

1 **Title:** Systematic bias in real world tonometry readings based on laterality?

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3 **Running title:** Systematic bias in real world tonometry

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17

18 **Abstract**

19 **Aims:** In research settings, the first eye examined tends to have a higher intraocular pressure (IOP)
20 than the second. We sought to verify whether clinicians in Yorkshire, UK, measure IOP in right eyes
21 before left and whether such behavioural factors affect IOP readings at the population level.

22 **Methods:** We observed 128 IOP measurements taken by 28 ophthalmologists using Goldmann
23 applanation tonometry (GAT) over a four-month period in 2018, recording which eye was examined
24 first. All IOP measurements on electronic patient records for Leeds Teaching Hospitals NHS Trust, UK,
25 between January 2002 and June 2017 were extracted, yielding IOP readings for 562,360 eyes,
26 analysed for evidence of systematic bias in IOP measurement.

27 **Results:** Right eye IOP was measured before left in 112/128 observations (87.5% (95% CI: 75.2%-
28 94.2%)). For IOP measured by GAT, there was no statistically significant difference ($p=0.121$)
29 between right and left eye IOP (mean IOP 16.95mmHg and 16.96mmHg respectively). Even values of
30 IOP were reported more frequently than odd values (136,503/214,628 (63.6%) were even). Identical
31 IOP readings for both eyes were recorded in 124,392/254,380 patients (48.9%) who had both eyes
32 measured.

33 **Conclusions:** Our study found no IOP difference based on laterality, but strong evidence of certain
34 trends associated with IOP measurement by GAT, such as a preference for even values and the same
35 IOP being recorded for both left and right eyes. Such effects may be explained by behavioural
36 aspects of GAT and suggest that there are substantial opportunities for improvement in the way GAT
37 is utilised in real world settings.

38

39 Introduction

40 Glaucoma is the third most common cause of blindness globally after cataract and uncorrected
41 refractive error, and despite increases in understanding of the aetiology, intra-ocular pressure (IOP)
42 remains the primary modifiable risk factor for progressive glaucomatous visual loss.[1] In
43 undertaking a large population-based cohort study in Nakuru, Kenya, which included measurement
44 of participants' IOP, it was noted that the IOP of right eyes were significantly higher than the fellow
45 left eyes.[2-4] This same observation has been described by other studies that report IOP difference
46 between right and left eyes,[5-8] despite no known physiological difference between right and left
47 eyes that could explain this difference. If this research finding were also present in routine clinical
48 practice, then a systematic bias in IOP measurement could lead to a systematic overtreatment of
49 right eyes relative to left, which at a population level may have implications for clinical outcomes
50 and resource allocation.

51 The possibility of publication or reporting bias exists, in that it would be of little interest to report
52 the finding that no difference was found in the IOP readings of right and left eyes in a population.
53 However, a prospective study prompted by the statistically significant finding from the Ocular
54 Hypertension Treatment Study (OHTS) that right eyes were 0.3 (SD +/-2.8) mm Hg more
55 hypertensive than left, demonstrated that IOP is measured higher in the first eye examined,
56 regardless of whether that is the left or right eye.[9]

57 The reason for the first examined eye being measured as having a higher IOP than the second eye, is
58 conjectured to relate to patients squeezing their lids or inadvertently performing a Valsalva
59 manoeuvre as they hold their breath for the first eye, which have both been shown to elevate
60 IOP.[9, 10] Patients squeezing their eyes during tonometry has been shown to reduce with
61 subsequent IOP readings,[9] which offers an explanation for the relatively lower second eye IOP
62 measurement. The reduced squeezing/Valsalva at second eye measurement would be compounded

63 by the fact that the elevated IOP during squeezing is expected to increase ocular outflow, thereby
64 tending the second examined eye to have a lower IOP on relative relaxation.

65 As with OHTS, the directionality of the difference in IOP (Right > Left) from the Nakuru data could be
66 explained by the examination protocol which stipulated that right eyes were to be examined first.[2]

67 The existence of corroborating studies reporting this same finding, and the absence of conflicting
68 results with no studies found identifying left IOPs higher than right, is postulated to be an artefact of
69 the prevailing culture within clinical ophthalmology and ophthalmic research to examine right eyes
70 first. There is no published evidence, to our knowledge, of the level of adherence of
71 ophthalmologists to the perceived cultural norm of examining right eyes before left eyes, and no
72 published report demonstrating the extent to which IOP readings between right and left eyes differ
73 in routine clinical practice.

74 We determined to verify, by opportunistic observation of clinicians performing tonometry, whether
75 ophthalmologists in Yorkshire (UK) routinely examine right eyes prior to left in their day-to-day
76 practice. We also sought to evaluate whether this cultural practice, if verified, has implications for
77 right and left IOP readings over a large population.

