

The role of ultrasound in the diagnosis and follow-up of large-vessel vasculitis: an update

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Received on March 14, 2017; accepted in revised form on March 17, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S194-S198.

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Key words: ultrasonography, giant cell arteritis, Takayasu's arteritis

ABSTRACT

Large-vessel vasculitides comprise giant cell arteritis and Takayasu's arteritis. In both conditions, early changes consist of transmural inflammation of the arterial wall, while later complications include lumen changes, such as stenoses or aneurysms. Colour Doppler sonography has the ability to depict the arterial wall as well as the lumen, and is therefore ideally suited both to diagnose early vasculitis and to monitor patients over time. In this review article, we addressed the following issues: 1) the role of colour Doppler sonography in the diagnosis of large-vessel vasculitis and its common pitfalls; 2) whether colour Doppler sonography can increase the yield of temporal artery biopsy in giant cell arteritis; 3) the role of colour Doppler sonography in monitoring patients with LVV over time; and 4) how colour Doppler sonography performs compared to other imaging techniques.

Introduction

The term 'large-vessel vasculitis' (LVV) encompasses the vasculitides that predominantly affect the aorta and its major branches, *i.e.* giant cell arteritis (GCA) and Takayasu's arteritis (TAK) (1, 2).

Since the pioneering papers in the 90's (3-6), vascular ultrasound has gained a central role in the diagnosis and the follow-up of patients with LVV. Currently, high-end ultrasound equipment is widely available. The advantages of ultrasonography are its ability to reveal vessel wall and lumen changes, its non-invasiveness, and the capability to examine several vessels in a single session. Moreover, follow-up scans can be obtained to monitor patients over time. In this review article, we addressed the following issues: 1) the role of ultra-

sonography in the diagnosis of LVV and its common pitfalls; 2) whether ultrasonography can increase the yield of temporal artery biopsy (TAB) in GCA; 3) the role of ultrasonography in monitoring patients with LVV over time; and 4) how ultrasonography performs compared to other imaging techniques.

Technical details

The equipment required for the study of LVV depends on the type of vessels we aim to study. High-frequency linear probes (18–22 MHz) are preferable for the thorough assessment of the superficial arteries, such as the temporal arteries (TAs), intermediate-frequency linear probes (10–15 MHz) for the study of the epiaortic vessels, and low-frequency convex probes (2–8 MHz) for the assessment of the aorta. The probe frequency is the main factor that influences the quality of images (axial and lateral resolution) and the penetration of the tissues by the beam. The basic principle is that the higher the frequency, the higher the resolution and the lower the tissue penetration.

The grey-scale study assesses the arterial wall. Changes associated with LVV are thickening/transmural oedema. The grey-scale assessment should be complemented by the assessment of flow by colour Doppler to detect lumen changes such as stenoses or aneurysms. Images of flow are essentially obtained from measurements of movement. In scanners, a series of pulses is transmitted to detect movement of blood. Echoes from stationary tissue are the same from pulse to pulse. Echoes from moving scatterers exhibit slight differences in the time by which the signal is returned to the receiver. These differences can be measured as a direct time difference or, more often, in terms of a phase shift

Competing interests: none declared.

from which the ‘Doppler frequency’ is obtained. Doppler signals are then processed to produce a colour flow display superimposed onto a B-mode image. Colour Doppler sonography (CDS) is therefore the ultrasonographic modality of choice to assess LVV.

Role of ultrasonography in the diagnosis of large-vessel vasculitis

In LVV, the inflammatory infiltrate of the vessel wall results in the loss of the normal echostructure of the intima-media complex. The major signs detectable with CDS are the thickening of the arterial wall with disappearance of the trilaminar structure of the intima-media complex, the presence of a perivascular halo, and the presence of stenoses or vascular dilatations (7). Characteristic features for TAs and large vessels, in the presence of arteritis, are presented below.

