Repeatability of corneal biomechanics waveform signal parameters derived from Ocular Response Analyzer in children

Abstract

Purpose: To investigate the repeatability of waveform signal parameters, measured with the Ocular Response Analyzer (ORA), in children.

Methods: Two sets of ORA measurements, with a 10-min break between them, were performed on children, aged six to <11 years old, either wearing single-vision spectacles (SVS) or orthokeratology (ortho-k) lenses. Intraclass correlation coefficients (ICCs) were used to assess agreements between two sets of measurements (37 waveform signal parameters). Bland-Altman (BA) plots were used to further analyse waveform signal parameters which have ICC 95% confidence interval (95% CI) between 0.50 to >0.90 (regarded as moderate to excellent agreement).

Results: A total of 30 subjects [15 SVS, 15 ortho-k (3.6 ± 2.4 months)] completed the study. Since no significant between-group differences were detected in demographic data (p > 0.28) and all waveform signal parameters (p > 0.05), data from the two groups of subjects were pooled for the analysis of repeatability. Six parameters, h2, h21, p1area, p1area1, p2area, and p2area1, achieved ICCs (95% CI) of 0.82 - 0.85 (0.61 - 0.93). The mean (SD) of these six parameters were 372 (91), 248 (61), 4077 (854), 1762 (399), 2359 (670), and 1020 (300), respectively. Bland-Altman plots and 95% limits of agreement (95% LoA) showed considerable agreement for all six parameters, the mean difference (95% LoA) were -3 (-101 to 94), -2 (-67.56 to 62.70), 111 (-723 to 946), 102 (-334 to 539), 25 (-718 to 768), and -3 (-

350 to 343), respectively.

Conclusions: Six waveform signal parameters (h2, h21, p1area, p1area1, p2area, and p2area1), which represent or are related to the areas under the waveform at the peaks in the signal, could achieve moderate to excellent agreement in children. Results of the current study provides fundamental information for further studies on the potential clinical application of these waveform signal parameters in children.

Keywords: Corneal biomechanics, orthokeratology, myopia

Introduction

The cornea is composed primarily of collagen fibrils. The stroma, which contributed to 90% of the total thickness of a hydrated human cornea, was lamellated by layers of well organised collagen fibrils and proteoglycan matrix. These corneal structures are associated with the corneal biomechanical properties [1]. Many factors could affect the corneal structure, including normal ageing, the level of corneal hydration, and pathologies [1]. Understanding the corneal biomechanical properties may therefore help to understand the effects of disease on cornea. Many methods had been developed to fulfil the compelling need of the investigation on corneal biomechanical properties.

Before the introduction of the dynamic bidirectional applanation device (Ocular Response Analyzer (ORA), Reichert Ophthalmic Instruments, Buffalo, NY) [2], corneal biomechanical properties could only be measured under a laboratory setting [3–5]. ORA measures corneal biomechanical properties in-vivo under a clinical setting by quantifying the change in corneal shape induced by the applanation of an air-puff. During the measurement, infrared light is emitted to the surface of cornea. Its signal intensity and the pressure of the air-puff are recorded during the whole period of corneal deformation (Figure 1).

The two basic ORA deprived parameters, corneal hysteresis (CH) and corneal resistance factor (CRF), have been shown to be affected by or associated with several corneal conditions and pathologies [6–9]. A higher reduction in CH has been shown in glaucoma patients [9]. A significantly lower CH and CRF was reported in eyes with keratoconus [7]. CH, combined with central corneal thickness, can enhance the diagnosis of glaucoma [8]. However, the clinical utility of CH and CRF was limited because of the differences between normal and problematic eyes were small with a relatively high standard deviation [10,11]. This resulted in a low sensitivity and specificity for clinical diagnosis.