78

79 **Subjects and methods**

80 To test the perception that ophthalmologists are habituated to check the IOP in the right eye first,
81 three ophthalmologists from Leeds Teaching Hospitals NHS Trust (LTHT) recorded, in the passage of
82 their daily work, which eye was examined first by any colleague observed using any form of
83 tonometry over a four-month period in 2018. They recorded the grade of the clinician being
84 observed to differentiate those within the 7-year ophthalmic training programme termed “trainees”
85 and those termed “senior”, being in career positions (consultant, staff grade or associate specialist).
86 The method of tonometry was recorded being divided between Goldmann Applanation Tonometry

87 (GAT), rebound tonometry with iCare (Icare Oy, Vanda, Finland), and air puff using Reichart
88 tonometer (Reichert Technologies, Buffalo, NY, USA). The GAT is a manual, analogue device whilst
89 the rebound and air puff tonometers are semi-automated, digital devices. It was recorded which eye
90 was measured first, and whether the clinician then went back to the first eye again to recheck IOP a
91 second time.

92 Search was performed of the electronic patient record (Medisoft Ltd, Leeds, UK) for Leeds Teaching
93 Hospitals NHS Trust between 1st January 2004 and 31st August 2016 including any IOP reading with
94 applanation, air puff or rebound tonometry. Statistical analysis was performed, and all figures
95 generated using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX:
96 StataCorp LLC). IOP for each eye was recorded and the electronic patient record enforces recording
97 of method of testing. This is a large teaching hospital, so includes specialist clinics such as glaucoma
98 clinics, but local referral patterns mean that there is not a large burden of tertiary referral patients
99 with complex glaucoma. The case-mix at this hospital, therefore, closely reflects the ophthalmic
100 needs of the catchment population, and can be taken as representative of a typical case mix of a UK
101 hospital providing comprehensive ophthalmic services.

102 Ethical approval for the Nakuru cohort study was obtained as reported previously,[2] and separate
103 ethical approval from the London School of Hygiene and Tropical Medicine Research Ethics
104 Committee was obtained for the observations from Yorkshire.

105 For the observations of ophthalmologists, the proportion of examinations where the right IOP was
106 the first to be measured (without subsequent return to this eye for repeat testing) was estimated.
107 The confidence interval was adjusted to allow for the clustering of observations by ophthalmologist,
108 as some individuals were observed multiple times.

109 From the electronic patient record, IOP summary statistics were reported along with the
110 distributions of IOP illustrated by IOP measurement method. Two other sources of bias beyond the
111 differences between right and left eyes were described; the proportion of even and odd number

112 values and the proportion of pairs of eyes with exactly the same IOP in each eye. A paired t-test was
113 performed to identify any systematic bias in the IOP between eyes. The expected proportion of even
114 and odd values for IOP was 50%, so a one-sample Z test was used to test whether the proportion
115 was different from this.

116

117 **Results**

118 **Practice of ophthalmologists in Yorkshire**

119 Twenty-eight ophthalmologists (12 senior and 16 trainees) were observed during 128 patient eye
120 examinations (44 by senior and 84 by trainee ophthalmologists), checking the IOP using GAT on both
121 eyes between 3rd January and 30th April 2018.

122 Of the 128 observations, 112 recorded the right eye being checked first without any return to the
123 first eye for repeat testing, resulting in an estimated prevalence of this practice of 87.5% (95% CI:
124 75.2%-94.2%).

125 Among observations of senior ophthalmologists, 95.5% of examinations followed this practice,
126 compared with 83.3% of those by trainees. This suggests a trend toward increased adherence to the
127 perceived cultural norm with seniority, however, evidence of a true difference between these
128 groups is weak ($p=0.125$).

129 **Leeds IOP Data Results**

130 The IOP of 562,360 eyes were obtained from 308,044 patients aged 0-114 years, attending Leeds
131 Teaching Hospitals NHS Trust between 1st January 2002 and 30th June 2017. The majority of patients
132 (85.7%) had their IOP measured using GAT, with the remaining patients having their IOP measured
133 using the rebound method (11.7%) or air puff (2.6%).

