Comparison of Corneal Pulse Entropy to Distinguish Healthy Eyes from Those with Primary Open-Angle Glaucoma

Michał M. Placek, Patryk M. Ząbkiewicz, and Monika E. Danielewska
Department of Biomedical Engineering, Faculty of Fundamental Problems of Technology,
Wrocław University of Science and Technology, Wrocław, Poland
Emails: michal.placek@pwr.edu.pl, 221394@student.pwr.edu.pl, monika.danielewska@pwr.edu.pl

***Abstract*—Corneal Pulsation (CP), as one of the manifestations of eye dynamics, has shown a great potential in the glaucoma diagnosis. The morphology of the CP signal, acquired noninvasively with a non-contact ultrasonic technique, has been found to alter in glaucoma patients. The aim of this preliminary study was to ascertain whether complexity of the CP signal may be a useful parameter to differentiate glaucoma patients from healthy individuals. *Refined Composite Multiscale Fuzzy Entropy* (RCMFE) was considered as a complexity measure. RCMFE of the CP signal was calculated in 25 glaucoma patients and 25 healthy subjects. Statistical analysis showed that, on average, glaucomatous eyes were characterized by higher entropy of the CP signal than healthy ones. This result suggests that RCMFE of the CP signal may support ophthalmologists in glaucoma diagnosis in its early stages.**

Keywords–multiscale entropy; corneal pulsation; glaucoma diagnosis.

I. INTRODUCTION

Corneal Pulsation (CP) reflects temporal corneal expansion related to ocular dynamics [1] and cardiovascular activity [2]. It has been shown that morphology of the noninvasively acquired CP signal changes with advancing age [3]. These specific changes, in the form of a double-peak wave in the CP signal during one heart cycle, have been named the Ocular Dicrotic Pulse (ODP) [4]. ODP has been detected more frequently in glaucoma patients than in healthy individuals, which has been explained by higher ocular rigidity of glaucomatous eyes [4][5].

Detection of ODP signal from the CP signal alone is not straightforward, since the CP signal is often noisy, irregular, and non-stationary. To overcome this problem, it has been proposed to synchronously measure reference cardiovascular signals—such as blood pulse or ECG, which, in contrast to the CP signal, exhibit clearly defined peaks—and to use, e.g., *Dynamic Time Warping* to synchronize these two classes of signals [3] and the wavelet transform to analyze the CP signal without the synchronization [6]. However, there is still a need to find such a feature of the CP signal, which would enable differentiating glaucoma patients from healthy subjects, without the necessity of explicit identification of the ODP signal or measurements of any auxiliary cardiovascular signal. To address this need, we propose to use the multiscale entropy algorithm to evaluate signal complexity.

Many previous studies have already shown that entropy of various physiological signals is altered in a wide range of pathological states [7][8]. To the best of our knowledge, entropy of the CP signal has never been considered so far. The aim of this preliminary study was to ascertain whether this entropy based approach applied to the CP signal is sufficient to differentiate Primary Open-Angle Glaucoma (POAG) patients from healthy individuals. The paper is organized as follows: Section 2 describes material and methods, Section 3 contains results, Section 4 discusses and concludes the study.

II. MATERIAL AND METHODS

The study sample consisted of 25 patients (8 males and 17 females) with POAG, aged from 59 to 79 (69.1 ± 6.0 years, mean ± SD), and a control, age-matched group of 25 healthy subjects (8 males and 17 females; 65.2 ± 6.4 years). Exclusion criteria were: systemic diseases, any previous ocular surgical procedure, conjunctival or intraocular inflammation, and corneal abnormalities such as edema or scars. Before the measurements, the purpose of the study and the protocol were explained to the participants. Afterwards, signed informed consent form was obtained from all patients and controls. The study had been approved by the Bioethics Committee of the Military Institute of Medicine in Warsaw (decision No. 67/WIM/2015) and adhered to the tenets of the Declaration of Helsinki.

Measurements of the CP signal of the glaucomatous eye in POAG patients and randomly selected eye in healthy subjects were performed using a non-contact ultrasonic distance sensor. The sensor allowed 10-second continuous data acquisition with the sampling frequency set to 400 Hz and *in-vivo* measurement of the CP amplitude with an accuracy below 1 μm [9]. For each eye, CP measurements were repeated five times and then three good-quality recordings, not affected by eye blink artifacts, as evaluated by an expert, were chosen for further analysis.

