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Orbital Ultrasonography for Measuring Meaningful Orbital Inflammatory Responses

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Abstract

Ultrasound being a portable imaging device that is capable of making fast regional estimates of body composition, is an attractive assessment tool in instances when other methods are limited (risks of contrast in MRI and or radiation in CT scan). Furthermore, much of the research suggests that it is reliable, reproducible, not only an accurate means of diagnosing Thyroid Associated Orbitopathy (TAO) pathology and predicting its clinical course, but as a way to follow the course of the disease and the response to treatment as well.

The available imaging modalities in the evaluation and management of TAO are varied, each one having advantages, disadvantages, and particular utilities. Orbital US is a widely used technique that may quantify extraocular muscle enlargement and inflammation (topographic, quantitative and kinetic echography), with the added benefits of ease, low cost, high accessibility, short exam time, and lack of radiation. The disadvantages of orbital US include poor visualization of the posterior orbit, inaccuracy in measurements, and investigator dependence.

The purpose of this review is to explain the technical principles of the ultrasound method, explain the procedures for taking a measurement and interpreting the results, evaluate the reliability and validity of this method for measuring meaningful orbital inflammatory responses, highlight the advantages and limitations of ultrasound in orbital inflammatory disorders.

Introduction

The fundamental principle of ultrasound imaging is reflection of ultrasound waves from tissue in the path of the beam. Piezoelectric crystals in the transducer of the scan head produce pulses of ultrasound with frequencies >2 MHz used for ultrasonic imaging. The ultrasound beam is transmitted through the skin. When the beam comes in contact with a tissue interface (e.g., skin-subcutaneous fat, fat-muscle, and muscle-bone), it is partially reflected back to the transducer as an echo signal. Thus, the transducer has a dual function of transmitting the ultrasound and receiving it. The echoes are converted into signals for processing by the transducer. The strength of each reflected wave is represented by a dot, and the position of the dot represents the depth from which the echo was received. The dots are combined to form an image [1].

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The amount of sound reflected is dependent on the changes in acoustic impedance between two tissue interfaces. Acoustic impedance is the product of tissue density and acoustic velocity [2]. Air has almost no impedance, while fat and muscle have impedances of 0.138 $g \cdot cm^{-1} \cdot s^{-1}$ and 0.170 $g \cdot cm^{-1} \cdot s^{-1}$, respectively, and bone has a relatively high impedance of 0.78 $g \cdot cm^{-1} \cdot s^{-1}$. Homogenous zones with relatively uniform acoustic impedance are free of echoes. Because the acoustic impedances of fat and muscle are similar, there is a weaker echo for the fat-muscle interface than for the muscle-bone interface. For example, the software for a relatively new portable ultrasound that converts ultrasound images to body fat percentages (Body View software, Intel Metrix, Inc., Livermore, CA) assumes an acoustic reflection coefficient of 0.012 for the fat-muscle interface, but 0.22 for the muscle-bone interface [3].

The relative strength, or amplitude, of echoes is represented by the brightness of the image on the computer screen. Strong reflections appear white; weaker reflections appear grey, and no echoes are black. This produces a two-dimensional grey-scale image with white borders for the skin-subcutaneous fat and muscle-bone interfaces and a visible, but less distinct, border for the fat-muscle interface.

Assessment of orbital inflammation using the combination of volumetric analysis and density of orbital soft tissues could potentially improve our ability to diagnose active TAO. The purpose of this study was to examine the usefulness of both volume and density measurements of orbital soft tissues to assess the inflammatory activity of TAO, using Clinical Activity Score (CAS) as the basis for clinical classification of TAO patients.

Thus, the purpose of this review of ultrasound technology is to explain the technical principles of the method and measurement procedures, evaluate the reliability and validity in orbit and oculoplasty specialty, address advantages and limitations.