134 Overall, mean IOP in the eyes measured was 16.6mmHg (SD 5.0mmHg). Where GAT was used, the
135 mean IOP was 16.9mmHg (SD 4.9), in rebound 14.9mmHg (SD 5.4) and air puff 15.9mmHg (SD 5.5).
136 Comparing right and left IOP where GAT was used (and restricting to only the 214,628 who had IOP
137 in both eyes recorded using GAT) found a mean IOP for right eyes of 16.95 mmHg (SD 4.9) and left
138 eyes mean IOP of 16.96 mmHg (SD 4.8). Resulting in an observed difference of 0.01mmHg (left IOP
139 higher than right) but no evidence of a true systematic difference between eyes ($p = 0.121$).
140 The distributions of IOP were right-skewed (Figures 1a-c) and when using GAT, a clear even digit
141 preference was observed (Figure 1a). For GAT measurements, even values of IOP were reported with
142 greater frequency than odd (136,503/214,628 (63.6%) of observations were even, $p < 0.0001$ from
143 one-sample Z-test). No material difference between odd and even numbers was observed when
144 either of the two electronic measuring techniques were used (49.9% even values with Air-puff,
145 50.7% even with rebound).
146 There were 254,380 patients who had the IOP of both right and left eyes measured. The distribution
147 of the difference in the IOP in the right and left eyes (IOP in right eye minus IOP in left eye) for each
148 measurement is shown in figures 2a-c. When using air puff or rebound tonometry (figures 2b and 2c)
149 the data were normally distributed. However, when using GAT there were far more patients with an
150 identical IOP recorded in both eyes than would be expected (figure 2a), in fact 124,392/254,380
151 patients (48.9%) of patients had the same IOP in each eye.

152

153 **Discussion**

154 With repeated published studies showing that, under research protocol conditions, the first eyes
155 measured have systematically higher pressures than the second eyes measured, it was considered
156 an important research question to see if this same effect was at play in routine clinical practice. Our
157 assumption that there is a prevailing cultural norm within ophthalmology to examine right eyes first

158 was borne out by observations of colleagues measuring IOP, with seven out of every eight
159 measurements following that pattern, and although evidence of a difference between senior and
160 more junior ophthalmologists was weak, the seniors were observed more often to adhere to this
161 unwritten rule.

162 The effect of this cultural norm on the population of right and left eye IOP readings was evaluated by
163 examining routinely collected data from over half a million readings on our electronic patient record
164 – and no meaningful difference between right and left measurements was found. GAT is the
165 established gold-standard method of IOP measurement, with some well described sources of
166 error,[11] however, analysis of our data has raised more questions than anticipated.

167 A very strong preference for even numbers was found with GAT, being recorded with almost double
168 the frequency of odd numbers (63.6% versus 36.4%). Non-human IOP measuring methods (rebound
169 and air puff) did not exhibit this same even number preference, clearly indicating that there is a
170 substantial behavioural element to our measurement of IOP with GAT or recording thereof. This
171 even number preference has been demonstrated before to a very modest extent in a 1966
172 population based study.[12]

173 Further demonstration of behavioural biases is given by the fact that around half of all pairs of
174 readings using GAT had both right and left eyes with exactly the same IOP. It should be expected
175 that plotting a graph of the difference between right and left eye IOPs would form a normal
176 distribution centred around zero (which is what was observed in the non-human measuring
177 methods); or, if we factor in the effect of first eye measurement being higher than second as
178 demonstrated in RCT and previous epidemiological surveys, we could expect a normal distribution
179 centred around 0.3mmHg. However, the distribution is far from normal, which again suggests that
180 factors other than “the actual IOP” influence the recorded IOP. Candidate explanations for the “even
181 number preference” and the “same-IOP preference” found with GAT centre around the way that IOP
182 is tested with GAT in real-life settings.

183 In a research setting, IOP testing protocols are set out that dictate a highly standardised method,
184 such as *“with one examiner measuring the IOP and rotating the tonometer dial and a second*
185 *examiner reading and recording the IOP measurement from the tonometer dial. The tonometer dial*
186 *was rotated to 10mmHg prior to all measurements.”*[9] A description of real-world IOP
187 measurement might describe *“testing of the right eye first with the dial starting at whatever IOP*
188 *reading the previous patient happened to have had; a mental note is then taken of the nearest even*
189 *number to the dial reading before moving to the left eye – which if it is approximately the same will*
190 *be recorded as such, but if the mires are far apart then the dial will be adjusted to the best-fit even*
191 *integer”*.

192 The observations in this study might encourage further exploration of the extent to which
193 ophthalmologists can be encouraged to adopt research quality protocols in their daily IOP checking
194 routines. The argument for the continued promotion of GAT in clinical practice is that glaucoma
195 research has, for decades, been based on GAT – and all guidelines and treatment thresholds are
196 based on this GAT driven data. The inference is that clinical decisions based on that research must
197 therefore also utilise GAT. However, our study suggests that what is occurring in research settings
198 and what is occurring in real-life clinics, whilst both being referred to as GAT, are not the same thing.
199 “Real-world GAT” may be no more similar to “Research-GAT” than the rebound and air puff
200 techniques, which were not found to have the same problems with biases and might therefore not
201 be as inferior in routine practice as is sometimes suggested. Better adherence to gold standard
202 behaviour in GAT would be expected to be totally achievable but requires inculcation from the
203 inception of ophthalmic training to create good habits that can last a career.