Besides CH and CRF, the analysis of the waveform signal could provide more information on the corneal biomechanical properties [12,13]. CH and CRF depend on the two pressure measurements at corneal applanation during both inward and outward movements, which different waveform signal morphologies could generate the same CH and CRF values [14]. Thirty-seven parameters can be derived from the features of the waveform signal of ORA. Each waveform signal parameter represents a specific physical meaning related to the features of the signal. They can be divided into seven groups according to their represented features. The groups are height (h1, h2, h11 and h21), width (w1, w2, w11 and w21), slope (uslope1, upslope2, uslope11, uslope21, dslope1, dslope2, dslope11, dslope21, slew1, and slew2), length (mslew1, mslew2 , dive1, dive2, path1, path2, path11 and path21), area (p1area, p2area, p1area1 and p2area1), aspect ratio (aspect1, aspect2, aspect11 and aspect21), the degree of irregularity (aindex and bindex), and the high frequency noise between two peaks (alphf). These waveform parameters could associate with the corneal biomechanical properties. A greater width could be related to a stiffer cornea [12], a larger area under peak 1 could relate to a softer cornea [12] and a larger area under peak 2 could represent a cornea with a better ability in energy damping [15]. Some of the waveform signal parameters have been shown to have potential in providing more information than the basic parameters in keratoconic patients [16–18].

However, before exploring the potential clinical applications of these corneal biomechanical parameters, there is a need to determine the repeatability of the measurements. The repeatability of CH and CRF measurements has been evaluated by several studies both in adults and children [19–25], however, waveform signal parameter repeatability has only been determined in adults [26]. Since children may have more difficulty with steady fixation compared to adults, which can affect ORA measurements [27], this study aims to investigate the repeatability of the waveform signal parameters in children.

Methods

Chinese children, aged six to <11 years old, who wore single-vision spectacles (SVS) or orthokeratology (ortho-k) lenses, participating in myopia studies conducted at The Hong Kong Polytechnic University, were recruited. For detecting the smallest possible value of 0.70 for ICC (two observations per subject) with a power of 0.90 and alpha value of 0.05, at least of 15 subjects were required [28]. All procedures in this study followed the Declaration of Helsinki and the protocol was reviewed and approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. Informed consent and assent from parent(s) and subjects, respectively, were obtained before measurements were performed.

At the commencement of the study, all subjects had myopia 0.50 to 4.00 D and with-the-rule (axes 180 ±30) astigmatism (negative cylinder) not more than 1.25 D or 0.50 D at other axes. The between-eye difference in spherical equivalent refraction was equal to or less than 1.50 D. All subjects either had been wearing ortho-k lenses for one to six months or had no prior experience of contact lens wear.

Only the right eye of each subject was assessed. External ocular health was examined with slit lamp biomicroscopy before the ORA measurements to ensure that all subjects were free from ocular surface problems. Two sets of ORA measurements were performed, with a maximum of 12 consecutive measurements in each set. A 10-min break was arranged between sets during which the ORA was reset and restarted. All the measurements were saved, regardless of the waveform score. After the completion of the second set of measurements, external ocular health was reassessed with slit lamp biomicroscopy to ensure no adverse effects caused by the ORA measurements.

The first four measurements with waveform score higher or equal to 4.0 (objectively regarded as a measurement with good quality) [29] were averaged and used as the representative value of that set. If four measurements with waveform score higher or equal to 4.0 could not be achieved within the 12 consecutive measurements, the four measurements with the highest waveform score were averaged and used in the analysis.

Treatment of data

Statistical analyses were performed using SPSS software version 23 (IBM corporation, NY, USA). Shapiro-Wilk test was used to test the normality of each parameter because the sample size was smaller than 50 in each group. Unpaired t tests or Mann Whitney U tests for parametric or non-parametric parameters, respectively were used to compare for differences between groups. Intraclass correlation coefficients (ICC; Two-way mixed effects, mean of measurements, absolute agreement) were used to assess the level of agreement. ICCs values with less than 0.5 indicate poor reliability, between 0.5 and 0.75 indicate moderate reliability, between 0.75 and 0.9 indicate good reliability, and greater than 0.90 indicate excellent reliability [30]. The mean differences and the within subject standard deviation (SDw) were calculated. Bland–Altman plots (difference plot) were used to assess the width of the agreement interval [31,32] for waveform signal parameters which showed moderate to excellent agreement [ICC with 95% confidence interval (CI) 0.50 to >0.90]. The 95% limits of agreements (95% LoA) were defined as mean differences ± 1.96 x SDw. The Pearson correlation test was used to test the correlation between the differences and the average of the two sets of measurements.

