Case Series

Photoacoustic imaging for non-invasive examination of the healthy temporal artery – systematic evaluation of visual function in healthy subjects

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ABSTRACT.

Purpose: Photoacoustic (PA) imaging has the potential to become a non-invasive diagnostic tool for giant cell arteritis, as shown in pilot experiments on seven patients undergoing surgery. Here, we present a detailed evaluation of the safety regarding visual function and patient tolerability in healthy subjects, and define the spectral signature in the healthy temporal artery.

Methods: Photoacoustic scanning of the temporal artery was performed in 12 healthy subjects using 59 wavelengths (from 680 nm to 970 nm). Visual function was tested before and after the examination. The subjects’ experience of the examination was rated on a 0–100 VAS scale. Two- and three-dimensional PA images were generated from the spectra obtained from the artery.

Results: Photoacoustic imaging did not affect the best corrected visual acuity, colour vision (tested with Sahlgren’s Saturation Test or the Ishihara colour vision test) or the visual field. The level of discomfort was low, and only little heat and light sensation were reported. The spectral signature of the artery wall could be clearly differentiated from those of the subcutaneous tissue and skin. Spectral unmixing provided visualization of the chromophore distribution and overall architecture of the artery.

Conclusions: Photoacoustic imaging of the temporal artery is well tolerated and can be performed without any risk to visual function, including the function of the retina and the optic nerve. The spectral signature of the temporal artery is specific, which is promising for future method development.

Key words: giant cell arteritis – human – photoacoustic imaging – temporal arteritis – ultrasound

Introduction

Surgical biopsy and histopathological analysis of the temporal artery are considered the gold standard in the diagnosis of giant cell arteritis (GCA). However, although this technique has high specificity, it has low sensitivity (Luqmani, Lee et al. 2016), and is associated with complications such as injury to the facial and trigeminal nerve, and peri- and postoperative haemorrhage (Guffey Johnson, Grossniklaus et al. 2009; Borchers & Gershwin 2012; Gunawardene & Chant 2014). Attempts have been made to implement non-invasive imaging techniques, in particular ultrasonography, for the diagnosis of GCA. However, ultrasound is highly operator-dependent (Hauenstein, Reinhard et al. 2012), and the sensitivity and specificity in the diagnosis of GCA have proved inadequate (Arida, Kyprianou et al. 2010; Borchers & Gershwin 2012; Buttgereit, Dejaco et al. 2016; Luqmani, Lee et al. 2016).

Photoacoustic (PA) imaging is currently one of the most rapidly developing biomedical imaging techniques, providing non-invasive, high-resolution images (Valluru & Willmann 2016). It is unique in that it uses pulsed laser light and optical absorption detected by ultrasound to provide high-resolution images with high spatial resolution. PA imaging provides an
absorption spectrum of the tissue that depends on the molecular composition, and thus has a greater ability to discriminate between small differences in tissue composition than previously tested techniques. Another advantage of PA technology is that it is user-independent, since the spectral signature obtained is an objective measure. Encouraging results have been obtained in animal studies, showing detailed images of small blood vessels with high resolution (Jeon, Song et al. 2017). However, no clinical studies have been performed to evaluate the suitability of PA imaging for diagnosing GCA. We have recently adapted the PA technique for use in humans and resolved problems associated with motion artefacts and disturbances from other endogenous chromophores, in a previous study including seven patients undergoing surgery for suspected GCA (Sheikh et al., 2019). However, detailed investigation of safety regarding visual function or patient tolerability was not performed in that pilot study.

The main aim of the present study was to examine the temporal artery in 12 healthy subjects with PA imaging, and to evaluate the effects on visual function in detail, in terms of the visual acuity, colour vision and visual field, in order to confirm the safety of the method. Best corrected visual acuity was measured with the Snellen letter chart (Ortho-KM, Lund, Sweden). Colour vision was measured using the VisualSonics Vevo LAB 3.1.0 software and MATLAB R2017b (MathWorks Inc., Natick, MA, USA). Further details of the method can be found in Sheikh et al. (Sheikh et al., 2019).

Visual function was tested before and after PA imaging to evaluate the safety of the method. Best corrected visual acuity was measured with the Snellen letter chart (Ortho-KM, Lund, Sweden). Colour vision was measured with both Sahlgren's Saturation Test (SST, VISUMETRICS AB, Göteborg, Sweden) and the Ishihara colour vision test (Luxvision, US Ophthalmic, Doral, USA), since combining these tests allows discrimination between congenital and acquired defects (Frisen & Kalm 1981). Neither visual acuity nor colour vision was affected by PA examination. The visual field was measured with a Humphrey visual field analyzer, using the 24-2 test protocol (Carl Zeiss Meditec AG, Jena, Germany). A slight improvement was seen in the results after PA imaging, which could be due to a learning effect. Detailed results are given in Table 1.

