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Microstructural Macular Changes after Pars Plana Vitrectomy for Primary Rhegmatogenous Retinal Detachment

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1 **Microstructural macular changes after pars plana vitrectomy for**
2 **primary rhegmatogenous retinal detachment.**

3 **Maurizio Mete¹, Emilia Maggio¹, Francesca Ramanzini², Massimo Guerriero³, Giulia**
4 **Airaghi¹, Grazia Pertile¹**

5 ¹ Department of Ophthalmology, IRRCS Sacro Cuore-Don Calabria Hospital, Negrar, Verona,
6 Italy

7 ² Eye Clinic, Department of Neuroscience and Sensory Organs University of Genoa,
8 Policlinico San Martino Hospital IRCCS Hospital-University San Martino

9
10 ³ Department of Computer Science, University of Verona, Verona, Italy

11
12 **Corresponding author:**

13 Maurizio Mete, MD

14 Department of Ophthalmology, IRRCS Sacro Cuore-Don Calabria Hospital

15 Via Don A. Sempereboni 5

16 37124 Negrar, Verona, Italy

17 e-mail: maurizio.mete@sacrocuore.it

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19
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24
25 **Running title:** OCT finding after retinal detachment surgery

26
27 **Keywords:** Air tamponade; Ellipsoid zone; External limiting membrane; Optical coherence
28 tomography (OCT); Pars-plana vitrectomy; Retinal detachment.

30 **ABSTRACT**

31 Purpose. To describe the foveal microstructural changes after pars-plana vitrectomy (PPV)
32 with air tamponade for reghmatogenous retinal detachment (RRD).

33 Methods. External limiting membrane (ELM) and ellipsoid zone (EZ) integrity, cystoid macular
34 edema (CME) and subretinal fluid blebs (SBs) presence were analyzed with optical
35 coherence tomography (OCT) in 59 eyes undergone surgery for RRD, divided between
36 macula-on (n=30) and macula-off (n=29) and followed up 6 months. The association between
37 ELM and EZ recovery and best-corrected visual acuity (BCVA) was investigated. Predictive
38 factors for ELM and EZ recovery were also identified.

39 Results. The nterval between symptoms and surgery didn't significantly differ between the
40 groups. Macula-on patients showed ELM and EZ integrity. In macula-off patients, ELM and
41 EZ were namely restored in 89.7% and in 86.2% of cases. Final BCVA was higher when ELM
42 and EZ were restored. Significant associations were found at several time points between
43 ELM/EZ recovery and macular preoperative involvement and EMC development, and
44 between BCVA and preoperative BCVA and EZ recovery. EMC and SBs development were
45 equally distributed between the groups.

46 Conclusion. Prompt surgery for macula-off RRD usually allows a progressive recovery of
47 outer retinal layers. Thus, a high visual gain can be achieved, regardless of macular
48 involvement.

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62 INTRODUCTION

63 Retinal detachment (RD) is defined as the separation of neurosensory retina from underlying
64 retinal pigment epithelium (RPE). Retinal apposition to the RPE is essential for supporting
65 vision, and RD involving the foveal center can lead to significant visual loss.
66 Rhegmatogenous RD (RRD) is the most frequent form of RD, where a retinal break allows the
67 fluid passage from the vitreous chamber into the subretinal space, resulting in retinal
68 separation. RRD can occur at any age, with a peak prevalence of 13 cases per 100000
69 amongst individuals aged 60 to 70 years. Pars plana vitrectomy (PPV) has been increasingly
70 adopted for the treatment of RRD, with recent advances in its techniques having improved its
71 outcomes. Several factors, such as RD duration, macular involvement, proliferative
72 vitreoretinopathy (PVR), epiretinal membrane (ERM) development, cystoid macular edema
73 (CME) occurrence, retinal fold formation and pigment migration, seem to affect postoperative
74 functional outcomes ^{1,2}. Regardless of these macroscopic features, poor visual recovery can
75 also occur in retinas of normal appearance, suggesting the existence of microstructural
76 alterations not detectable upon fundus examination. The advent of high-resolution spectral-
77 domain optical coherence tomography (SD-OCT) has allowed macular microstructural
78 abnormalities detection and a better understanding of the discrepancies between anatomical
79 and functional surgical outcomes.

