Lower ocular pulse amplitude with dynamic contour tonometry is associated with biopsy-proven giant cell arteritis

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ABSTRACT ●

Objectives: To determine the role of the ocular pulse amplitude (OPA) from Pascal dynamic contour tonometry in predicting the temporal artery biopsy (TABx) result in patients with suspected giant cell arteritis (GCA).

Design: Prospective validation study.

Participants: Adults aged 50 years or older who underwent TABx from March 2015 to April 2017.

Methods: Subjects on high-dose glucocorticoids more than 14 days or without serology before glucocorticoid initiation were excluded. The OPA from both eyes was obtained and averaged just before TABx of the predominantly symptomatic side. The variables chosen for the a priori prediction model were age, average OPA, and C-reactive protein (CRP). Erythrocyte sedimentation rate (ESR), platelets, jaw claudication, and eye findings were also recorded. In this study, subjects with a negative biopsy were considered not to have GCA, and contralateral biopsy was performed if the clinical suspicion for GCA remained high. An external validation set (XVAL) was obtained.

Results: Of 109 TABx, 19 were positive and 90 were negative. On univariate logistic regression, the average OPA had 0.60 odds for positive TABx ($p = 0.03$), with no statistically significant difference in age, sex, CRP, ESR, or jaw claudication. In suspected GCA, an OPA of 1 mm Hg had positive likelihood ratio 4.74 and negative likelihood ratio 0.87 for positive TABx. Multivariate regression of the prediction model using optimal mathematical transforms (inverse OPA, log CRP, age >65 years) had area under the receiver operating characteristic curve (AUROC) = 0.85 and $AUROC_{XVAL} = 0.81$.

Conclusions: OPA is lower in subjects with biopsy-proven GCA and is a statistically significant predictor of GCA.

Giant cell arteritis (GCA) is an idiopathic vasculitis that most commonly affects individuals aged >50 years. It is classified as a large-vessel vasculitis but typically also involves medium and small arteries.[1] Of the patients with GCA, 8% to 49% may develop vision loss, which is usually irreversible.[2] Less commonly, stroke,[3] myocardial infection, aortic aneurysm,[4] and even death[5] can occur with GCA.

The incidence of GCA is predicted to increase with our aging population. DeSmit estimates that by 2050 there will be 3 million cases of GCA worldwide and that 500 000 patients will have significant vision impairment.[6] Adjusting DeSmit's calculations to Canada's population, the economic costs of GCA-related vision loss in Canada alone will be approximately $7 billion by 2050.

GCA can be a diagnostic conundrum when it presents in an atypical[5,7–9] or occult fashion.[10,11] There is no highly specific biomarker for GCA to date.[12] Blood tests for inflammation have limited sensitivity, and "seronegative" GCA can occur in up to 4% of patients.[13,14] The 1990 American College of Rheumatology (ACR) classification criteria[15] for GCA are not diagnostic criteria. Some believe that temporal artery biopsy (TABx) is not required in all cases of suspected GCA,[16,17] but the ACR criteria misclassify up to 25% of ophthalmology patients with GCA.[18] Although TABx is an invasive and time-consuming test, most authorities believe that TABx remains the gold standard for the diagnosis of GCA.[19–22]

Emerging imaging techniques for the diagnosis of GCA include colour duplex sonography,[23] fluorodeoxyglucose positron emission tomography,[24] computed tomography angiography, magnetic resonance imaging angiography,[25,26] and transdermal optical coherence tomography (OCT),[27] but British and French guidelines state that TABx remains the first-line investigation.[22,28] The non-TABx technologies may have limited sensitivity and/or specificity,[29] require standardization, need specialized interpretation, not provide pathologic confirmation of disease, and be difficult for a community ophthalmologist to arrange within a 1–2-week time window.

Although the most common complication of GCA is visual loss, most clinical prediction algorithms for

https://doi.org/10.1016/j.jcjo.2017.10.027
ISSN 0008-4182/17

Canadian Ophthalmological Society | Société canadienne d'ophtalmologie
EYE PHYSICIANS AND SURGEONS OF CANADA | MÉDECINS ET CHIRURGIENS OPHTALMOLOGISTES DU CANADA

GCA[15,30] do not incorporate an ocular blood flow measurement. Methods to assess reduced blood flow in GCA include fluorescein angiography, oculoplethysmography, dynamic contour tonometry (DCT), and perhaps in the future ultra-wide-field OCT angiography. Delayed choroidal filling greater than 20 seconds on fluorescein angiography is more suggestive of GCA than nonarteritic ischemic optic neuropathy but is not specific for GCA.[31,32] In patients with GCA, Bosley et al. showed that there is reduced ocular pulse amplitude (OPA) with their pneumo-oculoplethysmography technique,[33] which is a cumbersome technique that requires an ocular suction cup with peak pressures of up to 145 mm Hg[34] and is rarely performed presently.

