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Utility of Pupillary Light Reflex Metrics as a Physiologic Biomarker for Adolescent Sport-Related Concussion

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IMPORTANCE Concussion diagnosis remains clinical, without objective diagnostic tests available for adolescents. Known deficits in visual accommodation and autonomic function after concussion make the pupillary light reflex (PLR) a promising target as an objective physiological biomarker for concussion.

OBJECTIVE To determine the potential utility of PLR metrics as physiological biomarkers for concussion.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort of adolescent athletes between ages 12 and 18 years recruited between August 1, 2017, and December 31, 2018. The study took place at a specialty concussion program and private suburban high school and included healthy control individuals (n = 134) and athletes with a diagnosis of sport-related concussion (SRC) (n = 98). Analysis was completed June 30, 2020.

EXPOSURES Sports-related concussion and pupillometry assessments.

MAIN OUTCOMES AND MEASURES Pupillary light reflex metrics (maximum and minimum pupillary diameter, peak and average constriction/dilation velocity, percentage constriction, and time to 75% pupillary redilation [T75]).

RESULTS Pupillary light reflex metrics of 134 healthy control individuals and 98 athletes with concussion were obtained a median of 12.0 days following injury (interquartile range [IQR], 5.0-18.0 days). Eight of 9 metrics were significantly greater among athletes with concussion after Bonferroni correction (maximum pupil diameter: 4.83 mm vs 4.01 mm; difference, 0.82; 99.44% CI, 0.53-1.11; minimum pupil diameter: 2.96 mm vs 2.63 mm; difference, 0.33; 99.4% CI, 0.18-0.48; percentage constriction: 38.23% vs 33.66%; difference, 4.57; 99.4% CI, 2.60-6.55; average constriction velocity: 3.08 mm/s vs 2.50 mm/s; difference, 0.58; 99.4% CI, 0.36-0.81; peak constriction velocity: 4.88 mm/s vs 3.91 mm/s; difference, 0.97; 99.4% CI, 0.63-1.31; average dilation velocity, 1.32 mm/s vs 1.22 mm/s; difference, 0.10; 99.4% CI, 0.00-0.20; peak dilation velocity: 1.83 mm/s vs 1.64 mm/s; difference, 0.19; 99.4% CI, 0.07-0.32; and T75: 1.81 seconds vs 1.51 seconds; difference, 0.30; 0.10-0.51). In exploratory analyses, sex-based differences were observed, with girls with concussion exhibiting longer T75 (1.96 seconds vs 1.63 seconds; difference, 0.33; 99.4% CI, 0.02-0.65). Among healthy control individuals, diminished PLR metrics (eg, smaller maximum pupil size 3.81 mm vs 4.22 mm; difference, −0.41; 99.4% CI, −0.77 to 0.05) were observed after exercise.

CONCLUSIONS AND RELEVANCE These findings suggest that enhancement of PLR metrics characterize acute adolescent concussion, while exercise produced smaller pupil sizes and overall slowing of PLR metrics, presumably associated with fatigue. Quantifiable measures of the PLR may serve in the future as objective physiologic biomarkers for concussion in the adolescent athlete.

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Invited Commentary
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Supplemental content

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Visual and autonomic dysfunction occur following sport-related concussion (SRC),[1,2] a form of mild traumatic brain injury (mTBI), negatively affecting adolescents in academic and athletic pursuits.[3,4] Convergence and accommodation deficits after concussion predict prolonged recovery,[5] while exercise intolerance is another manifestation of autonomic dysfunction after SRC.[6] The pupillary light reflex (PLR) is involved in both convergence and accommodation, driven by the parasympathetic system for constriction and the sympathetic system for dilation. It can be quantitatively measured via dynamic, infrared pupillometry (DIP) in a rapid, reproducible manner.[7] Quantitative PLR metrics may provide insight into autonomically influenced visual dysfunction following SRC, making the PLR a promising objective physiologic biomarker of concussion.[8]

Normative values for PLR metrics have been described, with adults demonstrating decreasing pupil size with increasing age.[9-11] In children across the age span, latency and average constriction/dilation velocities are similar; however, adolescents, specifically boys aged 12 to 18 years, have larger maximum pupil diameters, slower maximum constriction velocities, and smaller percentage constriction compared with younger children aged 6 to 11 years.[10] These neurodevelopmental influences on the PLR[11] make results of adult studies following concussion difficult to translate to children.