Results

A total of 30 subjects (15 SVS, 15 ortho-k) were recruited and completed the study. The mean (SD) duration of ortho-k lenses wear in ortho-k subjects were 3.6 (2.4) months. There were no significant differences in demographic and baseline data (ie. when they participate in the myopia control study) between ortho-k and SVS subjects (all $p > 0.28$) (Table 1). No significant differences (all $p > 0.05$) in any of the waveform signal parameters (both sets of measurements) were found between ortho-k and SVS subjects, and so data from two groups were combined for repeatability analysis (Table 2). No significant difference was found between the two sets of measurements ($p > 0.71$). ICC values (95% CI) of these six waveform signal parameters ranged from 0.82 - 0.85 (0.61 - 0.93) (h2, h21, p1area, p1area1, p2area, and p2area1), indicating moderate to excellent agreement. No significant correlations was found between differences between two measurements and their means ($p > 0.51$), The mean (SD) of h2, h21, p1area, p1area1, p2area, and p2area1 were 372 (91), 248 (61), 4077 (854), 1762 (399), 2359 (670), and 1020 (300), respectively. Bland-Altman plots (Figure 2) showed the width of variations for h2, h21, p1area, p1area1, p2area, and p2area1, the mean between-measurement differences (95% LoA) were -4 (-101 to 94), -2 (-67.56 to 62.70), 111 (-723 to 946), 102 (-334 to 539), 25 (-718 to 768), and -3 (-350 to 343), respectively. h2 and h21 were significantly correlated with p2area and p2area1 ($p < 0.001$). The Pearson correlation coefficients were 0.69 to 0.83.

Discussion

In terms of ICCs, the agreements of all 37 waveform signal parameters obtained in the currently study were better that those reported by Landoulsi et al.[26], who investigated the agreement of the waveform signal parameters of ORA in normal and adults after refractive surgery. Landoulsi et al.[26] adopted the guideline by Landis and Koch [33], where ICCs greater than 0.6 were regarded as having a substantial strength of agreement, but no 95% CI were reported. Of the waveform signal parameters investigated, six (p1area, p1area1, p2area, p2area1, h1, and h11) were reported to have ICCs greater than 0.6, of which only p1area and p1area1 achieved ICC of 0.75 or above. The differences in results between Landoulsi and co-workers and the current study could be due to differences in measurement protocol. In their study, 10 measurements were acquired from each eye and the three measurements with the highest waveform score (an objective index represents the quality of the measurement) were analysed. In the current study, four measurements with waveform scores of 4.0 or above were analysed. Although the methods used in Landoulsi's study [26] were different from the current study, the results of current study suggested that the repeatability of waveform signal parameters may not necessarily be better in adults.

The values of p1area, p2area, p1area1, and p2area1 represent the area under the signal curve of the two peak signals, whereas, h2, and h21 represents the height of the signal at P2 (Figure 3) [16]. h2 and h21 were highly correlated with p2area and p2area1. Since they represent the height of the second peak of the signal waveform, a higher peak should lead to a larger area under the waveform. As h2 and h21 were highly corelated with p2area and p2area1, and they may represent similar nature in corneal properties, further investigation could potentially focus on the areas under the peak signals. The areas (p1area, p1area1, p2area, and p2area1) under the waveform have been suggested to be associated with the corneal applanation area at peak 1 and peak 2 [12,15]. The area under peak 1 (p1area and p1area1) could be related to the stiffness of the cornea and a stiffer cornea could lead to a larger p1area and p1area1 [12]. The area under peak 2 might be related to the corneal viscosity property since the corneal applanation area at peak 2 is proportional to the remaining energy stored in the cornea. Therefore, p2area and p2area1 could be potential indicators of the corneal characteristics in energy absorption, or in other words, the energy damping capacity [15].