80 In our center, PPV with air tamponade represents the technique of choice in case of
81 uncomplicated primary RRD. Gas or silicon oil are usually used in case of a supposed risk of
82 RD recurrence (giant retinal tears, PVR stage higher than B). The aims of this study are to
83 investigate microstructural changes after primary uncomplicated RRD repair and to identify
84 both preoperative and postoperative factors that could affect healing processes and functional
85 outcomes.

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87 METHODS

88 PATIENT SELECTION

89 This is a retrospective study based on a review of consecutive patients' medical records who
90 were affected by uncomplicated primary RRD and underwent PPV with air tamponade at
91 IRCCS Sacro Cuore-Don Calabria Hospital in Verona (Italy) between 2017 and 2019. Patients
92 having undergone baseline as well as 1, 3 and 6-month follow-up postoperative visits were
93 included. Exclusion criteria were: axial length > than 26 mm; previous retinal surgery;
94 inadequate imaging due to low quality; any ocular condition that could influence best-corrected
95 visual acuity (BCVA), with the exception of lens opacity; and the absence of a complete 6-month
96 follow-up. All procedures adhered to the tenets of the Declaration of Helsinki. This study was
97 approved by the Institutional Review Board Committee of IRCCS Sacro Cuore-Don Calabria
98 Hospital and by the Ethical Committee of Verona and Rovigo (reference number: Prot. Negrar-
99 2020 K).

100

101 Patients were divided into two groups (macula-on and macula-off) according to macular
102 involvement in the RRD. At baseline and at each follow-up visit, a complete ophthalmic
103 examination was performed, including BCVA measurement, slit-lamp biomicroscopy,

104 intraocular pressure (IOP) evaluation, dilated fundus examination with a 90 diopters indirect
105 lens and SD-OCT evaluation (Spectralis HRA-OCT, Heidelberg Engineering GmbH,
106 Heidelberg, Germany). At baseline, axial length was also measured in phakic eyes (IOLMaster;
107 Carl Zeiss Meditec, Jena, Germany). A Snellen Chart was used for the assessment of BCVA
108 and converted into the logarithm of minimum angle of resolution (LogMAR) for statistical
109 analysis purposes. The semi-quantitative scale "counting fingers" was transposed into logMAR
110 2 and "hand motion" into logMAR 3 (Holladay 2004).

111
112 RRD duration was also considered and was defined as the length of time between the onset
113 of central or peripheral vision loss, and surgery as opposed to the length of time between
114 clinical evaluation and surgery. Macular microstructural changes were evaluated by OCT.
115 The hyperreflective outer retinal bands (external limiting membrane (ELM) and ellipsoid zone
116 (EZ)) were defined according to the International Nomenclature for OCT panel classification.
117 The ELM was defined as a discrete hyperreflective band at the outermost border of the outer
118 nuclear layer, located above the inner segment/outer segment (IS/OS) junction. The EZ line
119 was defined as the second hyperreflective band above the RPE. The following OCT features
120 were recorded at each visit: (1) external limiting membrane (ELM) integrity, (2) ellipsoid zone
121 (EZ) integrity, (3) the presence of cystoid macular edema (CME), (4) the presence of an
122 epiretinal membrane (ERM), and (5) the presence of subretinal fluid blebs (SBs). The integrity
123 of the foveal ELM and EZ was assessed as follows: line not visible or disrupted in at least one
124 scan (band defect) and continuous line in both the horizontal and vertical scans (intact band).
125 The same analysis was always performed also in fellow eyes to minimize potential bias
126 arising from artefacts. The eye-tracking dual-beam technology (TruTrack™ Active Eye
127 Tracking Software, Heidelberg Engineering, Heidelberg, Germany) mitigated eye movement
128 artefacts and ensured point-to-point correlations between the OCT scan and fundus images.
129 The "automatic real-time" (ART) function provided by the software was used to reduce noise
130 and increase image quality. With ART activated, multiple frames (B-scans) of the same
131 scanning location being performed during the scanning process, and only scans with elevated
132 ART (range 90–100) being considered. Follow-up visits were scheduled at 1, 3 and 6 months
133 after the operation.