In the subacute phase after mTBI in adults, 2 to 8 weeks after injury, longer latency, lower average constriction/dilation velocities, and longer time to 75% pupillary redilation (T75) were found compared with control individuals.[12] Another cross-sectional study in symptomatic adult chronic mTBI (greater than 3 months following injury) also found slower responses, with smaller initial pupil diameters, lower maximum and average constriction/dilation velocities, and lower constriction amplitudes compared with control individuals.[13,14] In other adult studies, conflicting data have been reported, with one study finding no differences acutely after concussion but noting changes 2 to 4 weeks after injury,[15] while another study found differences acutely (<72 hours following injury) compared with control individuals.[16] In SRC, subclinical decrements in percentage pupil constriction and maximum constriction/dilation velocity were associated with high-acceleration head impacts.[17] The utility of pupillary assessment in SRC remains unclear, especially in children. Thus, the objective of our study was to determine whether differences in quantitative PLR metrics could serve as an objective physiologic biomarker for adolescent SRC.

Key Points

Question Do quantitative metrics of the pupillary light reflex (PLR) distinguish athletes with concussion from healthy control individuals?

Findings In this cohort study, 8 PLR metrics (maximum and minimum pupillary diameter, percentage constriction, peak and average constriction velocity, peak and average dilation velocity, and time to 75% pupillary redilation) were greater among adolescent athletes with concussion compared with healthy control individuals.

Meaning These results suggest that quantitative metrics of the pupillary light reflex are enhanced in adolescent sport-related concussion and distinguish athletes with concussion from healthy control individuals and may serve as a fast, portable, objective physiologic biomarker for adolescent sport concussion.

Methods

Study Design, Setting, and Participants

Athletes aged 12 to 18 years were prospectively enrolled between August 1, 2017, and December 31, 2018, as part of a prospective observational cohort study approved by the Children's Hospital of Philadelphia institutional review board. Athletes and/or their parents/legal guardians provided written assent/written informed consent. Healthy control individuals (n = 143) were recruited from a private suburban high school with pupillometry assessments prior to their sport seasons. Athletes with a diagnosis of SRC (n = 110) were recruited from a concussion program as well as the high school. Athletes with concussion enrolled after injury and thus did not have preinjury pupillometry. Ten participants who enrolled as healthy control individuals subsequently sustained an SRC and, for the purposes of this analysis, were included only in the concussed cohort. The diagnosis of SRC was made by a trained sports medicine pediatrician according to the most recent Consensus Statement on Concussion in Sports.[18] All athletes with concussion had PLR assessments completed within 28 days of injury. If the injured patient had multiple assessments, the first assessment was used in this analysis. Exclusion criteria for both cases and controls included a concussion within 1 month of injury or preinjury assessment, ongoing chronic postconcussion symptoms, eye trauma, any ocular or neurologic condition, or medication that could affect pupillary responses. Forty-six control individuals received gift cards as compensation for participation in the second year of the study. The remaining healthy athletes with concussion were not compensated for their participation.

Instrumentation

Pupillary dynamics were measured in response to a brief, step-input, white light stimulus (154 milliseconds' duration; 180 microwatts' power) via a Neuroptics PLR-3000 handheld, infrared, automated, monocular pupillometer[13] (Neuroptics). This device is US Food and Drug Administration approved and has been used in similar studies of mTBI in adults.[8,13,14,19] The pupillometer captures dynamic responses 32 times per second, analyzing a continuous, 5-second, digital video of the pupillary response to light. Eight metrics are quantified by the device software: maximum pupil diameter (steady-state pupil size before the light stimulus); minimum pupil diameter (pupil size after maximum constriction in response to the light stimulus); percentage pupil constriction; latency (time to maximum constriction in response to the light stimulus); peak and average constriction velocity; average dilation velocity; and T75 (time for pupil redilation from minimum diameter to 75% maximum diameter). A ninth metric, peak dilation velocity, was cal-

