   | 36          | 27 (67.5)            | 40   | 0.17                |
| Height, cm                      | 165.9 ± 8.9             | 70      | 166.0 ± 9.4                 | 35          | 164.0 ± 12.4         | 40   | 0.54                |
| Weight, kg                      | 73.6 ± 15.2             | 70      | 70.0 ± 13.9                 | 35          | 75.8 ± 14.1          | 40   | 0.85                |
| Disease duration, months        | 47 (16–137)             | 73      | 50 (16–105)                 | 36          | n.a.                 | n.a. | 0.77                |
| ESR, mm/h                       | 26 (7–35)               | 9       | 20.5 (8–33)                 | 2           | n.a.                 | n.a. | 0.90                |
| CRP mg/dl                       | 7.4 (3–45)              | 13      | 3.45 (3–4)                  | 2           | n.a.                 | n.a. | 0.17                |
| Immunosuppressive treatment, n %|                         |         |                             |             |                      |      |                     |
| Methotrexate                    | 18 (24.7)               | 73      | 5 (13.9)                    | 36          | n.a.                 | n.a. | 0.19                |
| Leflunomide                     | 0 (0.0)                 | 73      | 0 (0.0)                     | 36          | n.a.                 | n.a. | n.a.                |
| Azathioprine                    | 1 (1.4)                 | 73      | 1 (2.8)                     | 36          | n.a.                 | n.a. | 1.00                |
| Cyclophosphamide                | 0 (0.0)                 | 73      | 0 (0.0)                     | 36          | n.a.                 | n.a. | n.a.                |
| Tocilizumab                     | 0 (0.0)                 | 73      | 1 (2.8)                     | 36          | n.a.                 | n.a. | 0.33                |
| Glucocorticoids, n %            | 36 (50.7)               | 71      | 12 (33.3)                   | 36          | n.a.                 | n.a. | 0.08                |
| Prednisolone treatment, mg      | 1 (0–70)                | 71      | 0 (0–10)                    | 36          | n.a.                 | n.a. | 0.15                |
| Diabetes mellitus II, n %       | 17 (23.3)               | 73      | 10 (27.8)                   | 36          | 6 (18.8)             | 32   | 0.97                |
| Arterial hypertension, n %      | 51 (69.9)               | 73      | 28 (77.8)                   | 36          | 20 (62.5)            | 32   | 0.93                |
| Osteoporosis, n %               | 48 (72.7)               | 66      | 20 (66.7)                   | 30          | n.a.                 | n.a. | 0.54                |
| PMR diagnosis, n %              | 57 (78.1)               | 73      | 25 (69.4)                   | 36          | n.a.                 | n.a. | 0.32                |
| Myocardial infarction, n %      | 3 (4.1)                 | 73      | 3 (8.6)                     | 36          | 2 (6.5)              | 31   | 0.682               |
| Stroke, n %                     | 4 (5.6)                 | 72      | 0 (0.0)                     | 36          | 1 (3.2)              | 31   | 0.71                |
| Other rheumatic diseases, n %   |                         |         |                             |             |                      |      |                     |
| Rheumatoid arthritis            | 7 (9.9)                 | 73      | 4 (11.1)                    | 36          | n.a.                 | n.a. | 1.00                |
| Psoriatic arthritis             | 1 (1.4)                 | 73      | 1 (2.8)                     | 36          | n.a.                 | n.a. | 1.00                |
| Pathologies at diagnosis, n %   |                         |         |                             |             |                      |      |                     |
| PMR                             | 55 (75.3)               | 73      | 22 (69.4)                   | 36          | n.a.                 | n.a. | 0.13                |
| Eye involvement                 | 13 (17.8)               | 73      | 7 (19.4)                    | 36          | n.a.                 | n.a. | 0.84                |
| Headache                        | 36 (49.3)               | 72      | 24 (66.7)                   | 36          | n.a.                 | n.a. | 0.10                |
| Jaw pain                        | 32 (43.8)               | 73      | 17 (47.2)                   | 36          | n.a.                 | n.a. | 0.74                |
| Palpable temporal artery        | 22 (30.1)               | 72      | 16 (44.4)                   | 36          | n.a.                 | n.a. | 0.15                |

(Continued)
the non-axGCA group as compared with HCs (for details see Supplemental Table 1).

**IMT change over time**

Next, we evaluated whether IMT changed over time by comparing IMT from baseline with those obtained at different follow-up visits (from both retrospective and prospective study visits). For all time points, 326 and 43 IMT measurements were available for all 73 axGCA and all 36 non-axGCA patients respectively. IMTs of axGCA patients were generally higher than those of patients in the non-axGCA group and decreased under treatment (see Figure 2). The largest median IMT reduction in axGCA patients was seen within the first 18 months after start of GC with −0.50 mm (range −2.77 to 0.50) with an ongoing slight decline in the subsequent months (see Supplemental Table 2).