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136 SURGICAL TECHNIQUE

137 All patients underwent the same surgical technique. General or local anesthesia was chosen
138 according to both the patient preference and the anesthesiologist's indication. Local
139 anesthesia was induced by retrobulbar nerve block. A 23-gauge PPV was performed using
140 EVA (Dutch Ophthalmic Research Centre, DORC, The Netherlands) or Constellation (Alcon,
141 USA) platform. Cataract surgery was also performed during the same procedure, on a case-
142 by-case basis as required. Patients underwent complete vitrectomy and peripheral vitreous
143 shaving. A posterior hyaloid separation from the retina was obtained if needed.
144 Perfluorocarbon liquid (PFCL) was used to reattach the retina. Subretinal fluid was drained
145 through retinal breaks during fluid-air exchange. The procedure was completed using 360°
146 endolaser photocoagulation around retinal breaks and on the peripheral retina. Postoperative

147 positioning was determined according to the retinal breaks position.

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150 STATISTICAL ANALYSIS

151 Demographic and clinical data were summarized using descriptive statistics, variability and
152 precision measures and plots. Statistical tests were used based on the type of variables, test
153 assumptions and sample dimension. All parameters were reported with 95% confidence
154 intervals. Statistical models were adjusted for covariates if necessary.

155 T-test and Wilcoxon rank-sum test were used to compare continuous variables in independent
156 groups whereas one-way analysis of variance was adopted to compare continuous variables
157 stratified in more than two groups. The Chi-square test and the Fisher test were used to
158 compare categorical variables.

159 Multivariate linear regression models and multivariate logistic models were used to model
160 continuous and binary dependent variables respectively.

161 A p-value of less than 5% was considered as statistically significant. Data were analyzed by
162 STATA vers. 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX:
163 StataCorp LLC.).

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167 RESULTS

168 Fifty-nine patients met the inclusion criteria. Macula-on group included 30 patients, while
169 macula-off group comprised 29 patients. Demographic and the baseline characteristics of
170 patients are summarized in Table 1. The two groups were homogeneous with no statistically
171 significant differences at baseline other than BCVA. Phacoemulsification was performed
172 together with PPV in 13 cases (22%) from within the entire cohort. The median interval
173 between symptoms being reported and surgery was 4 days for both groups and so was not
174 significantly different ($p = 0.85$).

175 In the macula-on group, the mean BCVA was 0.24 (SD 0.18) logMAR (20/35) at baseline,
176 and 0.14 (SD 0.16) logMAR (20/28), 0.13 (SD 0.21) logMAR (20/27) and 0.14 (SD 0.25)
177 logMAR (20/28) at 1, 3 and 6 months after surgery, respectively. In the macula-off group,
178 BCVA was 1.33 (SD 0.18) logMAR (20/400) at baseline, and 0.36 (SD 0.40) logMAR (20/45),
179 0.31 (SD 0.42) logMAR (20/40) and 0.20 (SD 0.25) logMAR (20/32) at 1, 3 and 6 months after
180 surgery, respectively. The difference in BCVA between the macula-on and macula-off groups
181 was statistically significant at baseline ($p < 0.01$), and at 1 month ($p = 0.01$) and 3 months ($p =$
182 0.05) after surgery, while there was no significant difference in BCVA between groups at 6
183 months after surgery ($p = 0.33$) (fig. 1).

184 In the macula-on group, no ELM or EZ defects were detected at any time point. In the
185 macula-off group, the number of eyes showing complete recovery of both the ELM and EZ at
186 1, 3 and 6 months after surgery is shown in figure 3. ELM and EZ foveal defects both
187 decreased progressively up to 6 months after surgery. At the end of follow-up, the ELM was
188 restored in 89.7% of the patients studied, while EZ reached completion in 86.2% of cases (fig.
189 2). Figure 3 also provides examples of macula-on and macula-off cases, in which the
190 progressive recovery of the ELM and EZ was observed during follow-up.