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Table 1. Demographic and Clinical Characteristics of the Study Cohort

Characteristic	No. (%) Athletes with concussion (n = 98)	Healthy control participants (n = 134)
Age, mean (STD), y	15.7 (1.54)	15.3 (1.61)
Sex		
Female	55 (56)	78 (58)
Male	43 (44)	56 (42)
Race/ethnicity		
Non-Hispanic White	83 (85)	109 (81)
Non-Hispanic Black	8 (8)	11 (8)
Other/unknown	7 (7)	14 (10)
History of prior concussion[a]		
No	47 (48)	99 (74)
Yes	50 (51)	35 (26)

[a] One athlete with concussion did not have history of prior concussion documented.

culated from automated slope-based measures obtained by the pupillometer (Microsoft Excel 2016; Microsoft Corporation).[1,4]

Procedures

Trained research staff conducted PLR assessments in an athletic training room or sports medicine office, with a room illumination of approximately 350 lux (moderate photopic viewing conditions) and were not blinded to athlete concussion status because pupillometry is an objective measure requiring no subjective interpretation of results. Athletes focused on a 3-m distance target with the nontested eye for ocular fixation and accommodation during the 5-second measurement period. Monocular measurements were repeated at least 3 times for each eye, alternating 1-minute time intervals to allow rapid visual light adaptation, to obtain 2 to 3 artifact-free responses per eye. The combined mean of each pupillometry metric was calculated for at least 2 assessments without artifacts, defined as blinks or eye movements occurring within the first 3 seconds of the response. Approximately 6% of data were removed from each cohort owing to artifacts. This simple objective criterion approach to artifact removal with minimal postprocessing was used to maximize the translational potential of this paradigm to future clinical settings, including the sideline. Only artifact-free responses were analyzed. Among control individuals, staff recorded whether the assessment was conducted before or within 60 minutes after practice with each control assessed under one condition only. No athletes with concussion exercised before assessment.

Statistical Analyses

We compared distribution of demographic and clinical characteristics for athletes with concussion with controls using χ^2 statistics for categorical variables (sex, race/ethnicity, and history of prior concussion) and *F* tests for age. The means of the PLR metrics were compared among athletes with concussion and controls with 1-way analysis of variance using *F* tests. We accounted for multiplicity by calculating Bonferroni corrections for the 9 PLR metrics; we present the 99.44% CIs around the mean values and the mean differences between comparison groups.[20] Additionally, receiver operating characteristic curves and area under the curve were calculated for each metric.[21] The planned primary analysis was based on previously published work by members of our team.[13,14] In sensitivity analyses, we further stratified the analysis comparing the subgroup of athletes with concussion within 7 days of injury. In exploratory analyses, we examined PLR metrics within athletes with concussion and controls by sex, by history of prior concussion, and between those who did and did not exercise before assessment. With Bonferroni correction, the level of significance (α) was .0056 (0.05/ 9). We used 2-sided tests of statistical significance. Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc).

Results

Study Population

Of the 253 athletes enrolled, valid PLR assessments were obtained for 134 of 143 healthy control individuals (93.7%) and 98 of 110 athletes with concussion (89.1%). Among those without a valid assessment, 7 were too symptomatic to continue (eg, eye pain/irritation, light sensitivity, and eye fatigue; 2 control individuals and 5 with concussion), 4 could not keep eyes open (2 control individuals and 2 with concussion), and 10 had insufficient analyzable measurements owing to artifact (<2 valid measurements for at least 1 eye; 5 control individuals and 5 with concussion). Among participants with evaluable pupillometry measurements, athletes with concussion (n = 98) and control individuals (n = 134) did not differ with respect to sex or race/ethnicity. Compared with controls, athletes with concussion were slightly older (median age, 15.7 years vs 15.2 years) and more likely to have a history of prior concussion (50% vs 26%). Athletes with concussion had pupillometry assessments performed a median of 12 days following injury (interquartile range [IQR], 5-18) (**Table 1**).