**Cut-off value for IMT in longstanding GCA of the axillary artery**

Table 2 summarizes the results of the IMT measurements at the prospective study visit and the resulting cut-off values to differentiate between patients with and without chronic axillary vasculitis. The control group consisted of non-axGCA patients and HCs. IMTs for non-axGCA and HCs separately are depicted in Supplemental Table 1. Supplemental Figure 2 displays the ROC curve with cut-off values for the diagnosis of axGCA and their respective sensitivity and specificity. The optimal cut-off value for an optimality criterion of at least 95% specificity is 0.88 mm for the left, 0.87 mm for the right axillary artery, and 0.87 mm when pooling right and left arteries (Table 2).
When comparing IMT values between all GCA patients (axGCA + non-axGCA) and HCs the optimal cut-off value was slightly smaller with 0.79 mm and less sensitive (sensitivity: 52%, specificity: 96%, area under the curve: 81%).

Sensitivity analysis without the five patients with indeterminate ultrasound diagnosis at the prospective follow-up visit led to comparable results. Separate analyses for men and women, or considering IMT measurements from all follow-up visits and categorizing them according to disease duration (first 5 years), all revealed similar cut-off values, as detailed in Supplemental Table 3.

Agreement of IMT measurements
Excellent inter- and intra-rater agreement was observed. The ICC for intra-rater agreement for the two ratings per sonographer was 0.98 (95% CI 0.97–0.99), 1.00 (1.00–1.00) and 0.96 (0.93–0.98) for K.-D.S., V.S.S. and W.A.S., respectively. The overall ICC for inter-rater agreement of all three investigators was 0.87 (CI: 0.81–0.91) at the first and 0.89 (0.83–0.93) at the second rating.

Discussion
Our study demonstrated that IMT of axillary arteries decreased in axGCA patients with GC therapy, while values were consistently higher in the axGCA as compared with the non-axGCA
group. Accordingly, IMT of axillary arteries remained abnormal as compared with controls in the majority of axGCA patients (61%) even years after GC therapy. An IMT of $\geq 0.87$ mm was selected as a highly specific cut-off value for the diagnosis of chronic vasculitis of axillary arteries in GCA patients after GC therapy.

Our finding that axillary arteries remained enlarged in 61% of axGCA patients with longstanding treatment is similar to a previously published study using computed tomography angiography, where thickening of the wall of axillary arteries persisted in two-thirds of LVGCA patients despite 1 year of GC treatment. Our data further suggest that decline of IMT is most prominent in the first 12–18 months of follow-up and remains relatively stable thereafter. The reason for persistent vessel wall thickening in axillary and other large arteries as compared with temporal arteries, where IMT seems to normalize much more frequently, remains unclear but might in part be related to an insufficient resolution of so-far available ultrasound probes to detect persisting small thickening of temporal arteries. Inflammation might certainly persist despite GC therapy in a proportion of patients; however, the initial reduction and subsequent stabilization of IMT favours a hypothesis that acute inflammation is followed by myo-intimal proliferation and remodelling of the arterial wall that persists for years or is even life-long. Repeated biopsies, as have been performed in temporal arteries (and where ongoing inflammation in one and remodelling in another subset have been found), would be desirable to answer this question, but are unfortunately of course not possible.

The clinical implications of our findings are the following: (1) use of ultrasound to diagnose GCA in the context of chronic vasculitis, and (2) to distinguish GCA patients with and without involvement of the axillary artery which is of prognostic relevance, as patients with extracranial GCA, for example, were found to suffer more frequently a relapse and require higher cumulative GC doses.

GCA and polymyalgia rheumatica patients with refractory or relapsing symptoms, as well as those with severe constitutional manifestations, are those in whom large vessel involvement is frequently detected. As many of these patients are on chronic GC already when they undergo vascular screening, the cut-offs and definitions used to diagnose acute large-vessel GCA are not applicable to this group any more. Our results will also inform an OMERACT ultrasound subgroup developing a definition and score for chronic vasculitis of large arteries that could be used as a monitoring tool in future studies.