After preprocessing, including filtering in the range of 0.5–20 Hz and removing linear trend, signal entropy was estimated using the *Refined Composite Multiscale Fuzzy Entropy* ($RCMFE_\mu$) [8] up to scale factor No. 50. $RCMFE_\mu$ is defined as a sequence of fuzzy entropies computed for selected scale factors, where consecutive scales correspond to decreasing granularity of the analyzed time series. The average value of $RCMFE_\mu$ was calculated from three repeated measurements for each participant and scale factor. Since the null hypothesis of normality of $RCMFE_\mu$ was not rejected by the Kolmogorov–Smirnov test, the values obtained for each scale were compared between the two groups using the unpaired *t*-test. In the range of scales where *p*-values were below a significance level $\alpha = 0.05$, scale-averaged entropies

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were computed for each participant and finally compared between the two groups using the unpaired *t*-test.

III. RESULTS

Figure 1a shows group-averaged values of $RCMFE_{\mu}$ represented as a function of scale factor in the two groups, whereas Figure 1b presents results of statistical comparison between the groups for each scale factor. It can be seen that mean values of $RCMFE_{\mu}$ are significantly different between the groups for scales in the range of 25–34. Results of the unpaired *t*-test applied for entropies averaged over the abovementioned scale range are shown in Figure 2.

IV. CONCLUSION AND FUTURE WORK

According to the decomplexification theory of illness, a loss in complexity is usually associated with pathological states [10]. Hence, it could be expected that a glaucomatous eye should be characterized by lower entropy of the CP signal than a healthy one. Our results, however, reveal the opposite tendency, which can be related to higher ocular stiffness (higher mechanical resistance of cornea) in glaucomatous eyes caused by the elevation of intraocular pressure [11]. Nevertheless, $RCMFE_{\mu}$ applied in this study satisfied our goal, as the measure was sensitive enough to differentiate between glaucoma patients and healthy subjects without the need for detecting the ocular dicrotism. To obtain results with higher degree of confidence, the analysis should be repeated on a larger study sample. More male participants need to be recruited if gender-specific differences are to be investigated. Ten-second measurements of the CP signal

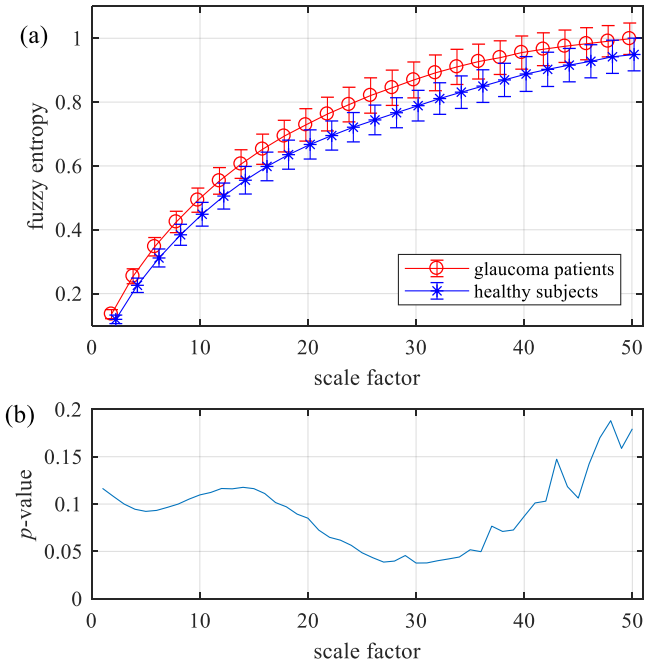

Figure 1. Refined composite multiscale fuzzy entropy ($RCMFE_{\mu}$) of the corneal pulse (CP) signal. (a) Means of grouped data ± 1.96 standard error of means. For better visibility, only even numbers of scale factor are shown. (b) *p*-values resulting from the comparison between the two groups using unpaired *t*-test.

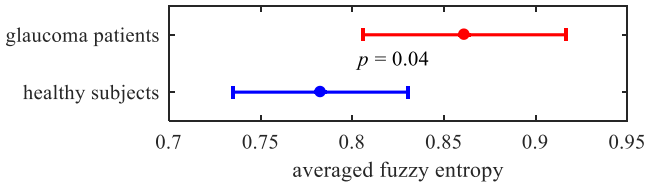

Figure 2. Mean values of scale-averaged entropies ± 1.96 standard error of means. Entropies were averaged in the scale range 25–34.

appear to be sufficiently long to reliably estimate entropy using $RCMFE_{\mu}$. The proposed $RCMFE_{\mu}$ of a CP signal may, in the future, constitute a sensitive indicator of changes in ocular stiffness and support ophthalmologists in glaucoma diagnosis in its early stages.

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