PLR Metrics in Concussion

There were significant differences between athletes with concussion and controls for all PLR metrics except latency, after Bonferroni correction for multiple comparisons (**Table 2**). Athletes with concussion had larger maximum pupil diameter (4.83 mm vs 4.01 mm; difference, 0.82; 99.44% CI, 0.53-1.11), minimum pupil diameter (2.96 mm vs 2.63 mm; difference, 0.33; 99.4% CI, 0.18-0.48), and greater percentage constriction (38.23% vs 33.66%; difference, 4.57; 99.4% CI, 2.60-6.55). Additional enhanced PLR metrics (higher average constriction velocity, 3.08 mm/s vs 2.50 mm/s; difference, 0.58; 99.4% CI, 0.36-0.81), peak constriction velocity (4.88 mm/s vs 3.91 mm/s; difference, 0.97; 99.4% CI, 0.63-1.31), average dilation velocity (1.32 mm/s vs 1.22 mm/s, difference, 0.10; 99.4% CI, 0.00-0.20), peak dilation velocity (1.83 mm/s vs 1.64 mm/s; difference, 0.19; 99.4% CI, 0.07-0.32), and T75 (1.81 seconds vs 1.51 seconds; difference, 0.30; 99.4% CI, 0.10-0.51) were observed in athletes with concussion compared with control individuals. Receiver operating characteristic curves were plotted for

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Table 2. Pupillary Light Reflex Metrics Distinguishing Healthy Control Participants and Athletes With Concussion Within 28 Days Following Injury

Variable	Mean (99.44% CI)			
	Athletes with concussion (n = 98)	Healthy control participants (n = 134)	Difference	AUC (95% CI)
Pupil diameter, mm				
Maximum	4.83 (4.62 to 5.05)	4.01 (3.83 to 4.20)	0.82 (0.53 to 1.11)	0.78 (0.72 to 0.84)
Minimum	2.96 (2.84 to 3.08)	2.63 (2.53 to 2.73)	0.33 (0.18 to 0.48)	0.73 (0.67 to 0.80)
% Constriction	38.23 (36.73 to 39.74)	33.66 (32.38 to 34.95)	4.57 (2.60 to 6.55)	0.74 (0.67 to 0.80)
Latency, ms	208.40 (203.56 to 213.24)	208.50 (204.36 to 212.63)	−0.09 (−6.46 to 6.27)	0.50 (0.43 to 0.58)
Constriction velocity, mm/s				
Average	3.08 (2.91 to 3.25)	2.50 (2.35 to 2.64)	0.58 (0.36 to 0.81)	0.76 (0.70 to 0.82)
Peak	4.88 (4.62 to 5.14)	3.91 (3.69 to 4.13)	0.97 (0.63 to 1.31)	0.78 (0.72 to 0.84)
Dilation velocity, mm/s				
Average	1.32 (1.24 to 1.40)	1.22 (1.15 to 1.28)	0.10 (0.00 to 0.20)	0.60 (0.52 to 0.67)
Peak	1.83 (1.74 to 1.93)	1.64 (1.56 to 1.72)	0.19 (0.07 to 0.32)	0.66 (0.59 to 0.73)
T75, s	1.81 (1.66 to 1.97)	1.51 (1.38 to 1.64)	0.30 (0.10 to 0.51)	0.65 (0.58 to 0.72)

Abbreviations: AUC, area under the curve; T75, time to 75% pupillary redilation.

each PLR metric, with maximum pupil diameter and peak constriction velocity achieving the greatest area under the curve (both = 0.78) in distinguishing athletes with concussion from control individuals (eFigure 1 in the Supplement). Anisocoria was not clinically observed in anyone in either cohort nor detected by pupillometry (mean [SD] pupillary diameter [MPD] among healthy control individuals, 4.08 [0.84] mm right eye vs 3.94 [0.85] mm left eye; among patients with concussion, MPD [SD], 4.80 [0.83] mm right eye and 4.72 [0.76] mm in left eye; both nonsignificant). The median minimum and maximum pupillary diameters were also normally distributed (eFigure 2 in the Supplement).