204 Promotion of the use of GAT that more closely adheres to research standards would be the
205 preferred option, as although a move towards increased utilisation of non-human methods of IOP
206 measurement would eliminate behavioural biases, it would require extensive investigation of the

207 validity of applying management principles established by GAT-based research to clinical practice
208 based upon another method of IOP measurement.

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216

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261

262 **Figure 1: Histogram of IOP for each measurement method (a) GAT, (b) Air-puff and (c) Rebound.**

263 **The graphs are curtailed at 40mmHg as each have a few extreme observations.**

264

265 **Figure 2: Histogram of differences in IOP between individuals' eyes (right eye – left eye) IOP for**

266 **each measurement method (a) GAT, (b) Air-puff and (c) Rebound. A curve representing the**

267 **expected distribution if the data were normally distributed around zero is overlaid. Graphs are**

268 **curtailed at +/- 15mmHg.**

269

Figure 1

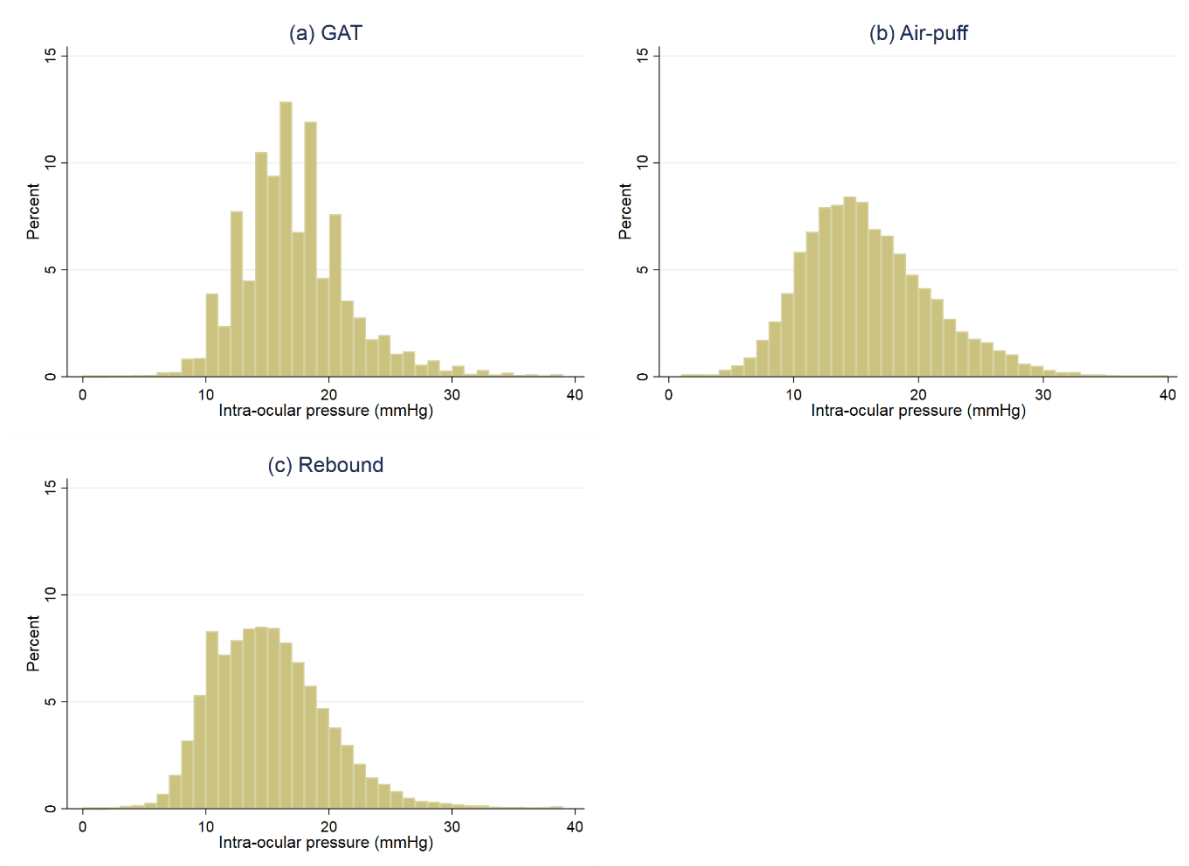


Figure 2