191 The analysis of the relationship between visual outcomes and outer retinal layers revealed a
192 higher mean BCVA when the ELM and EZ were restored. No significant relationship was
193 found between BCVA and ELM or EZ status 1 month after surgery ($p = 0.33$), and although a
194 clinical difference was reported 3 months after surgery, it was not statistically significant ($p =$
195 0.07). However, a statistically significant difference was found 6 months after surgery ($p =$
196 0.04) (fig. 4).

197 After surgery, 6 macula-off patients (20.7%) and 5 macula-on patients (16.7%) developed
198 CME, with no statistically significant difference between groups ($p = 0.69$). CME was
199 observed in 3 of 13 patients (23.1%) who underwent phacoemulsification and PPV, and in 6
200 of 46 cases (13.1%) in which PPV alone was performed. CME occurrence was significantly
201 more frequent when phacoemulsification and PPV were both performed ($p = 0.04$). In the
202 majority of cases, CME reabsorption was achieved within 3 months of topical 1%
203 prednisolone acetate tapering administration. In three cases, CME was still present at the end
204 of follow-up.

205 Three macula-off patients (10.3%) and 4 macula-on patients (13.3%) presented with SBs,
206 with no significant difference between groups ($p = 0.72$). ERM formation was not detected in
207 either group.

208 Of the patients that did not undergo phacoemulsification, clinically relevant cataract onset was
209 observed in 1 macula-off (3.5%) and in 2 macula-on patients (6.7%).

210 Only 1 case of RRD recurrence was observed in the macula-off group, which was due to PVR
211 development.

212 Multivariate logistic regression models revealed the following significant associations. 1 month
213 after surgery, ELM restoration was directly associated with preoperative macular non-
214 involvement (odds ratio, OR = 45.13, $p = 0.05$), while it was inversely associated with age
215 (OR = 0.83, $p = 0.02$) and EMC development (OR = 0.3, $p = 0.04$). At 3 months, ELM
216 restoration was directly associated with preoperative macular non-involvement (OR = 17.27, $p =$
217 0.03), while it was inversely associated with EMC development (OR = 0.03, $p = 0.02$). The
218 model could not reach statistical convergence for the 6-month follow up data, due to the
219 extremely low number of ELM disruption cases. As expected, 1 month after surgery, EZ
220 restoration was strongly associated with preoperative macular non-involvement (OR = 71.23,
221 $p = 0.01$). At 3 months, EZ restoration was strongly associated with preoperative macular
222 non-involvement (OR = 27.11, $p = 0.01$), while it was inversely associated with EMC

223 development (OR = 0.05, p = 0.03). A marginal inverse association with age was also found
224 (OR = 0.88, p = 0.07). As for ELM, the model could not reach statistical convergence for the
225 data regarding EZ recovery at 6 months. 1 month after surgery, BCVA was directly associated
226 with baseline BCVA (beta coefficient, $\beta = 0.10$; p = 0.05) and inversely associated with EMC
227 development ($\beta = 0.28$; p = 0.03). At 3 months, BCVA was directly associated with baseline
228 BCVA ($\beta = 0.13$; p = 0.03) and with EZ recovery ($\beta = -0.35$; p = 0.03). BCVA at 6 months was
229 directly associated with EZ recovery only ($\beta = -0.30$; p = 0.04). No significant associations
230 were found with SBs, RRD duration and RRD recurrence. Preoperative macular involvement
231 was not significantly associated with final BCVA ($\beta = 0.01$; p = 0.98), confirming the results of
232 the direct comparison between macula-on and macula-off BCVA at 6 months. No statistically
233 significant association was found between preoperative macular involvement and RRD
234 duration (OR = 1.00, p = 0.84).

235

236 **DISCUSSION**

237 Despite successful retinal reattachment, functional results can vary greatly among eyes
238 treated for RRD. With the SD-OCT introduction, several studies have demonstrated that outer
239 retinal layer defects correlate with low visual gain after surgery in patients with macular
240 involvement³⁻⁸.