Sensitivity Analyses of Subgroups

In our sensitivity analyses, we examined a subgroup of athletes with acute concussion assessed within 7 days following injury (n = 35) compared with control participants. After Bonferroni correction, differences between control participantsand athletes with concussion within 7 days following injury were no longer significant for average dilation velocity and T75 but continued to be significant for the remaining 7 parameters (eTable 1 and eFigure 3 in the Supplement). Next, we examined PLR metrics by sex. No sex differences were found in control participants for any metric. After Bonferroni correction, differences were observed, with girls with concussion exhibiting longer T75 (1.96 seconds vs 1.63 seconds; difference, 0.33; 99.4% CI, 0.02-0.65) (eTable 2 and eFigure 4 in the Supplement). A subgroup of control participants assessed within 60 minutes after practice manifested smaller maximum pupil diameters, smaller maximum pupil size (3.81 mm vs 4.22 mm; difference, −0.41; 99.4% CI, −0.77 to 0.05), lower average constriction velocity (2.32 mm/s vs 2.67 mm/s; difference, −0.35; 99.4% CI, −0.64 to −0.06), peak constriction velocity (3.65 mm/s vs 4.17 mm/s; difference, −0.52; 99.4% CI,−0.96 to −0.09), average dilation velocity (1.11 mm/s vs 1.33 mm/s; difference, 99.4% CI, −0.22; −0.34 to −0.10), and peak dilation velocity (1.50 mm/s vs 1.78 mm/s; difference, −0.28; 99.4% CI, −0.44 to −0.13) compared with control individuals who did not exercise before assessment (eTable 3 and eFigure 5 in the Supplement). Pupillary light reflex metrics were similar between those with and without a history of prior concussion among control participants. In athletes with concussion, those with a history of concussion had longer latency after Bonferroni correction (212.9 milliseconds vs 203.7 milliseconds; difference, 9.21; 99.4% CI, 0.28-18.14) (eTable 4 and eFigure 6 in the Supplement).

Discussion

Concussion diagnosis remains clinical, based on a history of injury and onset of a well-characterized but subjective and nonspecific constellation of symptoms.[18] Additional support for concussion diagnosis may come from clinical physical examination.[22] There is heightened interest in identifying biomarkers for concussion, using quantitative eye tracking, which captures some visual manifestations occurring after SRC.[23,24] Pupillometry may be an ideal objective physiologic biomarker for SRC because autonomic dysfunction also occurs following SRC.[1,2] To our knowledge, our study is the first to demonstrate that quantitative PLR metrics obtained via DIP differentiate concussed adolescent athletes from healthy control participants. Enhancement of PLR metrics characterizes acute concussion, with larger pupil sizes and increased average and peak constriction/dilation velocities. The association of concussion with PLR metrics appears robust, with significant differences between athletes with concussion and control participants in all metrics except for latency. The results presented here may be clinically relevant because these metrics are easily obtained via automated dynamic infrared pupillometry, and the measurable objective differences discriminate well between adolescents with and without concussion, indicating potential future utility in the diagnosis of concussion in the sports setting.

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Enhancement of PLR Metrics in Concussion

The enhancement of PLR metrics reflects relative sympathetic predominance after concussion, which also affects exercise intolerance after concussion.[25] Pupillary light reflex enhancement has been described in infants at risk for autism, attributed to possible cholinergic system disruption during infant neurodevelopment resulting in an excitatory-inhibitory autonomic imbalance.[26] In concussion, an analogous, traumatically acquired, autonomic dysfunction is described, with excessive sympathetic tone.[27] Our results support this hypothesis with findings of larger maximum pupillary diameters, permitting more light to enter the eye, thus influencing the downstream dynamics of both constriction and dilation as evidenced by higher peak and average constriction/dilation velocities and greater percentage constriction in adolescent athletes with concussion.

Of interest, PLR latency did not differ between athletes with concussion and control individuals, which might have been expected in concussion.[28] However, the lack of slowing may be owing to the high-intensity light stimulus producing a response saturation effect, such that differences in latency might only be detected at lower luminosity.

Sex-Based Differences in the PLR in Concussion

We found prolongation of T75 in girls with concussion, lending support to previously described sex-based differences following concussion,[29,30] reflecting differential adverse effects of trauma on the sympathetic system. There are no previously reported sex differences in T75 in control participants,[9-11,31] in either adults or children,[11] which we also confirmed, making the sex differences in T75 in girls with concussion of particular interest.