Temporal arteries

- Halo sign: hypoechoic shadow, typically homogeneous and concentric, visible both in longitudinal and transverse planes, due to oedema of the arterial wall (6, 8).
- Compression test: apply a slight pressure via the transducer until the artery lumen is occluded and no arterial pulsation is detectable. If a thickened vessel wall remains visible, the sign is positive, suggesting the presence of vasculitis (9). The interobserver agreement of the compression test is excellent (10).
- Stenosis: it is characterised by aliasing and an accelerated rate of colour Doppler flow through the area of stenosis (≥ 2 times higher than the flow velocity proximal or distal to the stenosis) (8). It may also be seen in other conditions, particularly arteriosclerosis (7).
- Occlusion: lack of colour Doppler flow through an artery filled with hypoechoic material (8).

Large arteries

- Halo sign: in subclavian and axillary arteries a circumferential wall swelling ≥ 1.5 mm is considered pathognomonic for vasculitis (11). In TAK, the wall thickening is less hypoechoic (mid-echoic) than in GCA and has been described as the “macaroni sign” in the common carotid arteries (4).

- Stenoses and occlusions: frequent, especially in TAK.

- Aneurysm: aneurysms have been described in up to 20% of the patients with LVV. However, sonographic examination is often unhelpful since the typical involvement of the ascending aorta and the aortic arch cannot be adequately visualised by CDS (12).

Published data have shown that CDS is a valuable screening tool for patients with suspected LVV. In patients with GCA, the halo sign in the TAs has a sensitivity of 75% and a specificity of 83% for biopsy-proven GCA (13); the specificity approaches nearly 100% when the halo sign is bilateral (14, 15). On a note of caution, the sensitivity of the halo sign in the TAs appears to be satisfactory (83%) only in patients who have a classical transmural inflammatory infiltrate, while it drops to 20% in those who have adventitial or periarterial small-vessel inflammation (16). Therefore, if CDS of the TAs is negative but there is a strong clinical suspicion of GCA, TAB should be performed to confirm the diagnosis.

In large-vessel GCA (LV-GCA) and TAK, CDS of the epiaortic arteries is also useful as a first-line screening test. In particular, the sensitivity of CDS of the epiaortic arteries for the diagnosis of TAK has been estimated to be as high as 95%, at least in Caucasian patients (17), while in LV GCA its sensitivity is about 85% (the main limitation of CDS in this setting is that it cannot identify patients with isolated aortitis, who are approximately 15% of patients with LV GCA) (18) (additional data on the frequency of isolated aortitis provided by the Authors).

Common pitfalls of ultrasound in the diagnosis of LVV

Incorrect probe frequency

It is essential to choose the correct probe for each anatomical structure. In particular, the use of an excessively low frequency probe will not allow an accurate morphological evaluation of the vessel, decreasing the sensitivity of the exam.

Halo sign, present or absent?

The “halo sign” is considered the most important ultrasound finding to diag-

nose LVV (8). False-positives are often related to incorrect setting of the machine, in gray-scale, in colour Doppler mode, or both. During grey-scale evaluation, the B-gain control should carefully be adjusted to modulate the overall amplification of the returning reflections displayed on the ultrasound image. If the B-gain is set too low, false-positives can occur due to a darker image. Conversely, too high B-gain poses the risk of false-negative results.

By colour Doppler evaluation, the choice of an incorrect pulse repetition frequency (PRF) can lead to misinterpretation of the halo sign. In particular, the use of frequencies higher than those needed can lead to the visualisation of the flow only in the inner part of the vessel (where the blood velocity is greater) thus creating a false halo, known as “pseudo-halo”. On the other hand, lower frequencies can obscure a halo sign due to perivascular overflow. The same is true if the colour-gain is set too low (potential “pseudo-halo”) or too high (perivascular overflow).

A false halo sign can also be related to an incorrect Doppler angle, causing a poor visualisation of the blood flow. Since colour Doppler is angle-dependent, the angle formed between the interrogating sound beams and the blood flow should be optimised, manually (tilting the transducer) or by electronic steering.