Pascal DCT (Ziemer Ophthalmic Systems AG, Port, Switzerland) occupies the same footprint as a Goldmann tonometer and became popularized for glaucoma over the last decade.[35] DCT provides a painless digital readout of intraocular pressure as well as an estimation of the OPA. The OPA is the difference in intraocular pressure during the cardiac cycle and represents the pulsatile wave front produced by the varying amount of choroidal blood flow between systole and diastole.[36] The DCT OPA painlessly estimates the ocular blood flow in 7 seconds. At the time of institutional review board approval for this project, the use of DCT in GCA had not been reported. We hypothesized that the DCT OPA would be reduced in patients with positive TABx compared with negative TABx.

In July 2015, Knecht published a study of 31 subjects with suspected GCA using DCT.[37] This study was underpowered to show a statistical difference in OPA between TABx-positive and TABx-negative groups, and up to 26% of the patients assessed were excluded for various reasons.

Our primary aim was to determine whether there was a difference in OPA in suspected GCA with positive versus negative TABx. Our secondary aim was to develop a logistic regression prediction rule for GCA incorporating OPA and to perform an external validation.

Our prediction scheme used the a priori objective predictors of age, OPA, and C-reactive protein (CRP) to overcome some of the limitations of prediction or classification schema. Some prediction models still use erythrocyte sedimentation rate (ESR),[14,15,30,38,39] even though CRP has higher sensitivity and specificity.[14] When continuous predictor variables are converted to categorical variables[37] there may be loss of statistical power.[41] We sought to determine whether it was feasible to maintain our bloodwork data as a continuous variable, without impeding the development of a user-friendly prediction algorithm.

Methods

This study was institutional review board approved and compliant with the Declaration of Helsinki. Informed consent was obtained from all patients undergoing TABx from March 2015 to April 2017 for suspected GCA in this prospective study. The side ipsilateral to the predominant patient symptoms/signs (vision loss, scalp tenderness, headache, jaw claudication) was biopsied. If the initial biopsy was negative and clinical suspicion for disease remained high, a contralateral biopsy was performed.

Sample size calculation was based on an expected difference in OPA of 0.5–0.7 between the positive and negative biopsy groups; alpha 0.05, power 0.8, and allocation ratio 0.2 (given expected biopsy utility rate of 20%) was between 100 and 195 subjects, which was believed to be feasible over the planned 2-year study.

Subjects were excluded from the study if they refused DCT, were seen more than 14 days after steroid initiation, or did not have CRP measurement before steroid initiation.

For the purposes of this study the pathologic diagnosis was considered the final diagnosis: "There are no independent validating criteria to determine whether giant cell arteritis is present when a temporal artery biopsy is negative. The American College of Rheumatology criteria for the classification of giant cell arteritis may assist in the diagnosis. However, meeting classification criteria is not equivalent to making the diagnosis in individual patients."[42]

The rule of thumb for logistic regression is 10 events per predictor variable. Given the anticipated number of TABx that would be accrued over the 2-year study and a 20% utility rate, at most 3 a priori variables could be chosen. Based on literature review, OPA,[33,37] CRP,[14] and age[40] were selected as the 3 objective predictor variables.

Objective variables were chosen because there would be less physician cognitive bias and patient response bias than with subjective variables. The OPA was obtained just before TABx procedures, which were almost all performed in the afternoon. DCT measurements were performed until a quality reading of 1 or 2 was obtained. The average OPA of the right and left eye was averaged to avoid statistical errors of inter-eye correlation. The CRP result obtained before glucocorticoid initiation was divided by each lab's upper limit of normal.

Sex, Westergren ESR corrected by Miller's method,[43] platelets, jaw claudication, and ocular examination findings were also recorded but were not used in the a priori analysis.

Data were processed using Stata 14.2 (StataCorp LLC, College Station, Tex.) and JMP Pro 13 (SAS, Cary, N.C.) predictive analytics software.

The a priori variables were graphically analyzed, and the appropriate data transformations were chosen. Age was examined as a continuous, quadratic variable, as well as a categorical variable given its histogram characteristics. The inverse of the OPA appeared almost linear on logistic fit graph. Although normal data are not required for logistic regression, the right skew distribution of the CRP