In adults, these parameters had been shown to be useful in clinical applications. p1area, p1area1, p2area and p2area1 have been shown to be highly sensitive in distinguishing keratoconic eyes from normal eyes [16,18]. The p1area, p1area1, p2area, and p2area1 in normal subjects were about 2000, 850, 1500, and 700 units, respectively, higher than keratoconic subjects [16]. Another study also showed similar differences in magnitude of p1area and p2area between normal and keratoconic subjects [18]. Apart from the detection of keratoconus, p2area could be used in predicting the progression of visual field defects in patients with glaucoma and appears to be more sensitive than CH in detecting the corneal biomechanical changes after corneal cross-linking surgery [15,34]. After a year of corneal cross-linking surgery, the mean (SD) p2area increased significantly from 1262 (623) to 1704 (732) [34].

Besides ICC, Bland-Altman plots were used to further analyse the repeatability of h2, h21, p1area, p1area1, p2area, and p2area1 in the current study, since the plots could provide the width of the agreement interval for assessing the possibility in clinical application. Although the six waveform signal parameters showed satisfactory agreement, the width of the 95% LoA between two repeated measurements were relatively large. Comparing the width of the 95% LoA of p1area (1669 units), p1area1 (873 units), p2area (1486 units), and p2area1 (693 units), and the reported mean differences in adult keratoconic subjects compared with normal subjects[16,18], the repeatability of these measurements were marginally smaller than or nearly the same as the differences detected in keratoconic subjects. The relatively wide 95% LoA could limit the usefulness in clinical application for subtle corneal biomechanical changes. Further studies are required to determine whether these parameters could be clinically important or useful.

In children, while the clinical application for the waveform signal parameters is unclear, the study of corneal biomechanical properties could be important in children. Corneal biomechanical properties could be potential biomarkers for detecting children who have an elevated risk of developing rapidly progressing myopia [35]. The exact mechanism for myopia development in children is not yet fully understood. The mechanical stress exerted to eyeball was hypothesized to be one of the possible mechanisms [36]. The mechanical stress could be caused by changes in intraocular pressure (IOP) [36]. Many daily life activities could cause rapid changes in IOP [37]. Studies had shown an elevation in IOP could be associated with axial elongation [37,38]. The 24-hour diurnal rhythms of IOP were in phase with axial elongation [39]. This may imply that if an eye with a good energy damping capacity against mechanical stress due to an increase in IOP, it may have a lower risk for axial elongation. This hypothesis is supported by results from a retrospective study where young fast myopia progressors wearing single-vision spectacles have been shown to have a lower baseline CH and CRF [35]. Since the cornea and sclera potentially share similar biomechanical properties owing to their similar constitution of the same types of collagen [40], the corneal biomechanical properties could represent the overall ocular biomechanical properties. It is unclear whether waveform signal parameters could provide more information in detecting the children who are at risk of rapid myopia progression but the waveform signal parameters identified with good agreement in the current study may provide further insight into the role of corneal biomechanics in myopia control study.

The second possible application for the waveform signal parameters in children is monitoring the corneal biomechanical changes induced by wearing ortho-k lenses. It was reported that CH and CRF were altered after ortho-k treatment [41,42]. In current study, no significant differences were detected for all waveform signal parameters between ortho-k lenses and single-vision spectacles wearing children. However, the mean (SD) duration of ortho-k lenses wear was only 3.6 (2.4) months. The relatively short lens wear history may not yet reflect changes to corneal biomechanical changes induced by ortho-k lenses wear. A further longitudinal study is required to investigate the role of waveform signal parameters in monitoring the changes of corneal biomechanical properties after ortho-k lens wear.

Another commercially available equipment that can measure corneal biomechanics non-invasively under clinical setting is the Corneal Visualization Scheimpflug Technology (Corvis ST, Oculus Optikgeräte GmbH, Germany). It also deforms the cornea by applying an air-puff. Corvis ST and shared the same drawback with the ORA in that the repeatability of some parameters was not good [43–45].