Potential role of ultrasonography in guiding a temporal artery biopsy

The classical picture of TAB in GCA is of transmural inflammation, although in some patients inflammatory changes may be more restricted (19). Oedema (“halo sign”) of the TA wall on CDS is thought to represent inflammation. Therefore, the question arises as to whether a TAB performed at the site of CDS oedema may more frequently yield a positive result. This point has been debated in the literature. In a prospective study of 55 patients with suspected GCA, 18 of 22 patients with biopsy-proven GCA had a positive halo sign (20). TAB performed at the site of the halo sign confirmed the diagnosis in all 18 patients. However, this study was not designed to compare CDS-guided TAB with standard TAB, and

only 20 of the 49 biopsies were CDS guided.

In a prospective randomised study we compared CDS-guided TAB with standard TAB in a cohort of 112 unselected patients with suspected GCA. One hundred and five patients were included in the final analysis, 50 patients in the CDS-guided group and 55 in the group in whom TAB was not directed by CDS. The study revealed that CDS-guided TAB did not increase the sensitivity for GCA diagnosis over that provided by a careful physical examination, suggesting that the halo sign on CDS and TA physical abnormalities are strictly related. Essentially, in the presence of the halo sign on CDS the probability of a positive TAB is high regardless of an ultrasound-guided procedure or not (21). On the other hand, TA CDS may be helpful for marking the segment to be biopsied in cases with small or deeply localised TAs. In our study, the surgeons more frequently failed to harvest an artery in the standard TAB group than in the CDS-guided group (21).

There are no standardised methods for CDS guided TAB. Our protocol includes the common ultrasonographic setting for the study of the TAs (22). The ultrasonographer marks with a dermographic pen the skin overlying the TA segment with the largest halo. In the absence of a halo sign on CDS, a TA branch is marked in the site of symptoms, thickening, stenosis or occlusion. The ophthalmologist subsequently performs the TAB in the segment marked by the ultrasonographer (21).

The role of ultrasound in monitoring patients with LVV

The role of CDS in measuring disease activity in GCA is still uncertain. There are reports documenting resolution of the halo sign in the TAs only two days after starting glucocorticoids (23) or alternatively, a persistence of halo for more than 6 months after treatment initiation (24). Studies of large-vessel GCA tend to show a longer persistence of the halo sign compared to studies focused on the temporal arteries, perhaps reflecting the larger oedematous mass of the larger arteries (11, 25). De

Miguel reported that patients with halo disappearance had normal or lower values of inflammatory markers when compared to patients with halo persistence. In addition, a higher number of TAs branches affected before treatment initiation was related to greater values of inflammatory markers and to a slower resolution of the halo sign, allowing correlation between CDS changes and laboratory response (26). In the TABUL (Temporal Artery Biopsy versus Ultrasound in diagnosis of GCA) study (27), a cross-sectional analysis was performed on patients with a clinical diagnosis of GCA and a presence of halo in at least one TA branch (n=131) (28). The halo size was found to be consistently smaller over the seven days of glucocorticoid treatment in which the ultrasound was performed, supporting its use as a potential monitoring tool to assess therapy response. Moreover, the presence of visual symptoms and physical examination abnormalities of the TAs correlated significantly with the presence of halo in the homolateral ultrasound, supporting its use as a potential prognostic marker for ischaemic features. Clinical differences between extra-cranial GCA (*i.e.* involvement of the carotid and/or proximal arm arteries) and cranial GCA, assessed by CDS, have also been reported, with cranial involvement being associated with older age, presence of jaw claudication and permanent vision loss (29). Contrary to the TAs, the presence of halo in the axillary and/or subclavian arteries usually persists for a much longer time, although with an increase in echogenicity; however, this does not seem to be related to severe ischaemic complications during the disease course (30).