Although 179 patients participated in the prospective part of this study, several of them were excluded due to unclear classification into axGCA or non-axGCA throughout the retrospective and prospective part of the study period. In 29 cases, who were excluded from our analysis, IMTs of axillary arteries were considered normal at baseline, but pathological at one or more follow-up visits. Five patients (who were included in the final analysis) with normal IMT at baseline and multiple follow-up visits, had indeterminate results at the prospective follow-up visit. This indicates the challenge to distinguish between enlarged and non-enlarged vessel walls in the absence of a cut-off value. The next steps will be the validation of this novel cut-off, ideally using an external reference standard and external cohort, the inclusion of the cut-off into an ultrasound composite score for chronic large-vessel vasculitis and to test the sensitivity to change of ultrasound findings of chronic vasculitis at axillary arteries by means of a prospective interventional study.

The major strength of this study is the longitudinal design of data collection and the long period of follow-up, since baseline visits reach back to 2006. Major limitations are the moderate cohort size, the partially retrospective design and the fact that we obtained IMT only from axillary arteries and not also from other large arteries.

The limitation of the 1990 ACR criteria, giving high weight to cranial symptoms and biopsy result (although the 2018 EULAR recommendations suggest to use imaging as the first diagnostic test in GCA instead of biopsy), was recently recognized and supplemented of the 1990 ACR criteria by non-cranial symptoms and imaging has been suggested. Using these revised criteria resulted in classification of 100% of cases as GCA. We recognize that the same technique has been used as index test and reference standard, provoking some concerns of circular reasoning. At
time of diagnosis when the reference standard was established, however, the current analysis was not yet planned and it can therefore be considered independent, as investigators performing ultrasound at the prospective follow-up visit (index test) were not aware of ultrasound results at the time of diagnosis (reference standard).

Ultrasound results at the time of diagnosis were extracted from the patient notes (including IMT values). Images at this time were unfortunately not available for reassessment, due to a change of the ultrasound machines. While the axillary artery is by far the most commonly affected extracranial vessel in GCA, with a prevalence of 94–98% among patients with LVGCA,\(^5,24\) isolated inflammation of the aorta, or the carotid- and subclavian arteries, cannot be excluded in our non-axGCA group. Positron emission tomography studies indicate that carotid and subclavian arteries are commonly involved despite a negative ultrasound result, which might be explained by the difficulties to distinguish vasculitis from soft plaques at carotids and the limited penetration of the ultrasound beam in the body and the deep course of subclavian arteries.\(^25\) For the purpose of developing a cut-off for GCA patients with and without chronic involvement of axillary arteries, however, this issue is probably less relevant. This is also supported by the observation that IMTs of non-axGCA patients and HCs were very similar.

Cardiovascular risk factors were not routinely collected in our patients. Lipids, smoking and other factors might have had an impact on IMT thickness; however, the number of patients with available data in our cohort was too low to get a reliable result. Cardiovascular risk factors are being collected in our prospective validation study which is currently underway.

Another limitation is the retrospective analysis of images that have been acquired up to 14 years before the start of the study. Whether the reliability of these images would be comparable to those retrieved with modern ultrasound devices is unknown and needs to be addressed by a future study.

We performed intra- and inter-rater agreement measurements only using saved pictures and not in a live patient-exercise. Therefore, our results reflect reading and not image acquisition agreement. The high reproducibility among highly and less experienced investigators is nevertheless encouraging and indicates that sufficient expertise to evaluate chronic vasculitis at axillary arteries can be learnt relatively quickly.

Last, we used the subjective decision of a sonographer at baseline whether or not an axillary artery was enlarged as reference standard, rather than the published cut-off of \(\geq 1 \text{ mm}\) for acute vasculitis, because IMTs were only available in a fraction of (particularly non-axGCA) patients at baseline. On the other hand, if we had used baseline IMT as reference standard, this would have increased the concern of circular reasoning.

In summary, we report that an IMT of 0.87 mm is highly specific and sensitive for the diagnosis of chronic vasculitis of axillary arteries in patients with longstanding GCA after GC treatment. A prospective study validating this new cut-off value, using different imaging techniques, is currently underway.

**Availability of data**
All relevant data are available from within the manuscript and the Supplemental material.

**Conflict of interest statement**
C.D. reports personal fees and other from Roche/AbbVie, personal fees from Sanofi/Lilly/Pfizer/Novartis outside the submitted work; W.A.S reports speaker fees from Bristol-Myers-Squibb/Chugai/Medact, speaker fees and advisory board member at Celgene/Roche, speaker fees, advisory board member and PI at Novartis/Sanofi, outside the submitted work; V.S.S. reports personal fees from Roche/Sanofi/AbbVie/Lilly/Pfizer/Novartis/Hexal outside the submitted work; the other authors have declared no conflict of interest.

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**Supplemental material**
Supplemental material for this article is available online.
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