Conclusion

This study provided fundamental information for further study on corneal biomechanics regarding the waveform signal parameters generated by ORA. Investigation in the applications of waveform signal parameters, especially p1area, p1area1, p2area, and p2area1, in children is warranted in the future.

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Table 1. Demographics and baseline data of the 30 subjects (mean ± SD) or [median (range)]

	SVS	**Ortho-k**	**Combined**	***P value**
Age, year	9.3 ± 0.6	9.1 ± 0.7	9.2 ± 0.7	0.279
Sex, M/F	4/11	3/12	7/23	0.666#
Sphere, D	-2.47 ± 0.77	-2.25 ± 0.93	-2.36 ± 0.84	0.491
Astigmatism, D	-0.50 (0 to -0.75)	-0.25 (0 to -1.25)	-0.50 (0 to -1.25)	0.999†

Ortho-k: orthokeratology group; SVS: single-vision spectacles group;
* probability value of unpaired t-test for between group (SVS and ortjo-k) differences
# chi-square test
† Mann Whitney U test

Table 2. Mean (SD) and repeatability of waveform signal parameters with moderate to excellent agreement (95% confidence interval of Intraclass correlation coefficients ranged from 0.50 to >0.90) (alphabetic order)

	Mean	SD	Mean Difference	SDw	ICC (95% CI)
h2	372	90.83	-4	50	0.85 (0.69 - 0.93)
h21	248	60.55	-2	33	0.85 (0.69 - 0.93)
p1area	4077	854	111	425	0.85 (0.69 - 0.93)
p1area1	1762	399	102	222	0.82 (0.61 - 0.92)
p2area	2359	670	25	379	0.85 (0.69 - 0.93)
p2area1	1020	300	-3	177	0.83 (0.65 - 0.92)

SD: standard deviation; SDw: within subject standard deviation; ICC: intraclass correlation coefficient; 95% CI: 95% confidence interval