In TAK, serial measurements of the common-carotid intima-medial thickness (IMT) have been proposed to assess response to treatment. Sun and colleagues performed a follow-up study on six patients with established lesions and found progressive concentric thickening of the artery wall, rather than longitudinal progression, in two patients, despite treatment with glucocorticoids and aspirin (31). A small case series documented an ultrasonographic improvement of two patients with ac-

tive TAK under glucocorticoid therapy, with a decrease in the common-carotid IMT from 1.4 to 0.5 mm, after 2 months, and from 1.5 to 0.9 mm, after 9 months (32). Park and colleagues compared the characteristics of the common-carotid lesions with clinical, laboratory and computerised tomography-angiography (CTA) findings of 10 patients with TAK. Active lesions were found to have a mean IMT of 3.3 ± 0.8 mm and inactive lesions of 1.6 ± 0.4 mm (33). Besides this reduction in thickness, increase of wall echogenicity has also been associated with decreased inflammation in TAK (34, 35). Common-carotid IMT was compared to the National Institutes of Health (NIH) criteria of activity in TAK; a cut-off of 0.8 mm showed a sensitivity of 82% and specificity of 60–70% to identify active disease (36). A recent ultrasound score (Kolkata-scoring system), evaluating the IMT, occurrence of stenosis/aneurysms and flow patterns of 19 different vascular regions presented significant correlation with the Indian Takayasu's Activity Score (ITAS); however, further studies are still needed for its validation and widespread use (37).

Contrast-enhanced ultrasonography (CEUS) is increasingly being used for assessing disease activity in LVV (38–42). The detection of contrast within the arterial wall is indicative of neovascularisation, a potential indirect marker of vascular inflammation, but further studies are warranted to define its precise role as a monitoring tool.

Comparison of ultrasonography with other imaging techniques

Direct comparative studies of CDS with other imaging tools are scant. Czihal *et al.* (43) reported a good correspondence (83%) between CDS and ^{18}F -Fluorodeoxyglucose positron emission tomography (PET) in detecting proximal arm involvement in a case-series of LV-GCA. Similar results were confirmed by another study conducted on 24 patients with LVV (44). Reports support the ability of CDS to detect carotid involvement confirmed by PET (45, 46); nevertheless, the latter seemed superior to US in detecting vertebral arteries inflammation in LV-GCA (47). A

study demonstrated a very good correlation between CEUS of carotid arteries and PET findings in patients with LVV (48). However, occasional discrepancies were observed between CEUS and PET findings, which may suggest that, at least in some cases, contrast uptake of the arterial wall in ultrasonography may be due to reparative neoangiogenesis, rather than hypervascularity related to active inflammation (48).

Historically, PET has been considered superior to morphological imaging techniques in detecting LV involvement, but unable to capture changes in the TAs due to lower spatial resolution, and the physiological high uptake of the brain (7). A new finding that warrants further investigation and comparison with CDS is the report of a role for PET co-registered with CT (PET/CT), applying specific brain settings, to visualise inflammation of the TAs and its branches (49).

CDS diagnostic power is equal to that of high-resolution magnetic resonance (MRI) of TAs, detected as a bright mural enhancement, with a sensitivity of 67% and 69%, respectively, and specificity of 91% for both imaging techniques (50). On the other hand, a role for lower field strength MRI (1T MRI) has been excluded due to its low sensitivity compared to CDS and physical examination (51). Overall, despite having the advantage of providing a wide overview on several vascular regions, MRI has a 10-fold lower resolution on arterial wall compared to CDS and requires higher compliance and the use of contrast agents.

Similarly, CT can provide information on both vessel lumen and wall enhancement; however, compared to CDS, it provides a lower resolution (1 mm) and decreasing reliability on distal branches. Spatial resolution and detection of calcifications is greater than on MRI, but there is exposure to radiations and iodine contrast.

CDS is superior to conventional angiography (52) which is not informative on early vessel wall changes and now only confined to interventional treatment. CTA and MR angiography (MRA) effectively depict stenosis, occlusion and dilatation, and are superior to CDS in

terms of comprehensive evaluation of vascular damage (53).

Glucocorticoid treatment invariably affects all imaging modalities, with comparable very early reduction of sensitivity for CDS and MRI (54), and the well recognised decrease of PET positive findings under the course of treatment (55).

While CDS, MRA and CTA have a role in monitoring structural damage, the exact role of CDS and the other above-mentioned imaging modalities in assessing disease activity during follow up is still under investigation. Some discordant results between imaging, laboratory inflammatory markers, and clinical parameters still highlight the lack of a single reliable tool in the follow up of patients with LVV (53, 56, 57).

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