241 Wakabayashi was amongst the first to study SD-OCT foveal changes after RRD
242 surgery. They found that the postoperative recovery of the ELM may serve as a predictive
243 factor for the subsequent restoration of the photoreceptor layer⁴. Shimoda observed a
244 gradual IS/OS line recovery after PPV with sulfur-hexafluoride (SF₆) tamponade. Six months
245 after surgery, a disrupted IS/OS line was observed in 3 eyes (17%), a foveal detachment in 6
246 eyes (33%), and a continuous IS/OS line in 9 eyes (50%), with a significant association
247 between BCVA and IS/OS line restoration⁵. Other studies reported similar postoperative ELM
248 and EZ recovery rates^{3,6}. Although we have reported a higher outer retinal band recovery
249 rate, our data suggest an association between outer retinal layer recovery and BCVA
250 improvement after surgery. However, limitations of sample size have resulted in relatively few
251 EZ recovery cases in our study, especially at 6 months, which has affected the statistical
252 robustness of our findings (fig. 2, 4).

253 Park identified the detachment extent, macula-off duration, and ELM integrity as being
254 preoperative prognostic factors potentially influencing functional RRD surgery outcomes.
255 Postoperative EZ recovery was also found to impact the final visual outcome. The mean
256 macula-off duration was 18.44 ± 60.54 days. The final BCVA in patients with a macula-off
257 duration lasting less than a day, was significantly higher than in patients with a macula-off
258 duration lasting more than 7 days. However, there were no statistically significant differences
259 when compared with cases of macula-off duration lasting between 1 and 7 days⁸. Malosse
260 reported EZ and ELM defects in 100 (47.2%) and 64 (30.2%) eyes respectively, 1 month
261 after surgery and in 44 (17.4%) and 18 (7.1%) eyes respectively, 6 months after surgery. The
262 median macula-off duration was 5.0 days (range 1–90) and a multivariate analysis showed
263 that the duration of macular detachment was the only factor associated with ELM and EZ
264 damage at 6-months.⁷ While mean RRD durations, and ELM and EZ recovery rates that are

265 similar to our findings, other studies demonstrated that shorter delays in surgery correlate with
266 better ELM and EZ recovery and BCVA improvement⁹⁻¹¹. In addition, Narala have
267 demonstrated a significant positive association between photoreceptor volume, BCVA and
268 short surgery wait time¹².

269 Studies on animal models show that cell apoptosis occurs within hours of RD induction,
270 peaking at 2 to 3 days, and dropping at 7 days^{13, 14}. Diederer found that visual acuity rapidly
271 worsened when the macular detachment lasted longer than 6 days, concluding that surgical
272 repair can be undertaken within 7 days of macular detachment without negatively affecting
273 visual outcomes¹⁵. However, Frings reported a narrower time frame, observing worse final
274 visual outcomes from 3 days of macula-off RRD¹⁶. Taken together, these data support the
275 importance of a prompt RRD surgical repair. Interestingly, we have not observed any
276 significant difference in the final BCVA between macula-on and macula-off patients. This
277 might suggest that the short interval between diagnosis and surgery allowed us to minimize
278 functional impairment even in cases of macula-off RRD. This is an intriguing point that could
279 prompt a revision of current practices where macula-on RRD patients are prioritized for
280 surgery over macula-off cases. As such, surgery timing should carefully consider RRD
281 duration.