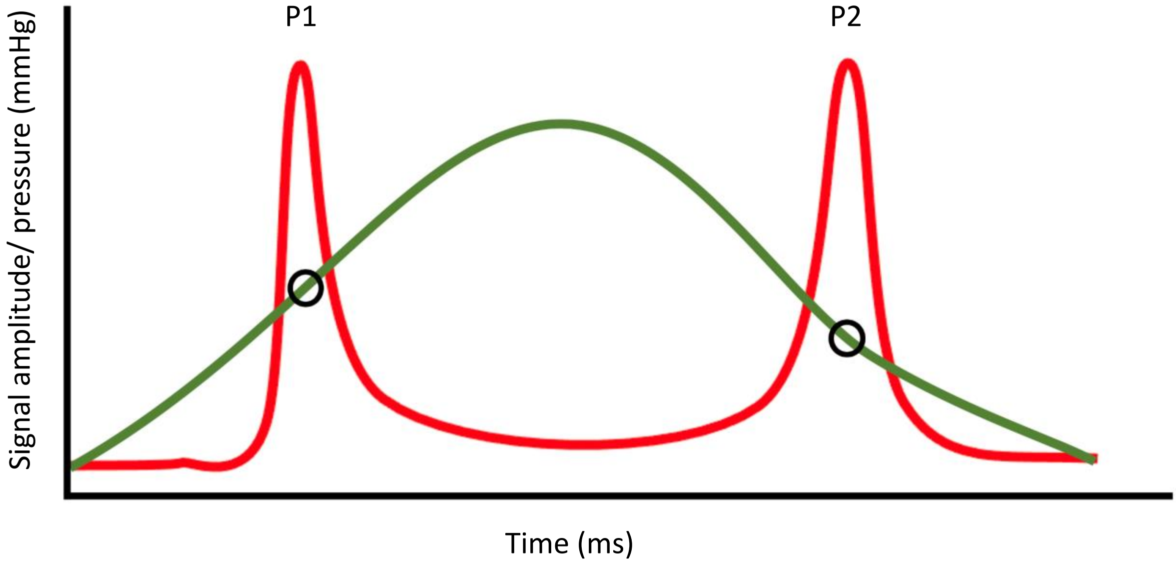

Figure 1. Illustration of peak 1 (P1) and peak 2 (P2) of Ocular Response Analyzer measurement. The red line represents the infrared signal. The green line represents the pressure of the air-puff. Two black circles represent the pressure at P1 and P2 causing the inward and outward applanation of the cornea (see the red line). Difference of the two pressures was defined as corneal hysteresis (CH).