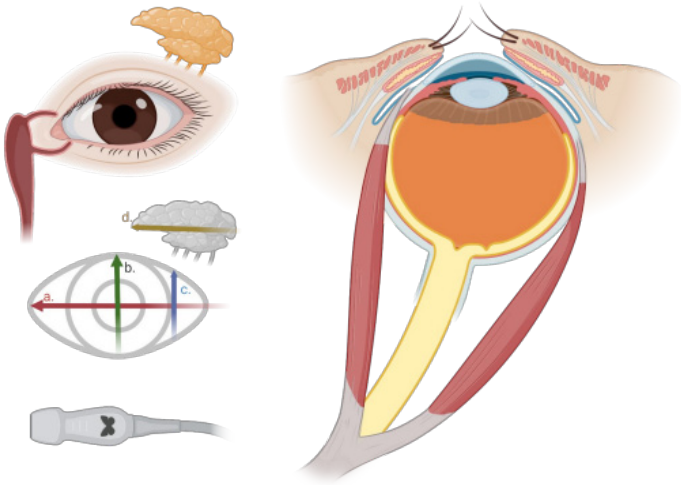
Methodology

The procedure for ultrasound scanning is simple. Gel is placed on the head of the transducer and/or the skin at the site to be measured. This creates a close bond between the transducer and skin reducing artifact and making it easier to move the transducer over the skin. With the ultrasound on, the transducer is slid across the measurement site without loss of contact with the skin. A scan takes only a few seconds. Once scanned, the image on the monitor can be saved for analysis.

Tissue thickness measurement is accomplished with electronic calipers. Identification and placement of the two caliper points defining the boundaries of the tissue to be measured requires practice to improve the objectivity of the measurement [4].

A basic orbital US screens the orbital fat, evaluates and measures the extraocular muscles, and assesses the optic nerves [5]. Targeted exams include topographic echography in which a mass may be isolated on the B-scan and then its dimensions were measured using the A-scan, 30° off sagittal plane tests to evaluate the subarachnoid optic nerve fluid versus inflammation, quantitative evaluation in which the A-scan uses sonar reflectivity to evaluate a lesion's tissue properties, and kinetic echography during which the physical pressure of the probe is used to characterize the compressibility of a lesion in question [5,7]. As a result, the trans ocular and orbital use of A-scan, B-scan, and Doppler US has persevered as a fast, inexpensive, and valuable tool in the evaluation of TAO [8,9]. Tissue changes in TAO is irregular and high internal reflectivity in contrast to a low reflectivity in the rare disorder of acute inflammatory orbital myositis. However, the muscle reflectivity has never been related to the stage of the disease, and we postulated that a high reflectivity might be typical for inactive disease caused by the acoustic interfaces produced by fibrosis within the muscle, whereas lymphocytic infiltration and oedema would result in low reflectivity (i.e., low echogenicity, as in acute orbital myositis). The orbital fat volume can be measured on fat images.

Orbital ultrasonography instructional diagram *(Created with BioRender.com)*



Standard operating procedure for orbital ultrasonography:

1) Obtain approved consent and authorization form.
2) Clean and prepare the site of interest and ultrasound probe.
3) Apply sterile coupling agents on ultrasound probe headpiece.
4) Connect the probe to mobile device and launch the app.
5) Select the appropriate preset to start scanning.

a. Horizontal linear scan (medial orientation) - adjust depth and ΔTGC

b. Vertical linear scan (superior orientation) - adjust depth and ΔTGC

c. Lateral vertical oblique scan (Ossoinig technique + doppler) - optic nerve assessment

d. Horizontal linear (Lacrimal gland) scan - volumetric and ΔTGC

6) 3D scan/Cine recording of orbit.

Discussion

Thyroid Associated Orbitopathy (TAO), also referred to as Graves' ophthalmopathy, Graves' orbitopathy, and thyroid eye disease, is a constellation of signs and symptoms resulting from chronic autoimmune-related orbital inflammation.

This disorder is characterized by inflammation, congestion, hypertrophy, and fibrosis of the extra-ocular muscles Because patients with TAO must be followed and treated on the basis of disease activity, several different classification systems based on the clinical assessment have been developed. The evaluation of Graves' orbitopathy activity is important for predicting medical treatment results because treatment is more effective in the ac-

tive phase. Different scores have been developed to detect activity of the disease, such as the Clinical Activity Score (CAS), the European Group on Graves' Orbitopathy (EUGOGO) classifications and the vision, inflammation, strabismus, and appearance (VISA) classification. The CAS is based on four classical signs of inflammation (pain, redness, swelling, and impaired function), and consists of 10 equally weighted items. The total CAS may range from 0–10. The higher the CAS, the greater the response to immunosuppression. The CAS in Graves' orbitopathy is correlated with immunosuppressant treatment response and laboratory tests such as thyroid-stimulating hormone.