282 Regarding complications, CME development occurred in about 6.5% of patients in our study,
283 with a similar prevalence the 2 groups. According to our regression models, it seemed to
284 affect ELM and EZ healing processes and, at least in the first part of the follow-up, BCVA
285 recovery. In the majority of cases, topical steroids were able to resolve this complication by
286 the follow-up. Our data suggest that CME could slow and critically compromise both
287 microstructural and functional recovery. In our series, patients who had undergone combined
288 surgery, showed a significantly higher CME prevalence during follow-up. Conversely, other
289 studies have not found any significant difference in CME prevalence between combined
290 surgery and PPV alone¹⁷. Some publications have speculated that the breakdown of the
291 blood–aqueous–barrier due to cataract surgery and of the blood–retinal barrier due to
292 vitrectomy together could cause stronger ocular inflammatory responses in RRD eyes,
293 leading to a higher reoperation rate following combined surgery than after PPV alone¹⁸.
294 However, this hypothesis is not widely confirmed by the literature. Other authors have
295 hypothesized that 360° retinopexy could increase CME risk¹⁹. In our surgical practice, 360°
296 retinopexy is performed in both combined surgery and in PPV alone. Further studies are
297 required, on larger series, to confirm the higher EMC prevalence in cases of combined
298 surgery that were observed in our study. Moreover, cases of EMC that persist for more than 6
299 months after surgery should be monitored for any resolution at a later time point. Preoperative
300 and intraoperative factors should also be examined to better predict the postoperative EMC
301 risk in patients treated for RRD.

302 SBs are relatively common after scleral buckling procedures having been described since the
303 1980s²⁰. They are confirmed by OCT in about 9% of buckling procedures²¹. Their
304 mechanism of formation has not yet been clarified, but they usually disappear spontaneously
305 within a year. Some authors have speculated that they could originate from vascular changes
306 resulting from cryotherapy used during scleral buckling procedures²¹, but it has been recently
307 demonstrated that they can also occur after PPV^{22, 23}. However, in our study, no significant

308 difference in SBs prevalence was demonstrated between macula-on and macula-off RRDs ⁴.
309 Another study has found that subfoveal located blebs may slow visual recovery, although the
310 final BCVA outcome is not affected ³. In our study, BCVA recovery was not affected by SBs at
311 any time point.

312

313 **CONCLUSIONS**

314 The main limitations of this study arise from its retrospective nature. However, taken together,
315 our data suggest that prompt surgery for macula-off RRD allows the recovery of outer retinal
316 layers in the majority of cases. As a consequence, a high degree of visual gain can be
317 achieved after surgery for RRD, regardless of macular involvement.

318

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325

326 **Statement of ethics:**

327

328 Patients have given their written informed consent.

329

330 The authors have no ethical conflicts to disclose.

331 Ethical Review Board: Ethical Committee of Verona and Rovigo (reference number: Prot. Negrar-2020 K).

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334 **Author contribution:** all the authors fulfill the ICMJE Criteria for Authorship

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336 **Word count:** 3233

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 394
 395
 396

397 **FIGURE CAPTIONS**

398
 399 Fig.1. Best corrected visual acuity (BCVA) changes during the follow-up in macula-on and
 400 macula-off patients. BCVA is expressed as a logarithm of minimum angle of resolution
 401 (LogMAR). The difference between macula-on and macula-off patients was significant at
 402 baseline, and 1 and 3 months after surgery, whereas no significant difference was observed 6
 403 months after surgery. Asterisks indicate a statistically significant difference between the two
 404 groups ($p < 0.05$).

405
 406 Fig. 2. External limiting membrane (ELM) and ellipsoid zone (EZ) recovery rate during the
 407 follow-up in macula-off patients.

408
 409 Fig. 3. Follow-up in a case of macula-on (A-D) and another of macula-off (E-H)
 410 rhegmatogenous retinal detachment (RRD). Both the ELM and EZ in the preoperatively
 411 detached retina progressively recovered during the follow-up. Preoperative (A, E). 1 month
 412 after surgery (B, F). 3 months after surgery (C, G). 6 months after surgery (D, H).
 413

414 Fig. 4. The relationship between best corrected visual acuity (BCVA) and external limiting
 415 membrane (ELM) and ellipsoid zone (EZ) recovery during the follow-up in macula-off patients.
 416 No significant relationship was found at 1 month ($p=0.33$); however, a clinical difference that
 417 was not statistically significant was found at 3 months ($p=0.07$), and a statistically significant
 418 difference was found at 6 months after surgery ($p = 0.04$). ELM- EZ- = neither ELM nor EZ
 419 recovery; ELM+ EZ- = ELM recovery; ELM+ EZ+ = ELM and EZ recovery. Asterisks indicate
 420 a statistically significant difference between the two contiguous points ($p < 0.05$).