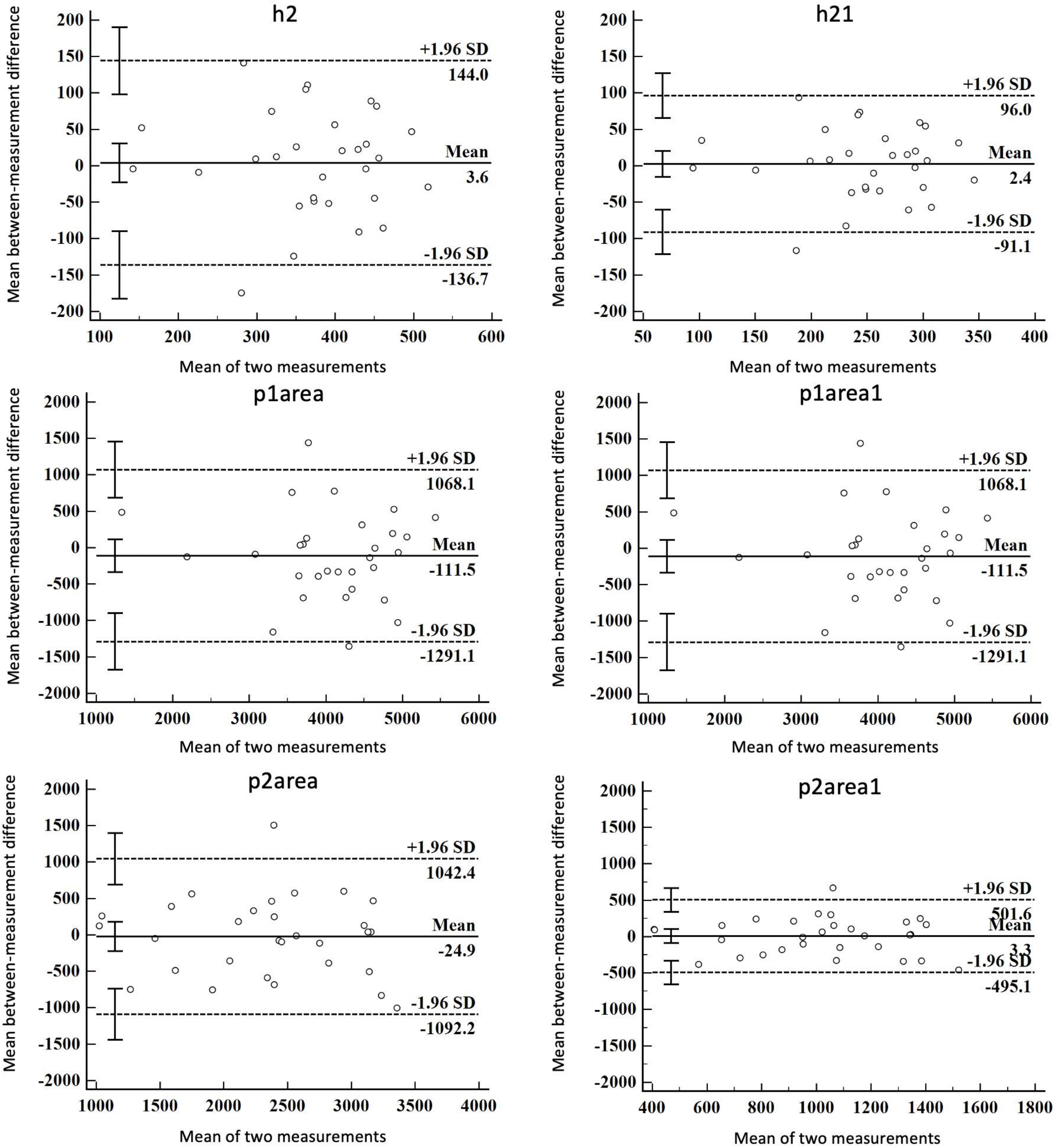

Figure 2. Bland-Altman plots (n = 30) of between-measurement difference against average of two measures for all waveform signal parameters with the 95% confidence interval of intraclass correlation coefficient ranged from 0.5 to >0.9. The solid line represents the mean difference and the two dashed lines represent the upper and lower limits of agreements, respectively. The error bars represent the 95% confidence intervals.

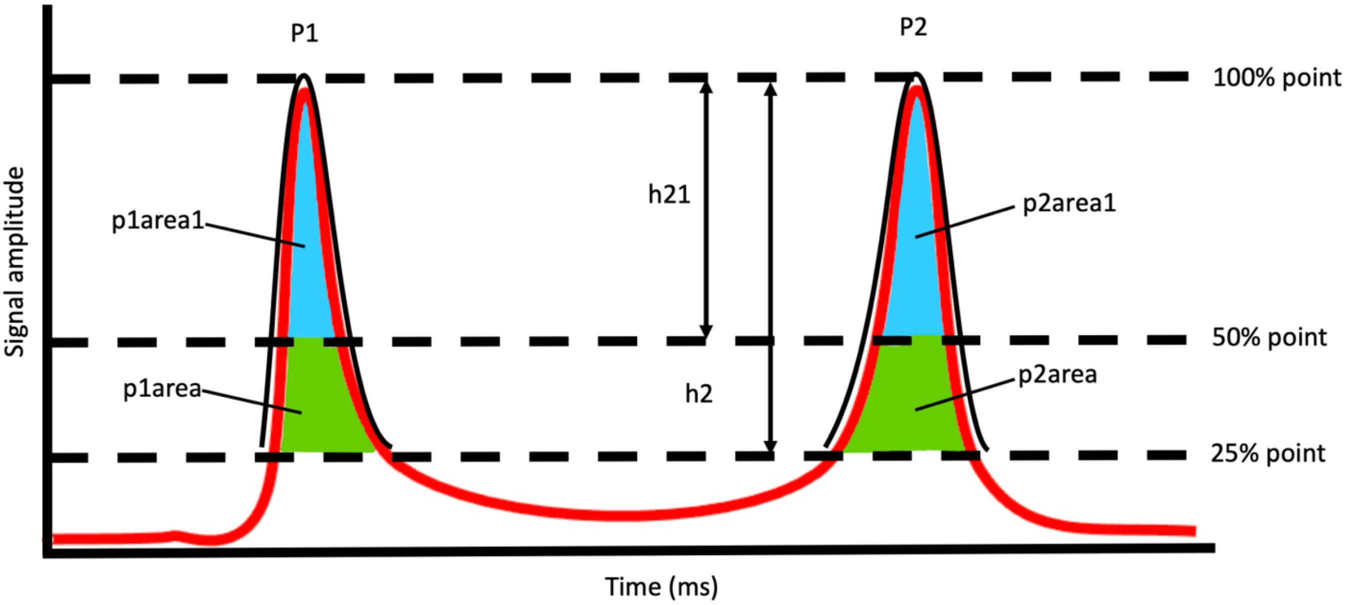

Figure 3. Illustration of waveform signal parameters with the 95% confidence interval of intraclass correlation coefficients ranged from 0.5 to >0.9. p1area: area under the curve from 25% point at P1; p1area1: area under the curve from 50% point at P1; p2area: area under the curve from 25% point at P2; p2area1: area under the curve from 50% point at P2; h2: the height of P2 from 25% point; h21: the height of P2 from 50% point