Studies investigating US in TAO demonstrated that extraocular muscle thickness, as measured via A- and B-scans, increases with increasing disease severity [9]. There is also a high degree of correlation between the right and left eyes, the symmetry of which is valuable in distinguishing TAO from other similar but often unilateral diagnostic entities, such as idiopathic orbital inflammatory syndrome and lymphoma [8,9]. Extraocular muscle thickness demonstrated on US has been shown to correlate with the degree of proptosis as well [10]. In fact, Werner et al. demonstrated that extraocular muscle enlargement is detected by US with more sensitivity than by clinical exam [8]. Additionally, other sonographic studies of TAO contributed that a significant association between proptosis and the volume of extraocular muscle and orbital fat exists [11].

The clinical phase of TAO and disease course may be evaluated and followed by echography as well. A-scan measurements have shown significantly lower extraocular muscle reflectivity in patients that respond to TAO therapy, indicating that tissue reflectivity is a marker of edema, inflammation, and disease activity [12]. Studies supportive of US cite this as an advantage over CT, which provides an excellent anatomic perspective but cannot evaluate disease activity [13].

Prummel et al. followed reflectivity in the extraocular muscles with the lowest echogenicity and found that, after a cut-off value (40%) was assigned, reflectivity under this value had a Positive Predictive Value (PPV) for response to TAO treatment of 73%. The Negative Predictive Value (NPV) of tissue reflectivity over 40% was 100% [12]. Contrastingly, a more recent publication by Prummel et al. shows significantly lower predictive values [14]. However, even though extraocular muscle reflectivity may not correlate with CAS, when a CAS over 4/10 is combined with US reflectivity the PPV and NPV for response to treatment are 74% and 72% respectively, which rise to 79% and 89% when the duration of eye symptoms is added to these clinical parameters [15]. Given-Wilson et al. reported that the medial rectus muscle width itself correlated with clinical score, as well as with CT measurements for the same muscle [16]. Similarly, several studies support orbital US as not only an accurate means of diagnosing TAO pathology and predicting its clinical course, but as a way to follow the course of the disease and the response to treatment as well [17,18].

The addition of color Doppler imaging to US in TAO also aids its diagnosis, as blood flow measurements in the ophthalmic artery, central retinal artery, and central retinal vein have all been correlated with extraocular muscle diameter and TAO [19]. Further, these blood flow parameters measured sonographically correlate with CAS levels, and may contribute to the distinction of active versus inactive disease [20]. Reversal and reduction of blood flow through the superior ophthalmic vein may independently be a sign of severe orbitopathy and progression to optic neuropathy [21,22].

Limitations

Ultrasound use in the diagnosis, prognosis, and monitoring of TAO is not without its shortcomings. The orbital apex may be poorly visualized [9]. US alone may be inadequately diagnostic, and may not differentiate TAO from other causes of large muscles [8]. Additionally, although many of the above references showed positive and encouraging results using US in TAO, they have also reported a wide range of average muscle widths and volumes with little consistency in different study [9,10,12,17]. In several studies looking at US in TAO the superior rectus is the largest muscle group [10,12]; Shammas et al. Explain that the superior rectus and superior oblique tendons may be measured as one on US, further confusing orbital measurements [23]. Moreover, the user-dependent nature of sonographic imaging may be detrimental to study consistency and reproducibility [9]. Extraocular muscle cross-sections are oval rather than round, with their maximum coronal volume occurring over a fixed area, making it difficult for a radiologist or ultrasound technician to reproduce the same angle and location along a muscle for serial measurements [24]. New ultrasound devices and accompanying software designed specifically for the purpose of body composition assessment might help to minimize these limitations.

Conclusion

The concept of disease activity originates from observations of the natural course of the eye signs in patients left untreated for the ophthalmopathy, and from a small number of histologic studies performed on orbital tissues from patients with variable duration of the eye disease.

Results of histologic examination of the extraocular eye muscles in the early stages typically show marked lymphocytic infiltration and interstitial edema, whereas in later stages fibrosis and fatty infiltration are seen. However, this process of inflammation and subsequent fibrosis is not always reflected in the clinical severity of the disease. It is conceivable that immunosuppression is effective only during the active stages, and that patients not responding to immunosuppression already had inactive disease. Hence, establishing the activity of the disease at initial presentation might have important clinical use. Measuring eye muscle reflectivity in TAO appears to be a reliable new method to determine disease activity, with a promising accuracy in predicting therapeutic outcome of immunosuppressive treatment.

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