We anticipated that the risk of PA imaging affecting visual function would be minimal since the PA probe is

### Table 1. Visual function before and after PA imaging, expressed as median values (range)

|                      | Right eye |                  | Left eye |                  |
|----------------------|-----------|-----------------|----------|-----------------|
|                      | Before PA | After PA        | p-value  | Before PA        | After PA        | p-value  |
| Visual acuity, logMAR (units) | 0.0 (0.0 to 0.39) | 0.0 (0.0 to 0.40) | >0.99    | 0.0 (0.0 to 0.10) | 0.0 (0.0 to 0.10) | 0.77    |
| Colour vision, Ishihara (number of correct plates) | 25 (1 to 25) | 24 (2 to 25) | 0.33    | 25 (2 to 25) | 25 (1 to 25) | 0.91    |
| Colour vision, SST (points) | 5 (0 to 20) | 5 (0 to 15) | 0.70    | 5 (0 to 20) | 5 (0 to 10) | 0.28    |
| Visual field (mean deviation in decibels) | −1.95 (−4.10 to 1.00) | −1.38 (−2.06 to 0.84) | 0.30    | −0.71 (−2.92 to 0.16) | −0.56 (−2.17 to 0.49) | 0.21    |
applied to the temple area, and the subjects' eyes were covered with eye shields that absorb all wavelengths. Diffusely scattered light can reach the eye from the temple region, although the energy levels are too low to cause any damage to the retina or the optic nerve. Flickering light was visually perceived by eight of the twelve

Fig. 1. The graphs above show the PA spectra obtained from the temporal artery, the subcutaneous tissue and the overlying skin. The results are presented as median values ± two standard deviations. Statistical analysis was performed using two-way analysis of variance (ANOVA) for repeated measures. Significance was defined as: p < 0.05 (*). A clear difference can be seen between the spectral signatures of the artery and the surrounding tissues. The images below show representative examples of an ultrasound image (left) and a photoacoustic image (right), obtained at 930 nm, of a cross-section of the temporal artery, in which the regions of interest for spectral analysis: artery wall (green), subcutaneous tissue (magenta), and skin (blue) and indicated. The size bar is 1 mm.
subjects. However, it was of very short duration and was not perceived as worrisome by the subjects. We therefore concluded that PA imaging was safe with regard to visual function.

The subjects’ experience of the PA examination was assessed using a visual analog scale (VAS) ranging from 0 to 100. The results show that the level of discomfort was low (median 8, range 1 to 17). Only little heat was felt from the probe (5, range 1 to 37), and only little light sensation was reported (22, range 5 to 80) on the VAS 0–100 scale. None of the examined subjects reported any negative experiences of the PA examination.

Photoacoustic imaging showed that the artery could be clearly delineated in the 3D scans. The multiwavelength 3D images were analysed using the spectral unmixing function in the Vevo LAB 3.1.0 software, providing clear visualization of the overall artery architecture and its extension. The spectral signature of the artery wall was clearly differentiated from those of the subcutaneous tissue (p < 0.05 in the wavelength range 830–895 nm) and skin (p < 0.05 in the wavelength range 795–940 nm) (Fig. 1). This is one of the first studies on human vasculature using PA imaging. A few studies have previously been reported on PA imaging of blood vessels in humans, for example, vessels of the skin (Zafar, Breathnach et al. 2015; Xu, Yang et al. 2016), coronary arteries (Daeichin, Wu et al. 2016), the radial artery (Bok, Hysi et al. 2017; Karlas, Reber et al. 2017), the tibialis posterior and dorsalis pedis arteries (Taruttis et al., 2016), the carotid artery (Kruizinga et al., 2014), the digital arteries (Hai, Zhou et al. 2015) and the palmar digital arteries (Matsumoto, Asao et al. 2018).

Limitations of the present study were that all the participants in this study had similar skin types (Fitzpatrick type I and II), and it was not possible to determine the effect of spectral colouring due to superficial tissue chromophores such as melanin. Melanin is an endogenous chromophore that may affect light propagation through the skin. Other factors that may affect the spectrum are the arterial depth, that is, the amount of tissue the light must propagate through, and the amount of haemoglobin and its oxygenation status.

There is some noise in the data, as can be seen from the irregularity of the plots in Fig. 1. The standard deviation in the results was high, particularly when the arteries were imaged with laser wavelengths shorter than 800 nm. This could be due to small variations in the energy between the laser pulses, motion artefacts, or the scattering of light by blood and other chromophores. Post-processing of the measured data, using spectral unmixing together with Monte Carlo simulations, may be necessary/useful to compensate for the variations in chromophores and measurement depth between patients. The problem of motion artefacts could be solved by the application of software to correct for motion artefacts in the image, or the use of electrocardiography to trigger image capture to compensate for arterial pulsation.

In conclusion, the present study shows that PA imaging of the temporal artery is well tolerated and safe with regard to visual function. The artery wall was clearly delineated, and unique spectral signatures were obtained for the artery, compared to the surrounding tissues. Further studies will be required to determine whether PA imaging can be used to identify anomalies in the temporal artery for the diagnosis of GCA. The next step in the development of PA imagining into a clinical diagnostic tool will require a larger clinical trial in which patients with suspected GCA are examined before undergoing surgical biopsy.

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