Age-Related Differences in the PLR in Concussion

Our results advance our quest for an objective physiologic biomarker for concussion, representing the first report of PLR metrics distinguishing adolescent SRC from healthy control athletes. In contrast, adult studies of blast mTBI found smaller pupillary sizes and slower responses compared with healthy control participants.[13] These differences may be neurodevelopmental in nature. First, age-related differences in the PLR exist. Within the healthy pediatric population, older adolescents aged 12 to 18 years have larger pupil diameters, slower peak constriction velocities, and smaller percentage constriction than younger children aged 6 to 11 years.[11] These differences in the PLR in childhood likely influence findings after concussion. Second, differences in recovery trajectories for concussion in adolescents vs adults have been previously demonstrated. Cerebral blood flow changes following concussion take longer to recover in children compared with adults; recovery of the PLR may also be affected by developmental factors affecting the autonomic nervous system.[32,33] Lastly, the timing of PLR assessments following injury may account for some of these differences with parameters changing over time after concussion. Our study assessed adolescents with concussion within 28 days of injury (acute to subacute time frame), whereas adult studies assessed symptomatic patients anywhere from 2 weeks to more than 3 months following injury (subacute to chronic time frame). Temporal changes in the PLR over the course of recovery may also account for observed differences.

Association of Exercise With the PLR

We also found that exercise had an effect on PLR metrics in control individuals. Those who exercised before pupillary assessment had smaller maximum and minimum pupil sizes with lower peak and average constriction/dilation velocities compared with control individuals who did not exercise before assessment. Pupillary light reflex metrics in the postexercise group were similar to those described in an adult cohort with mTBI in the chronic time frame,[13] indicating that the physiology of the PLR in symptomatic chronic mTBI may be similar to physical fatigue.

Limitations

Our study was limited to adolescents aged 12 to 18 years, and pupillary assessments were performed throughout the day for logistical reasons; analyses did not account for potential diurnal variation. Participants were predominantly white, which was comparable between cohorts but limits the generalizability of our results. In addition, 6% of control participants and almost 11% of athletes with concussion did not have adequate data collected owing to either artifacts or inability to complete the assessment secondary to symptoms. More specific instructions prior to assessment and lower luminosity may be helpful in the future to minimize artifacts and make the procedure more tolerable. Normal, physiologic anisocoria ranging from 0.4 to 1.0 mm would be expected to be found in approximately 19% of the general population[34] but was not found either clinically or by pupillometry in our cohorts. Owing to potential developmental differences in the PLR, our results should not be extrapolated to either younger pediatric or older adult populations until more is understood about neurodevelopmental and aging factors associated with the PLR.[9-11] Both younger age and older age populations demonstrate smaller pupil diameters, possibly associated with relative lower sympathetic tone than is observed in adolescents, and as such, our findings may not translate to those populations.[35]

Future Directions

Future work should examine multivariable modeling, including history of prior concussion and also the effect of using lower luminosity stimuli to determine whether differences in latency might be detected under these conditions. Additional studies should further explore PLR metrics in girls and after exercise, as well as longitudinally after concussion, to better understand PLR metrics as a potential objective physiologic biomarker for concussion and recovery.

Conclusions

These results suggest that PLR metrics may serve as robust objective physiologic biomarkers for adolescent SRC, with athletes with concussion manifesting PLR enhancement. Longer pupillary recovery T75 times were noted in girls with concus-

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sion, indicating a potential biologic basis for sex differences in concussion. In control participants, we found slower PLR responses after exercise indicating a fatigue effect. Further studies to confirm these findings beyond a single site, with attention to understanding the influence of lower luminosity and exercise, are warranted to determine whether PLR metrics have the potential to serve as quantitative physiologic biomarkers for adolescent SRC.

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Concept and design: Master, Podolak, Ciuffreda, Metzger, Joshi, McDonald, Grady, Arbogast.
Acquisition, analysis, or interpretation of data: Master, Podolak, Ciuffreda, Metzger, Joshi, McDonald, Margulies, Arbogast.
Drafting of the manuscript: Master, Podolak, Ciuffreda, Metzger, Margulies.
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